CURRENT ALLERGY & CLINICAL IMMUNOLOGY

JOURNAL OF THE ALLERGY SOCIETY OF SOUTH AFRICA

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SUBMISSIONS
The editors encourage articles, letters, news and photographs relating to the field of allergy and clinical immunology. Please send submissions to Robyn Marais, at robyn@jesser-point.co.za

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GUEST EDITORIAL

BIOLOGIC THERAPIES IN ALLERGIC DISEASE

Biologics are 'large molecules typically derived from living cells'; they are used in the treatment, diagnosis or prevention of disease. Despite the complexity of manufacture and the high costs involved, more than 200 biologic medicines have been brought to market around the world. In fact, the development of biological drugs is accelerating: in 2017, approximately 30 per cent of all new chemical entities approved by the US Food and Drug Administration (FDA) were biologics.[1]

Biologics include monoclonal antibodies, DNA vaccines, therapeutic and fusion proteins, and small interfering ribonucleic acids (siRNAs) and are used in almost every discipline of medicine:

- For the immunologist, they fascinate: many target immune receptors and ligands; most of those commercially available are monoclonal antibodies. Biologics themselves are antigenic, and much fundamental human immune pathway biology has been elucidated through their clinical application.
- For the clinician and allergist, they are offer new hope for treating many severe disease phenotypes, but, frustratingly, all too often they seem to remain unaffordable and out of reach.

This final edition of the journal for 2018 brings you a collection of excellent review articles covering state-of-the-art use of biologic therapy for allergic and selected rheumatological disorders. It also includes a discussion of the 'elephant in the room" - ethical access to biologic therapies in South Africa, a low middle-income country (MIC). Two illustrative cases demonstrate both the benefits and the complexities of managing biologic therapies.

Dr Waheba Slamang and Prof Chris Scott from the Division of Rheumatology, Department of Paediatrics, University of Cape Town, head up this edition with an excellent article that orientates us to biologics in the context of autoimmunity and autoinflammation. They provide a convenient summary table of specific biologics and their immune targets, and an equally useful figure that illustrates where different biologics may act on the immunopathogenesis of complex disease.

Dr David Masuku and Prof Richard van Zyl-Smit of the Division of Pulmonology, Department of Medicine, University of Cape Town, shift the focus to atopic disease and the life-threatening issue of severe asthma. Importantly for our setting, where access to biologic therapy is limited, they highlight the work-up and management of uncontrolled asthma before deciding on the use of a biologic, before considering what is available and in the late stages of clinical development. Similarly, Dr Thuraya Isaacs of University of Cape Town Private Academic Hospital and Profs Carol Hlela and Rannakoe Lehloenya of the Division of Dermatology, Department of Medicine, University of Cape Town, discuss the step-wise management of atopic dermatitis (AD) and approved and promising biologics for AD. The immune targets of novel biologics for both of these diseases highlight the newer cytokines that are important in allergic pathogenesis, such as TSLP, IL-31 and IL-22.

Dr Sipho Ntshalintshali and I, both from the Division of Allergy and Immunology, Department of Medicine, University of Cape Town, present an article on the morbid condition of chronic spontaneous urticaria (CSU). Practitioners dealing with this heartsink condition are offered new hope by the application of biologics. We have attempted to describe in detail the process for securing funding for therapy and also the obstacles to doing so. We include a helpful figure on the latest thinking about CSU pathogenesis that we hope will be of interest to our readers.

Following this article, Drs Zandile Spengane and Riyaadh Roberts and Prof Rannakoe Lehloenya and I present a complex case of urticarial vasculitis that we managed in our multidisciplinary clinic. We certainly learnt a lot from this experience, both about the treatment of urticarial vasculitis and about the possible associations between omalizumab and pulmonary embolus. We hope this case helps you to improve your practice as it has ours.

A second case report by Dr Ashley Jeevarathnum and Profs André van Niekerk and Robin Green of the Division of Pulmonology, Department of Paediatrics, University of Pretoria, details a success story about accessing international standard-of-care biologic therapy for a young woman with hereditary angioedema (HAE). The case illustrates the challenges of caring for HAE patients during pregnancy and the absolute necessity for biologics.

The ethics article for this edition is an excellent offering from Profs Bridget Hodkinson and Marc Blockman of the Divisions of Rheumatology and Pharmacology at Groote Schuur Hospital. They discuss strategies for and the ethics of obtaining equitable access to biologics. You will be unsurprised by the inequities that exist in accessing biologics, but the variance in the single exit pricing of the same biologic is shocking – surely the motivation for a real call to 'activism for equality'.

In additional, we have our regular occupational health and immunology articles as well as a research article to complete this issue. I hope you enjoy reading these excellent contributions to this final edition for 2018. In particular, may they help you to continue to fight for your patients' access to the best evidence-based therapies, be they non-pharmacological, small molecule or biologic.

Jonny G Peter

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Review Article

BIOLOGICS IN CHILDHOOD RHEUMATIC DISORDERS

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INTRODUCTION

The past decade has seen a substantial expansion in the number of biologic agents useful in the management of childhood rheumatic diseases. The ability to target specific pathways and the cytokines involved has changed the landscape of diseases that were previously associated with serious morbidity and in some cases mortality. The proliferation of these revolutionary medications poses other important considerations such as cost and the risk of complications. It is therefore important for clinicians who may encounter children with autoimmune and autoinflammatory conditions to be aware of the most commonly used biologic agents and to understand the mechanisms of action, indications and potential risks associated with them.

WHAT IS A BIOLOGIC?

Biologics are genetically engineered molecules or proteins that manipulate immunological pathways, usually by blocking cytokines or their receptors and are given intravenously or subcutaneously. Small-molecule kinase inhibitors are sometimes called 'biologics' because they manipulate these pathways in a manner that is reminiscent of the effect of biologics. However, these are produced synthetically and are taken orally.

The term 'biosimilars' was coined to refer to biologic agents manufactured after the original product patent had expired. The term 'generic' cannot be applied here as there is no *chemical* formula that can be perfectly copied and the production process of these very complex biological molecules are sensitive to even minor changes. The best product that can be manufactured is therefore 'similar' enough to have an equivalent biological effect.

REGULATION OF BIOLOGIC AGENTS IN SOUTH AFRICA

Because of the novelty of these agents, and their significant effects on the immune system, international registries have been formed to monitor their use and potential side-effects. In South Africa the South African Rheumatism and Arthritis Association (SARAA) implemented a biologic registry in 2004 with the aim of ensuring not only that data on safety of biologics in South Africa are collected for adults and children but also to monitor correct prescription and follow-up of biologic agents. SARAA also acts as an approval mechanism for funding of biologics for rheumatic conditions through medical insurers.

NOMENCLATURE

Biologic agents have complex names. These may seem confusing but reflect an agreed system of nomenclature which tells one much about the mode of action and production. For monoclonal antibodies, names typically have a unique prefix (which usually has no meaning other than to differentiate agents of the same class with the same target and the same origin), a sub-stem for the target of the agent, a sub-stem for the origin of the agent and a stem denoting the type of agent e.g. Adalimumab, Tocilizumab and Infliximab: Here the stem is -mab, indicating monoclonal antibody. The sub-stem for the origin is either -u-(human), -zu-(humanised) or xi-(chimeric). The sub-stem for the target in all three is -li-(immune system). Therefore, the class, target and origin of a biological agent can be deduced by decoding the name.

Name	Prefix	Sub-stem target	Sub-stem origin	Stem
Adalimumab	Ada	Li – immune system	U – human	_mab – monoclonal antibody
Tocilizumab	Toci		Zu – humanised	
Infliximab	Inf		Xi – chimeric	

USE IN RHEUMATIC DISEASES

AUTOIMMUNE DISEASE

The impact of biologic disease-modifying antirheumatic drugs (DMARDs) has been felt perhaps most keenly in the management of juvenile idiopathic arthritis (JIA).[2] JIA is the most common long-term health condition managed by Paediatric Rheumatologists and is one of the most common causes of paediatric musculoskeletal disability worldwide.[3] JIA is classified into different subtypes based on differing clinical phenotypes and pathogenesis.[4] Biologics are most often required in the polyarticular (rheumatoid factor negative and positive), psoriatic, enthesitis-related and systemic subtypes. Systemic JIA will be considered in detail in a separate section as the pathogenesis involves predominantly auto-inflammatory mechanisms. Whereas the majority of patients attain a satisfactory level of disease control using traditional DMARDs such as methotrexate, approximately 20% of patients do not and in these children the addition of biologic DMARD therapy can improve outcomes and reduce disability dramatically. Biologic agents can target several pathways known to be relevant in the pathogenesis of JIA[5] (see Figure 1). The most frequently used agents are the anti-tumour necrosis factor (TNF) biologics. The TNF inhibitors Etanercept and Adalimumab are registered for use in children in South Africa. Data from key clinical trials as well as long-term registries confirm the efficacy of these agents.[6–8] Infliximab, the earliest TNF inhibitor did not meet primary endpoints in paediatric

trials, but is registered for adults with rheumatiod arthritis (RA) and ankylosing spondylitis (AS), and is used off label in JIA, especially when uveitis is present.[9–11] Co-stimulatory molecules such as Abatacept and IL-6 blockers such as Tocilizumab have recently been added to the list of approved agents with demonstrated efficacy.[12–17] Newer agents such as Golimumab (TNF inhibitor), Secukinumab (IL-17 blocker) and the small-molecule Janus Kinase Inhibitor, Tofacitinib are currently under investigation for various subtypes of JIA.[18–21]

Juvenile dermatomyositis (JDM) is an immune-mediated vasculopathic disease of childhood. The defining feature is inflammation of the striated muscles, skin and internal organs (especially gastrointestinal and pulmonary involvement). The clinical manifestations include proximal muscle weakness and characteristic cutaneous lesions such as a heliotrope rash and Gottron's papules.[22] Corticosteroids, Methotrexate, Cyclosporin A, Cyclophosphamide and IVIG are utilised in the management of JDM, but biologic agents such as Rituximab, TNF inhibitors, Tocilizumab and Abatacept have all been reported to be useful. Given the challenges of performing clinical trials in rare diseases such as JDM, robust evidence does not exist for any of these agents in this context.[23]

Systemic lupus erythematosus (SLE) is a severe multisystem autoimmune condition for which many therapeutic challenges remain, especially in less-resourced countries.[24,25] While survival in SLE has improved dramatically in the past decades, current therapies for SLE are suboptimal in terms of efficacy and toxicity.[26] One biologic agent, Belimumab, is the first and only agent registered for use in adults with SLE.[27,28] Rituximab is widely used in refractory lupus and is considered an important addition in the management of refractory renal, neurological and haematological manifestations, despite the absence of high levels of evidence.[29,30]

AUTOINFLAMMATORY DISEASE

Disorders of the innate immune system have allowed for perhaps the most dramatic illustration of the potential efficacy of biologic agents in targeting specific cytokine pathways. Cryopyrin-associated periodic syndrome (CAPS) are a group of disorders in which mutations of the NLRP3 inflammasome result in excessive activation of the innate immune system by activation of IL-1Beta.[31] Therapies that target Interleukin 1 beta have proven dramatically effective in the three major subtypes that represent the spectrum of these disorders (neonatal onset multisystem inflammatory disease (NOMID), Muckle Wells and familial cold urticaria).[32–34] The dramatic effectiveness of IL-1 blockade in these conditions are balanced by cost and availability. With the exception of Anakinra, IL -1 inhibiting agents (Canakinumab and Rilonacept) are not available in South Africa and are among the most expensive agents manufactured.

Systemic Juvenile Idiopathic Arthritis (sJIA) is characterised by quotidian fever, evanescent rash, arthritis and major organ involvement with pleuritis, pericarditis, hepatosplenomegaly and haematological manifestations. Interleukin 1 and 6 have been shown to be important in the pathogenesis of sJIA and the potentially fatal complication of macrophage activation syndrome (MAS).[35] TNF-inhibitors, shown to be effective in other forms of JIA, were found to be less efficacious in sJIA, especially when systemic features dominate the clinical phenotype.[36] IL-1 inhibitors and IL-6 inhibitors have proven efficacious in the management of sJIA, the latter being registered in South Africa for the treatment sJIA.[15,16,37–40]

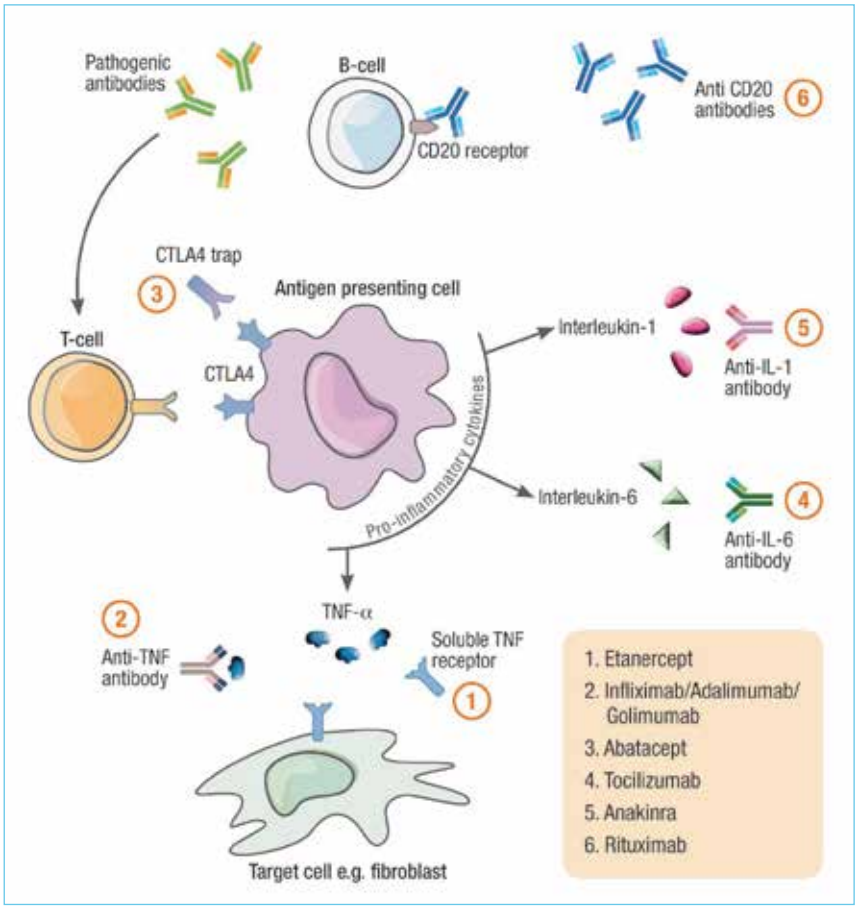

Figure 1: An illustration of the site of action of the biologic agents currently used in JIA

SAFETY CONSIDERATIONS

TNF-INHIBITORS

Injection site reactions and allergic reactions:

Localised injection site reactions are common with both Adalimumab and Etanercept and can occur in up to one-third of patients. These reactions tend to lessen with time and may be present for up to two months. The use of icepacks before and after injections and local anaesthetic cream may be useful in managing discomfort. In more severe reactions topical corticosteroid cream can be considered.[41]

TABLE 1: CLASSES OF BIOLOGICS

AGENT (TRADE NAME)	TYPE	FDA REGISTERED PAEDIATRIC INDICATION (YEAR APPROVED)	METHOD OF ADMINISTRATION
TNF INHIBITORS			
Etanercept *(Enbrel)*	Soluble TNF receptor fusion protein	Poly-JIA, ERA (2000)	s/c weekly
Adalimumab *(Humira)*	Fully humanised TNF monoclonal antibody	Poly-JIA (2008) Crohn's (2014) Uveitis (2016)	s/c every two weeks
Infliximab *(Revellex)*	Mouse/human Chimeric monoclonal TNF antibody	Crohn's (2006)	IV every 4–8weeks
Golimumab *(Simponi)*	Human monoclonal antibody binds to soluble and transmembrane TNF alpha	None (Not approved: Phase 3 clinical trials)	IV or s/c every four weeks
Certolizumab *(Cimzia)*	PEGylated fragmented human monoclonal antibody	None (Not approved: Phase 3 clinical trial)	s/c every 2–4 weeks
T-CELL INHIBITION			
Abatacept *(Orencia)*	CTLA4- IgG: T-cell co-stimulation inhibitor	Poly-JIA (2017)	IV or s/c weekly
ANTI IL-6			
Tocilizumab *(Actemra)*	IL-6 receptor inhibitor	sJIA, Poly-JIA (2013)	IV or s/c
ANTI IL-1			
Anakinra *(Kineret)*	IL-1 receptor antagonist	CAPS (NOMID) (2013)	s/c daily
Canakinumab *(Ilaris)*	Human monoclonal antibody targeting IL-1 beta	CAPS, sJIA (2009) TRAPS, HIDS, FMF (2016)	4–8 weekly s/c
Rilonacept *(Arcalyst)*	Monoclonal Antibody binding both IL-1 beta and IL-1 alpha	CAPS (2008)	s/c weekly
ANTI IL-17			
Secukinumab *(Cosentyx)*	Monoclonal antibody binding IL-17	None (Not approved)	s/c every four weeks
B-CELL DEPLETION			
Rituximab *(Rituxan)*	Chimeric mouse anti-human monoclonal antibody	None (Not approved)	IV 2 doses two weeks apart (six-monthly)
ANTI- BLYS			
Belimumab *(Benlysta)*	Anti BlyS	None (Not approved)	IV every four weeks

TNF: Tumour Necrosis Factor; Poly-JIA: Polyarticular Juvenile Idiopathic Arthritis; PEG: Poly Ethylene Glycol; CTLA4: Cytotoxic T-Lymphocyte Associated Antigen 4; IgG: Immunoglobulin G; IL: Interleukin; CAPS: Cryopyrin Associated Periodic Syndrome; NOMID: Neonatal Onset Multisystem Inflammatory Disease; TRAPS: Tumour Necrosis Factor Receptor Associated Periodic Syndrome; HIDS: Hyper IgD Syndrome; FMF: Familial Mediterranean Fever; BLyS: B-Lymphocyte Stimulating Factor; sJIA: Systemic Juvenile Idiopathic Arthritis

Infliximab carries the risk of more serious hypersensitivity reactions and even anaphylaxis because it is give intravenously and is a chimeric molecule of human and murine origin. This agent should therefore be given in facilities where therapy for this eventuality is readily available. In some cases, pre-treatment with antihistamines and corticosteroids may be useful. Anti-drug antibodies may develop to all of these agents, leading to loss of efficacy.[42] The use of methotrexate is not only synergistic in terms of efficacy, but it may also help to reduce the development of anti-drug antibodies (ADAs).[43]

Increased infection risk:

Patients on TNF inhibitor therapy suffer higher rates of infections, especially otitis media, bronchitis and tonsillitis. There is also an increased risk of severe infections in patients taking these agents, especially with the monoclonal antibodies.[44–46]

In South Africa the risk of tuberculosis (TB) is a particular concern. It is mandatory to screen all patients for latent infection prior to the commencement of anti-TNF therapy. Treatment of latent TB and possible longer-term prophylaxis in higher risk groups, is essential for the safe use of TNF inhibitors. Guidelines for the management of latent TB in South African patients have been developed and are available on the SARAA website.[47,48]

In children the increased risk for varicella zoster infection is a significant concern and pre-emptive immunisation should be considered in unexposed and unimmunised children, before the start of therapy.[49–52]

Risk of cancer:

Increased cancer risk in children using TNF Inhibitors has been a possible concern, especially after the Federal Drug Administration (FDA) published a warning in 2010, citing a study which investigated reported cancers for children on anti-TNF therapy in the FDA database.[53] This study compared the risk of cancer to the healthy population, and not to JIA patients not on TNF inhibitors, who are known to have a slightly higher risk of malignancy than the healthy population. Most long-term registries in children with JIA do not show a risk of cancer

which is greater than the existing risk for children with JIA on methotrexate.[54,55]

On the other hand, reports of cancer in children with Crohn's disease concurrently using Azathioprine, appear to be more concerning. In addition, a recent retrospective report from a single centre in North America, found that while the overall rate of malignancy in their cohort was not high, at 6/357 (1.68%), the children who developed malignancies did so late in therapy (Median five years) and four out of the six developed malignancies that were considered rare in the paediatric population. This study, and others, notes that only longer term, prospective data, with large numbers of patients will be able to adequately assess the true risk for malignancy in children on biologic therapies.

One other aspect of TNF inhibitors that is sometimes discussed, is the risk of developing other autoimmune conditions. Anecdotal reports of SLE, glomerulonephritis, thyroiditis, vasculitis and interstitial lung disease have been published.[56]

Tocilizumab:

The most common adverse effects with Tocilizumab appear to be related to infections of the respiratory tract and gastrointestinal tract (GIT). Infusion reactions are not uncommon and can range from mild to severe. Neutropenia has also been reported. TB risk has not been identified as a concern.

Abatacept:

Mild infusion reactions are fairly common if given intravenously but infectious risk does not appear to be increased, and neither does risk of malignancy.

Rituximab:

Infusion reactions are common and premedication is considered a standard part of the protocol. Infusion reactions can range from mild to severe, including anaphylaxis and hypersensitivity reactions.

As with other biologics the risk of infections in the respiratory or GIT is higher. In addition viral infections such as John Cunningham (JC) virus and hepatitis B reactivation have been reported in adults.[57] JC virus is associated with progressive multifocal leukoencephalopathy (PML), a fatal condition and, while no cases have been reported in children, caution is warranted.[58]

Haematological disturbances as well as prolonged hypogammaglobulinaemia are additional concerns with the use of Rituximab.[59]

Vaccinations:

Given the propensity for infections in children taking agents that have potent effects on the immune system, preventative measures such as vaccinations are critical. Because live vaccines are contra-indicated in children on immunosuppression, it is important to look for windows of opportunity before and after the initiation of therapy to optimally protect children. Guidelines for immunisations in children with rheumatic diseases have been published recently and offer guidance on how to navigate this important concern.[49,50,52]

COST AND AVAILABILITY OF BIOLOGICS

Biologics are expensive, and this limits their availability, especially in resource-constrained environments.[60] This coupled with a scarcity of healthcare workers skilled in the use of biologics, means that access is limited and available only to a relatively small proportion of patients who may benefit from their use.[61] Biologics form part of the accepted package of care in most well-resourced countries and cost-benefit studies have been conducted in European and North American countries. In South Africa access to biologics in public healthcare is variable and dependent on many local factors. They have not been included on the national essential medicines lists. Private medical funders allow access to biologics under strict conditions, after approval by the SARAA biologic registry panel and only as part of specific, higher cost plans.

BIOSIMILARS

A number of biosimilar agents for rheumatic diseases have been approved in the United States, including biosimilars of Infliximab, Adalimumab, Etanercept and Rituximab but to date these have not received approval in South Africa.[62–65] In order to be approved by American and European authorities, producers of these follow-on agents must prove similarity to the originator drug without necessarily having to undergo new clinical trials for each registered indication. The South African Health Products Regulatory Authority (SAHPRA) has published guidelines for assessing biosimilars and the first biosimilar, a follow on of Filgrastim, was approved late last year. It appears likely that others will follow.[66]

CONCLUSIONS

Biologic agents are useful additions to the package of care we are able to offer patients with rheumatic diseases. Their introduction has changed outcomes in many diseases, especially JIA and autoinflammatory conditions. Their utility is balanced against the challenge of availability due to limitations of cost and access to care as well as the risk of infections such as TB. Despite these limitations increasing numbers of patients are being managed with biologics and a good understanding of their action, indications and side-effects is important for generalists and specialists.

DECLARATION OF CONFLICT OF INTEREST

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Review Article

THE USE OF BIOLOGICS IN THE MANAGEMENT OF SEVERE ASTHMA

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ABSTRACT

Biological therapies, often referred to as 'monoclonal antibodies', are becoming increasingly available for the management of asthma. These injectable therapies provide great hope for those with severe asthma not controlled by inhaled therapies and even by oral corticosteroids. The challenges, however, that are now faced as these therapies become more easily available, is to decide on who needs them and how best to use them as they will undoubtedly be very expensive. Each of these monoclonal therapies target a specific receptor or pathway. Broadly speaking, they can be divided into a few groups, namely: anti-IgE, anti-IL5, anti-IL13/4 and novel targets. Many different drugs are in various stages of development. Some have undergone clinical trials in other allergic conditions such as atopic dermatitis or eosinophilic syndromes. These indications are outside the focus of this asthma-focused review which will concentrate on the major drugs in development or those near to approval for the treatment of asthma.

INTRODUCTION

Asthma affects more than 300 million individuals worldwide with a prevalence of 10–15% in South Africa.[1] The most recent global asthma report ranks South Africa third in age-standardised mortality, although not in the highest strata of prevalence.[1] The reasons for the high mortality in South Africa are potentially multifactorial including poor access to medication, incorrect inhaler technique, tobacco smoking, over reliance on short acting beta agonists, and lack of prescription of inhaled corticosteroids. Notwithstanding these basic factors contributing to mortality, severe asthma is estimated to occur in 5% of asthmatics and to carry significant morbidity and mortality potential. Although multiple new combinations of inhaled steroids, long-acting beta-agonists and newer once-daily preparations, the development of biological therapies that directly target the underlying inflammatory pathways involved in asthma has been a great stride forward. Although costly, they do provide hope for those asthmatics who are uncontrolled on appropriate high-dose therapy (>500 ug fluticasone/>800 ug budesonide daily; Global Initiative for Asthma (GINA) step 5).

Before deciding on which new expensive medication to add to the patient's asthma treatment regimen, a careful evaluation of the whole patient is required. It is critical to ensure that the basics of asthma care have been covered and the disease managed correctly, as simple interventions may negate the need for biologicals. This review will cover the basic work-up for a 'potentially severe asthmatic', a review of what drugs are being developed and how each of them works. Which drug is likely to be on the market or the most effective drug will not be reviewed. Given the unpredictability related to the availability and the specific indications in our setting, the focus will be the current evidence we have on the different agents.

WHAT IS SEVERE ASTHMA?

The international American Thoracic Society/European Respiratory Society (ATS/ERS) guideline on the definition, evaluation and treatment of severe asthma[2] promotes the following definition of severe asthma:

> 'Asthma which requires treatment with guidelines suggested medications for GINA steps 4–5 asthma high-dose inhaled steroids and [long-acting beta-adrenoceptor agonist] LABA or leukotriene modifier/theophylline) for the previous year or systemic corticosteroids for >50% of the previous year to prevent it from becoming "uncontrolled" or which remains "uncontrolled" despite this therapy.'

They define uncontrolled asthma as – at least – one of the following:

1. Poor symptom control: Asthma Control Questionnaire (ACQ) consistently >1.5, Asthma Control Test (ACT) <20 (or 'not well controlled' by the National Asthma Education and Prevention Program (NAEPP)/GINA guidelines).
2. Frequent severe exacerbations: two or more bursts of systemic corticosteroids (>3 days each) in the previous year.
3. Serious exacerbations: at least one hospitalisation, ICU stay or mechanical ventilation in the previous year.

MORE FREEDOM IN ACTION

XOLAIR® acts on the IgE pathway that is central to allergic asthma, providing efficacy for people with severe allergic asthma who are inadequately controlled on high-dose ICS/LABA.[1]

- **XOLAIR® reduced exacerbation rates by 72%** over 12 months vs. the 12 months before XOLAIR® initiation in a real-world study.[2]

Children (6 to < 12 years of age)

Xolair® is indicated as add-on therapy to reduce the dose of inhaled corticosteroids in patients with severe persistent allergic asthma who have a positive skin test or *in vitro* reactivity to a perennial aeroallergen and frequent daytime symptoms or night-time awakenings.[1]

References: 1. Xolair® MCC approved package insert. 2. Deschildre A, *et al.* Add-on omalizumab in children with severe allergic asthma: a one year real-life survey. *Eur Respir J* 2013;42:1224–33.

XOLAIR® 150 MG POWDER FOR SOLUTION FOR INJECTION. **SCHEDULING STATUS** S4 **PHARMACOLOGICAL CLASSIFICATION:** A34. Other. **COMPOSITION:** One vial of XOLAIR 150 mg powder and solvent for solution for injection contains 150 mg of omalizumab, a humanized monoclonal antibody manufactured from a mammalian cell line. Reconstituted XOLAIR contains 125 mg/mL of omalizumab (150 mg in 1.2 mL). **INDICATIONS: Allergic Asthma: Adults and adolescents (12 years of age and older)** XOLAIR is indicated for the prevention of asthma exacerbations and control of asthma symptoms, when given as add-on therapy for patients with severe persistent allergic asthma who have a positive skin test or *in vitro* reactivity to a perennial aeroallergen and who have reduced lung function (FEV, <80%), as well as frequent daytime symptoms or night-time awakenings, and who have had multiple documented severe asthma exacerbations, despite daily high-dose inhaled corticosteroids, plus a long-acting inhaled beta$_2$-agonist. **Children (6 to <12 years of age)** XOLAIR is indicated as add-on therapy to reduce the dose of inhaled corticosteroids in patients with severe persistent allergic asthma who have a positive skin test or *in vitro* reactivity to a perennial aeroallergen and frequent daytime symptoms or night-time awakenings. XOLAIR treatment should only be considered for patients with convincing IgE (immunoglobulin E) mediated asthma. Safety and efficacy have not been established in other allergic conditions. **Chronic Spontaneous Urticaria (CSU)** XOLAIR (omalizumab) is indicated for adults and adolescents (12 years of age and above) with chronic spontaneous urticaria refractory to standard of care. **CONTRAINDICATIONS:** Known hypersensitivity to the active substance or to any of the excipients. **WARNINGS AND SPECIAL PRECAUTIONS Anaphylaxis** Anaphylaxis has been reported to occur after administration of XOLAIR in pre-marketing clinical trials and in post-marketing spontaneous reports. Signs and symptoms in these reported cases have included bronchospasm, hypotension, syncope, urticaria, and/or angioedema of the throat or tongue. Some of these events have been life-threatening. In pre-marketing clinical trials the frequency of anaphylaxis attributed to XOLAIR use was estimated to be 0,1 %. In post-marketing spontaneous reports, the frequency of anaphylaxis attributed to XOLAIR use was estimated to be at least 0,2 % of patients based on an estimated exposure of about 57,300 patients from June 2003 through December 2006. Anaphylaxis has occurred as early as after the first dose of XOLAIR, but has also occurred beyond one year after beginning regularly scheduled treatment. XOLAIR should only be administered in a healthcare setting by healthcare providers prepared to manage anaphylaxis that can be life-threatening. Patients should be closely observed for an appropriate period of time after administration of XOLAIR, taking into account the time to onset of anaphylaxis seen in pre-marketing clinical trials and post-marketing spontaneous reports (see section Special Precautions). Patients should be informed of the signs and symptoms of anaphylaxis, and instructed to seek immediate medical care should signs or symptoms occur. XOLAIR should be discontinued in patients who experience a severe hypersensitivity reaction (see Contraindications). **INTERACTIONS:** Cytochrome P450 enzymes, efflux pumps and protein binding mechanisms are not involved in the clearance of omalizumab, thus there is little potential for drug-drug interactions. Medicinal product or vaccine interaction studies have not been performed with XOLAIR. There is no pharmacological reason to expect that commonly prescribed medicinal products used in the treatment of asthma or CSU will interact with omalizumab. **DOSAGE AND DIRECTIONS FOR USE:** For subcutaneous administration only. Do not administer by the intravenous or intramuscular route. **Dosage for Allergic Asthma:** The appropriate dose and dosing frequency of XOLAIR is determined by baseline IgE (IU/mL), measured before the start of treatment, and body weight (kg). Prior to initial dosing, patients should have their IgE level determined by any commercial serum total IgE assay for their dose assignment. Based on these measurements 75–600 mg of XOLAIR in 1 to 4 injections may be needed for each administration. At 16 weeks after commencing XOLAIR therapy patients should be assessed by their physician for treatment effectiveness before further injections are administered. The decision to continue XOLAIR should be based on whether a marked improvement in overall asthma control is seen. **Dosage for Chronic Spontaneous Urticaria (CSU):** The recommended dose is 300 mg by subcutaneous injection every four weeks. Some patients may achieve control of their symptoms with a dose of 150 mg every four weeks. Dosing of XOLAIR in CSU patients is not dependent on serum total IgE (IU/ml) or body weight (Kg). **ADVERSE REACTIONS: Allergic Asthma:** Common or very common (≥1/100 to <1/10, ≥1/10) side effects include headache, upper abdominal pain, pyrexia and injection site reactions such as swelling, erythema, pain and pruritus. **Chronic Spontaneous Urticaria (CSU):** Common or very common (≥1/100 to <1/10, ≥1/10) include nasopharyngitis, sinusitis, viral upper respiratory tract infection, headache, arthralgia, general disorders and administration site conditions. **IDENTIFICATION:** Glass vial containing a white to off-white cake (powder) for solution for injection after reconstitution with 2.0 ml water for injection. The reconstituted solution is a colourless to pale brownish- yellow solution. **REGISTRATION NUMBER** XOLAIR 150 mg: A39/34/0311.

13100

NOVARTIS

For full prescribing information, please refer to the package insert approved by the Medicines Regulatory Authority.
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Xolair® omalizumab

4. Airflow limitation: after appropriate bronchodilator withhold FEV_1 <80% predicted (in the face of reduced FEV_1/FVC defined as less than the lower limit of normal).[2]

Prior to an asthmatic patient being regarded as 'severe', several key factors need to be reviewed that may make the patient 'difficult to control asthma' rather than 'severe asthma'. These are outlined in Table I below. Is your diagnosis correct? Are there factors that are making the asthma difficult to control? Either intrinsically such as obesity, heart failure, or are there extrinsic factors such as tobacco smoke exposure, air pollution or allergen exposure? The final aspects requiring review are: What asthma medication is prescribed, what is actually dispensed by the pharmacy and, finally, what and how it is used? The prescription of the 'best biological therapy' is pointless if the inhaler technique does not allow for adequate deposition of the inhaled steroid in the first place.

TABLE I: EVALUATING THE PATIENT WITH POTENTIALLY SEVERE ASTHMA

PRIMARY QUESTIONS	ISSUES TO CONSIDER
Is your diagnosis correct?	Is the history compatible? • Are there elements that you have overlooked? Have you documented reversible obstruction? • Peak flow variability >20% • Lung function FEV_1 change 12% and 200 mL • Methacholine challenge Do you have supportive factors to support the diagnosis? • Immediate family history of asthma/atopy • Personal topy or allergic symptoms • Raised FeNO, Eosinophils, IgE, etc
Are there environmental factors at play?	Cigarette smoking? • Primary • Second hand Air pollution? • Indoor/outdoor – diesel, dust, etc Occupational exposure? • Air pollutants • Chemical or allergens (flour, isocyanates etc) Allergen exposure? • Dust mites, cats, cockroaches etc • Fungi and moulds
Are there co-morbid diseases/factors?	Medications? • Aspirin • Non-steroidal anti-inflammatory medications • Beta-blockers Cardiovascular disease? • Valvular heart disease • Heart failure Metabolic disease? • Thyroid • Diabetes
Is the patient using the correct medication?	What have you prescribed? What have they received from the pharmacy? When last did they receive it?
Is the patient using the medication correctly?	What are they using? How often are they using it? How are they using it?

BASIC WORK-UP BEFORE DECIDING ON A BIOLOGICAL THERAPY

Subsequent to the review of the basic asthma diagnosis, medications and adherence to therapy, certain additional tests should be considered in the evaluation prior to biological therapy. Phenotyping is a current 'buzz' word and the approach to, and understanding of phenotypes, and what tests should be performed is continually changing at present. As a starting point, an IgE level, blood eosinophil count and, if available, a sputum smear and cell count (specifically looking or eosinophils), and a fractional exhaled nitric oxide (FeNO) test would be of value. For each of the biological therapies currently on the market or in development, certain cut-offs have been derived to assist in identifying who will benefit. There is no single definition of high or low eosinophils and some may not need an eosinophil count prior to treatment so these additional tests will be reviewed drug by drug. For a drug with a unique target such as Omalizumab, there is a table of doses for corresponding weight and IgE levels. It is therefore not possible to prescribe Omalizumab without knowing that the IgE level is within the prespecified range. Chest X-ray or CT scans could also be considered to rule out allergic bronchopulmonary aspergillosis (ABPA) or bronchiectasis and some of the new drugs in development, have potential impact on TB susceptibility so an interferon gamma-release assay (IGRA) or a tuberculin skin test (TST) might be required.

BIOLOGICAL THERAPIES FOR SEVERE ASTHMA

Table II below outlines the major biological therapies on the market and those nearing approval internationally. Others are also in early stages of clinical development, but this table includes those 'likely' to be seen on the local market. It is worth noting at this point in 2018 that Omulizumab (Xolair) is the only biological therapy for asthma on the market in South Africa. The

TABLE II: CURRENT MONOCLONAL ANTIBODIES FOR ASTHMA IN ADVANCED STAGE OF DEVELOPMENT

GROUPING	DRUG	COMPANY	TARGET/MECHANISM	PATIENTS & BIOMARKERS
Anti IgE	Omalizumab	Novartis	Free IgE antibody	Severe asthma atopic & serum IgE 30–700 IU/mL
Anti IL-5	Mepolizumab	GSK	IL-5 antibody	Severe asthma raised blood eosinophils >150 cells/µl
	Reslizumab	Cephalon	IL-5 antibody	Severe asthma on ICS+ LABA
	Benralizumab	Astra Zeneca	IL-5Rα (receptor antibody)	High ICS; exacerbations; high blood eosinophils
Anti IL-13/ IL-4	Lebrikizumab	Roche	IL-13	(Recently stopped further development)
	Tralokinumab	Astra Zeneca	IL-13	(Further development currently on hold)
	Dupilumab	Sanofi	IL-4Rα (receptor antibody) also blocks IL-13	Mod-severe asthma with raised blood eosinophils
Anti TSLP	Tezepelumab	Astra Zeneca	TSLP	Mod-severe asthma, 'biomarker independent'

drug was launched internationally more than ten years prior to being marketed in South Africa. This is likely to have been a financial- and market-related decision rather than a lack of need or efficacy. Most reports suggest that less than 5% of asthmatics are truly severe, so the market for these drugs in a country such as South Africa is inevitably small and so we may not see them all available.

ANTI-IgE DRUGS

Omalizumab (Novartis) is registered both in the United States and South Africa as Xolair. It is a monoclonal antibody to circulating IgE. The primary studies were conducted nearly 20 years ago. The primary study was published in 2001 in the *Journal of Allergy and Clinical Immunology* (*JACI*).[3] Participants were required to be on moderate doses of inhaled steroids and have an atopy phenotype with positive skin-prick tests and an IgE level between 30 and 700 IU/mL. This requirement for the IgE level has remained as the drug is dosed at around 0.016 mg/kg IgE. A dosing table is required to ensure that the patient's weight and IgE level are appropriate for the dose to be given – if too overweight or too high IgE levels, the drug cannot be given. Several reviews have summarised the efficacy of Omalizumab in long-term follow-up. The Birmingham Regional Severe Asthma Service (BRSAS) reported an 80% reduction in exacerbations and 76% reduction in oral steroid dose from their registry.[4]

Xolair is currently available in South Africa and is an appropriate (albeit expensive) choice for severe asthmatics who have high IgE levels and fulfil the criteria for the weight-band dosing. The registered indications for Omalizumab are specific to an IgE body-weight chart. In the United Kingdom, for example, you may not prescribe the drug if the patient does not fit this chart, either by being overweight or having an IgE that is too high. Off-label usage is occurring in many settings with weight–IgE-inappropriate dosing. But given the cost of the drug, prescriptions should be as per registered indication only.

ANTI-IL5 DRUGS

There are two types of drug in this group: anti-IL5 antibodies (Mepolizumab and Reslizumab) and anti-IL-5 receptor antibodies (Benralizumab).

Mepolizumab (GSK) was the first registered in 2015 in the United States by the Food and Drug Adminstration (FDA) under the trade name Nucala. It is registered for use in patients over 12 years of age with eosinophilic type asthma. The primary registration study published in the *New England Journal of Medicine* (*NEJM*) in 2014[5] demonstrated a 53% reduction in exacerbations using a subcutaneous injection monthly. Patients were required to have an eosinophil count of at least 150 cells per microlitre and be on high-dose inhaled steroids.

In 2016 Reslizumab (TEVA) was registered in the United States under the trade name CINQAIR. It demonstrated a 42% and 50% reduction in exacerbations in the two parallel studies performed for registration.[6] Participants were required to have an eosinophil count of at least 400 cells per microlitre and be treated with medium to high dose inhaled steroids.

Benralizumab (AstraZeneca) was registered in the United States under the trade name Fasenra in 2017. It is registered for use in patients over 12 years of age with eosinophilic type asthma. This drug binds to the IL-5 receptor and results in removal of all eosinophils in circulation. Multiple registration studies were published in *The Lancet*.[7,8] The SIROCCO study recruited patients with an eosinophil count of more than 300 cells per microlitre and on high dose inhaled steroids. This study showed a 45% reduction in exacerbations using a subcutaneous injection monthly.

ANTI-IL-13/IL4

There are two types of drugs in this group: anti-IL13 antibodies (Lebrikizumab and tralokinumab) and anti-IL4 receptor antibodies (Dupilumab). The early phase II studies of Lebrikizumab and Tralokinumab showed good promise, but, unfortunately, in the phase III studies the results were not sufficiently efficacious for the companies to take these drugs to market.[9] (Lebrikizumab data not published.)

Dupilumab (Sanofi) is registered in the United States under the trade name Dupixent for eczema. It has been submitted for registration for asthma in 2018. This drug is a fully humanised IgG-4 monoclonal antibody that binds to the IL-4α receptor and results in blockage of both IL-13 and IL4. The primary study to support registration was published in the *NEJM* in 2018.[10] The study included patients over the age of 12 years with uncontrolled asthma on medium-to-high dose inhaled steroids. Overall the reduction in exacerbations was 54% but in those with high eosinophil counts it was 63%. A second study recruiting patients with oral steroids demonstrated a similar reduction in exacerbations and the ability to reduce steroid dose.[11]

ANTI-TSLP

Tezepelumab (AstraZeneca) is an anti-thymic stromal lymphopoietin (TSLP), a cytokine that affects lymphocyte maturation via activation of antigen-presenting cells. TSLP expression is high in the airways of asthmatics. The blocking of cytokine regulates type 2 inflammation upstream to where the majority of the newer monoclonal antibodies target. The phase II data published in 2017 showed reductions in annualised exacerbation rates of more than 60% and it was not dependent on eosinophil count.[12]

Several other compounds are under investigation and new molecules and targets are continually being discovered.

In low-resourced settings, the use of biological therapies to treat the most severe patients will be severely restricted given the expected costs of these drugs. In selected patients the results can be dramatic in relation to exacerbations and the reduction in steroid requirements. This, however, does not constitute a cure or currently any option to reduce background medication (except maybe reducing oral corticosteoirds). In future, though, a reduction in overall disease severity may occur, if control can be regained using these drugs and potentially long-term control of the disease requiring less medication. This currently remains a hope more than a reality from the currently published data.

CONCLUSIONS

Biological therapies for asthma provide hope for the most severe patients, although availability and affordability remain questionable. For all patients with severe asthma, the starting point should always be the basic steps described above, before prescribing an expensive medication. Confirming the disease, evaluating adherence and inhaler technique, excluding concomitant disease that may be exacerbating control and ultimately counselling on appropriate self-management and trigger avoidance are the basis for appropriate asthma management even when using expensive drugs such as monoclonal antibodies.

DECLARATION OF CONFLICT OF INTERESTS

David Masuku has no conflicts of interest. Dr Van Zyl-Smit has received honoraria for advisory board participation/academic presentations from: Aspen/GSK, Pfizer, Astra-Zeneca, Novartis, MSD, CIPLA and conducted clinical trials for Novartis, Astra Zeneca, GSK, Takeda, Merck, Almirall, Boehringer Ingelheim, Sanofi, Teva, Pearl, Pfizer, Roche and Genentech.

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Review Article

BIOLOGICS FOR THE MANAGEMENT OF ATOPIC DERMATITIS

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WHAT IS ATOPIC DERMATITIS?

Atopic dermatitis (AD) is a chronic, relapsing, pruritic inflammatory skin disease that clusters in families with atopic diseases. Atopic, or the allergic march, refers to a phenomenon in which AD in children is often followed by asthma and rhinitis, in sequence with an IgE antibody response to environmental antigens.[1,2] The diagnosis of AD is still based mainly on clinical features, because to date there have been no reliable biomarkers to define the disease stage, severity or therapeutic response.

NATURAL HISTORY AND EPIDEMIOLOGY OF AD

The natural history of AD in an individual cannot be predicted. Symptoms can start at any stage, with 60% of cases manifesting in the first year of life.[3] Although still primarily considered a disease of childhood, recent studies indicate that it can be a lifelong disease. AD is becoming increasingly prevalent (15–20% in children and 2–10% in adults) globally and much of this burden has been reported from industrialised countries.[4,5] Although developing countries reportedly have a lower prevalence of AD, time trends data from 1995 and 2002 (ISAAC phase 1 and 3 respectively) show an increasing prevalence of AD along with other atopic disorders.[3,6] In South Africa, the one-year prevalence rate among 13–14-year-old schoolchildren in Cape Town was 8.3%–13.3%, with 2.3% having the disease severely.[7,8] Among 3–11-year-old Xhosa children, the one-year prevalence rate was 1%–2.5% – the prevalence being higher among those who live in urban areas.[9]

The increasing prevalence is attributed to environmental factors, smaller families, increased income, higher levels of education, migration from rural to urban areas, reduced exposure to potential antigens in early life and the increased use of antibiotics.[8] AD persists in >5% of 20-year-olds who had the disease as children. However, a predisposition to contact dermatitis and skin susceptibility to irritants persists lifelong.[10] An estimated 2%–3% of patients with AD have a disease severe enough to require systemic therapy.[11]

PERSONAL AND SOCIETAL IMPACT OF AD

AD can have a profound impact on the patients' and their families' quality of life (QoL). The relentless pruritus gravely disturbs sleep for both the patients and their caregivers, affecting their functionality at school, work and in the social environment.[12] An analysis of the 2013 Global Burden of Disease attributed dermatitis as a skin disease with the highest global burden as measured by the disability adjusted life years.[3,13,14] More studies point to the systemic nature of AD.[15] German National Health Insurance data of beneficiaries <40 years of age (n = 655 815) show an increased risk of incident rheumatoid arthritis and inflammatory bowel disease (IBD) in AD.[16] Other non-atopic co-morbidities that have been reported to have a higher prevalence in AD include neuropsychiatric disorders, atherosclerosis, cardiovascular disease and cerebrovascular accidents.[17–19]

PATHOGENESIS OF AD

AD is a complex multifactorial disease influenced by genetic predisposition, skin-barrier abnormalities, immune dysregulation and environmental factors such as allergens, irritants, microbes, diet, stress and air quality.[20,21] Concordance rates among monozygotic twins with AD is as high as 86 per cent, which supports a strong heritability pattern.[22] Numerous genes have been associated with AD, most notably filaggrin (FLG), claudin-1 (CLDN1) and serine protease inhibitor Kazal-Type 5 (SPINK5) genes. Mutations of these genes are associated with abnormalities of barrier function via abnormalities in cutaneous pH, hydration, tight junction formation, skin-barrier homeostasis, desquamation, lipid-barrier construction and the formation of cornified cell envelopes.[22,23] The expression of CLDN1 on keratinocytes is regulated by interleukin-4 (IL-4) and IL-13, two of the most critical cytokines in AD. Patients with AD have reduced Toll-like receptor (TLR) function. TLR stimulation by microbes or trauma leads to the release of antimicrobial peptides and the strengthening of tight junction to limit penetration of allergens and microbes, functions that are impaired in AD.[22]

Dysregulated immune responses are central to the pathogenesis of AD. The skin in AD has a higher infiltration of T-cells, pro-inflammatory phenotypes of dendritic cells, type-2 innate lymphoid cells, eosinophils, mast cells and pro-inflammatory cytokines.[22,24,25] Immune responses in AD are globally attenuated and differentially polarised, that is, they are indicated by a decrease in T_H1 and an increase in T_H2/T_H17 responses and products.[26] Even non-lesional skin in individuals with AD has

TABLE I: A SUMMARY OF TARGET MOLECULES, ROLE OF THESE MOLECULES IN AD, CURRENT BIOLOGICS AGAINST THESE TARGETS, ROUTE OF ADMINISTRATION AND CURRENT STATUS OF THE BIOLOGIC IN AD.

MAIN TARGET	ROLE IN AD	TARGET MOLECULE	MECHANISM	BIOLOGIC	ROUTE	CURRENT STATUS IN AD	REFS
B cells	Produce IgE under influence of IL-4 and IL-13	CD20 receptor on cell surface	Chimeric mAb that is cytolytic on receptor binding	Rituximab	IVI	Unclear benefits: may work better in combination with omalizumab.	27, 28
IgE	Unclear role in AD but high levels in majority of AD cases	IgE receptor	Humanised mAb against Fc receptor of IgE	Omalizumab	SC	May be effective in a subset of AD cases	29
IL-4	Induction and perpetuation of the TH2 response	IL-4 receptor	Human mAb, competitively blocks IL-4/α and binding of IL-4 and IL-13 preventing activation of the JAK1/STAT6 signalling cascade	Dupilumab	SC	Approved for AD	30
Il-4	Induction and perpetuation of the TH2 response	IL-4α receptor	Mutant recombinant human IL-4 protein that blocked the alpha sub-unit of the IL-4 receptor	Pitrakinra	SC	Terminated	31
IL-1	Initiation and maintenance of Th2 responses	IL-1 receptor	Recombinant IL-1 receptor antagonist	Anakinra	SC	Terminated	75
IL-13	Induces B-cell maturation and differentiation, IgE secretion and eosinophil chemotaxis	IL-13 molecule	Human mAb against Fab fragment of IL-13 preventing docking in IL-13 receptor	Tralokinumab	SC	Phase III	32
IL-13	Induces B-cell maturation and differentiation, IgE secretion and eosinophil chemotaxis	IL-13 molecule	Human mAb against soluble IL-13 preventing IL-13Rα1/ IL-4Rα heterodimerisation and subsequent signalling	Lebrikizumab	SC	Phase IIb	33
IL-5	Drives for eosinophil growth, differentiation and migration	IL-5 receptor	Human mAb against IL-5 receptor alpha subunits on eosinophils	Mepolizumab	SC	Not effective	34
IL-31	Produced by Th2 cells and mast cells, sustains inflammation by inducing cytokines that recruit T cells to inflamed site. Major driver of itch in dorsal-root ganglia	IL-31 receptor	Human mAb against IL-31 receptor A, especially in neurons	Nemolizumab	SC	Phase III	35
IL-12 / IL-23	Activation of Th17 responses especially IL-17	IL-12 and IL-23 molecules	Human mAb against p40 sub-unit of IL-12 and IL-23	Ustekinumab	SC	Not effective	36, 37
IL-17	Produced mainly by Th17 cells under influence of IL-23. High expression in sites of acute AD	IL-17A	Human mAb against IL-17A	Secukinumab	SC	Phase II	38, 39
IL-22	Promotes epidermal hyperplasia and inhibits keratinocyte differentiation, impairing barrier function	IL-22 molecule	Human mAb against IL-22	Fezakinumab	IVI	Phase IIa	40
JAK-STAT	Signalling pathway that activates STAT3. STAT3 is a transcription factor, and also mediates mast-cell degranulation, Th17 differentiation, drives abnormal keratinocyte differentiation and epidermal barrier dysfunction in AD. STAT3 mutations cause hyper-IgE syndrome, which has AD features	JAK-STAT	Variable	Ruxolitinib, Baricitinib Upadacitinib Tofacitinib JTE-052 F-04965842	Oral or topical	Different stages of development	41-44

Abbreviations: AD – atopic dermatitis; SC – subcutaneous; IVI – intravenous

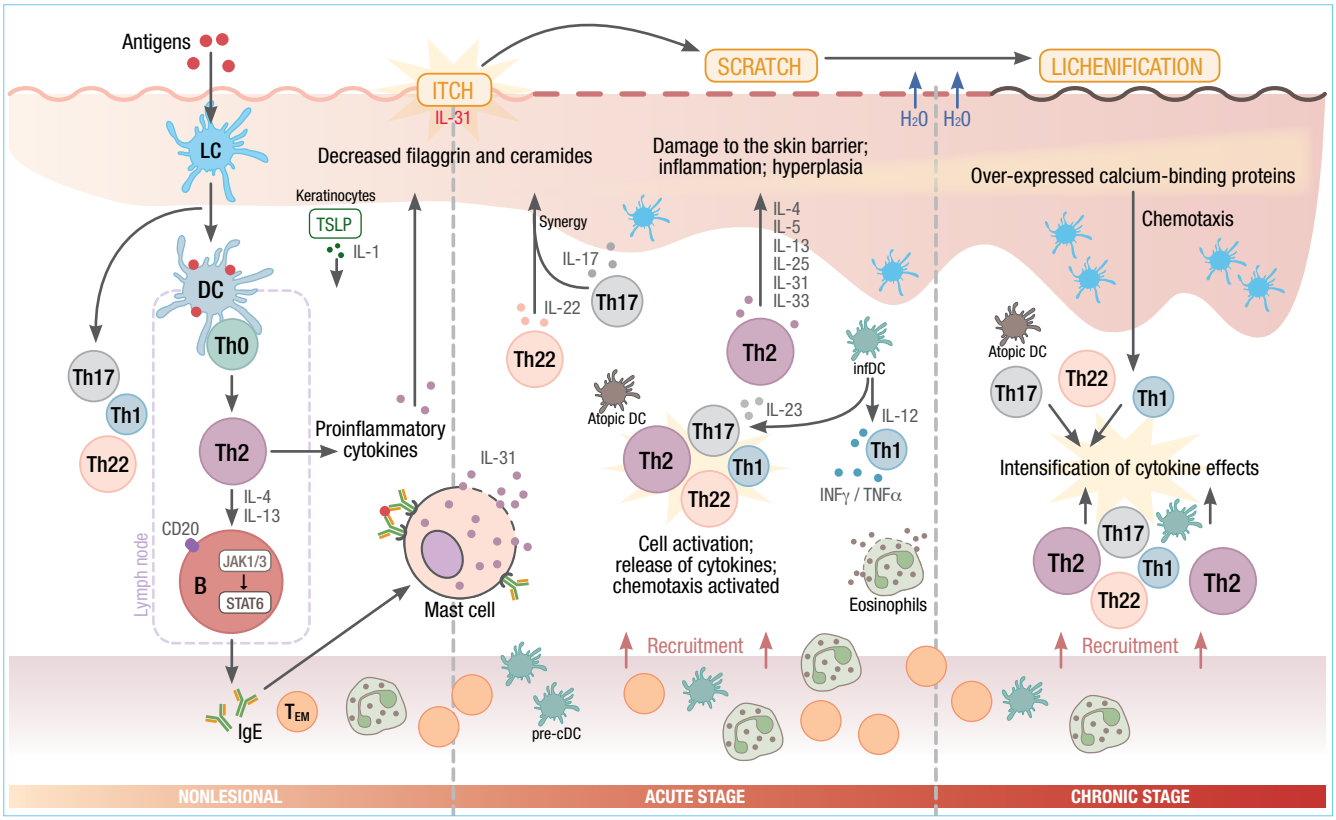

Figure 1: Immunopathologic mechanisms underlying AD

Abbreviations: LC – Langerhans cells; DC – dendritic cells; Th – T-helper cell type; IL – interleukin; JAK – Janus kinase; STAT – signal transducer and activator of transcription; TSLP – thymic stromal lymphopoietin; pre-cDC – precursor dendritic cells; Tem – effector memory T-cell

heightened systemic immune activation.[22] The centrality of T_H2 cytokines (thymic stromal lymphopoietin, IL-4, IL-5, IL-13, IL-25 and IL-33) in both acute and chronic AD, and the roles of T_H22 and T_H17 cytokines (IL-22 and IL-17) are well described.[3,45-50] Other cytokines thought to play a role in AD include IL-23, interferon- γ (IFN-γ) and tumour necrosis factor-α (TFN-α).[50] Any of these cells or cytokines can be a potential therapeutic target. The cytokines thought to play a role in AD are summarised in Table I and Figure 1.

CURRENT MANAGEMENT STRATEGIES FOR AD

Therapy is usually individualised according to the patients' age, severity and extent of AD, as well as the distribution. Treatment is categorised into basic general measures, standard medical treatment and adjuvant treatment, summarised in Table II.[5,51]

The standard medical treatment is either topical or systemic:

- Topical corticosteroids (TCS) are the mainstay of treatment and effective in controling symptoms and signs of AD. The selection of appropriate TCS depends on the patient's age, disease extent and severity, as well as anatomical distribution. Superpotent TCS are most effective for acute flares followed by a weaning regimen to weaker TCS on improvement. Topical calcineurin inhibitors (tacrolimus and pimecrolimus) offer an alternative to TCS. Their potency is equivalent to that of medium-potency TCS. Their main role is that of steroid sparing agents in sensitive areas such as the face and the eyelids, when prolonged therapy is required or as a preventive therapy in patients with frequent flares.[52] However, they are contra-indicated for patients under the age of two.
- Histamine is not the only mediator of AD-associated pruritus; the efficacy of antihistamines in AD is limited. However, sedating older-generation oral antihistamines are useful in preventing scratching at night and in improving sleep. Systemic treatment is reserved for severe recalcitrant cases that fail to respond to either topical or adjuvant therapy. For best results, these are usually combined with topical therapy.[53]
- Systemic corticosteroids are not recommended for treatment of AD; however, in acute cases they may be used for control followed by rapid weaning and replacement with topical treatment or other systemic agents.[4] Systematic corticosteroids can also can be used as co-treatment during the initiation and optimisation of phototherapy, and with other systemic immunosuppressants.
- Cyclosporine, an immunomodulator that inhibits cytokine transcription, is an effective AD treatment for recalcitrant and severe AD in both adults and children. However, hypertension and renal toxicity limit its long-term use and alternatives should be found on discontinuing the drug.[4]
- Azathioprine, alitretinoin (not registered in South Africa), methotrexate and mycophenolate mofetil are other immunosuppressants with established, but limited, efficacy in

TABLE II: STEP-CARE MANAGEMENT OF AD BASED ON SEVERITY (ADAPTED FROM BOGUNIEWICZ ET AL, 2018)[54]

NON-LESIONAL SKIN	MILD	MODERATE	SEVERE
Basic management **Skin care** • Moisturise liberally and frequently • Avoid excessively long and hot baths or showers • Use non-soap cleansers. Avoid washing > once a day • Moisturise after each wash, including normal skin **Trigger avoidance** • Avoid known allergens triggers and common irritants such as soaps, wool and temperature extremes **Consider comorbidities**	**Basic management +** **Antiseptic measures** • Dilute bleach baths <2 × a week, especially with recurrent infections • Systemic antibiotics, if indicated **Specific management** • Apply low- to medium-potency TCS 2 × a day to inflamed skin for 3–7 days beyond clearance • Consider TCI and crisaborole	**Basic management, antiseptic measures +** **Specific management** • Apply medium- to high-potency TCS to inflamed skin 2 × daily for 3–7 days beyond clearance • If not resolved within seven days consider: non-adherence infection, misdiagnosis, contact allergy to medications, and referral **Maintenance TCS** • Apply moderate to potent TCS on inflamed areas of previous or potential symptoms • Low-potency TCS 1–2 × daily (including face) • Medium potency 1–2 × weekly (except face) **OR** **Maintenance TCI** • 1–2 × daily • 2–3 × weekly OR **Crisaborole 2%** 2 × daily	**Basic management, antiseptic measures, topical anti-inflammatories +** **Referral to AD specialist** **Phototherapy** **Wet-wrap therapy** **Systemic immunosuppressants** • Cyclosporine A • Methotrexate • Mycophenolate mofetil • Azathioprine • Corticosteroids for some acute cases to gain control **Short-term hospitalisation** **Dupilumab**

Abbreviations: TCS – topical corticosteroids; TCI – topical calcineurin inhibitors

the treatment AD. They are also limited by their side-effect profiles, which range from hepatotoxicity, bone-marrow suppression to infections.[4]

Apart from systemic corticosteroids, none of the systemic immunosuppressants have been approved for the treatment of AD by the FDA.[55] Adjuvant therapies for AD include phototherapy and allergen immunotherapy. The currently recommended step-care management of atopic eczema is summarised in Table II.

Most of the current therapies for AD have been in use for decades and during this period they have all shown limited efficacy. Current therapeutic trends are geared towards understanding AD endophenotypes, personalised treatment approaches and targeting cytokines that mediate AD.[20] These approaches have spawned a new group of drugs commonly referred to as 'biologics'.

INDICATIONS FOR USE OF BIOLOGICS IN AD

There are currently no universally accepted guidelines for who should receive biologics. Indeed, their use and indication depend on the cost of the drug, the disease being treated, the country and the influence of healthcare funders. Limited data specific to AD are available, owing to the relative infancy of biologic use in AD exist, with one drug only currently approved by the US Food and Drug Administration (FDA). In general, biologics are indicated for moderate-to-severe disease that has failed to respond adequately to standard therapy. However, severity-based scoring systems alone should not determine the need for biologics – a holistic assessment is needed. Other points to consider before prescribing biologics include the certainty of diagnosis, co-morbidities and side-effects.

BIOLOGICS APPROVED FOR USE IN AD

Dupilumab is a fully human monoclonal antibody directed against the alpha sub-unit of the IL-4 receptor. The drug inhibits both IL-4 and IL-13 pathways as this sub-unit is shared between both receptors. A systemic review and meta-analysis found four double-blind, randomised-controlled trials (RCT) of dupilumab alone or associated with topical corticosteroids were assessing dupilumab for efficacy and safety. In this trial, dupilumab was found to induce rapid and dose-dependent improvements in the Eczema Area and Severity Index (EASI) score, the investigator's global assessment score, and in pruritus. At a dose of 300 mg there was an incremental improvement after 12 weeks of continuous treatment. At least 50% improvement of the scores was achieved in the 85% of patients. A significant reduction was seen in the pruritus scores. When dupilumab was used in combination with topical steroids for four weeks, 100% of patients reached these targets.[56] Adverse events associated with dupilumab include injection-site reactions, conjunctivitis, headache, nasopharyngitis, alopecia areata and erythrodermic psoriasis. Conjunctivitis that was severe enough to warrant the interruption of dupilumab has been reported.[43,57,58]

BIOLOGICS WITH PROMISING UTILITY IN AD BUT NOT APPROVED

Nemolizumab is a humanised antibody against IL-31 receptor A. IL-31 is a cytokine that is produced mainly by Th2 cells and it has an increased expression in acute and chronic lesions of AD.[59,60] It has been shown to play a role in the pathogenesis of AD, particularly pruritus.[61,62] In a phase 2, double-blind, placebo-controlled 12-week RCT, 264 adults with moderate to severe AD were assigned 1 : 1 : 1 : 1 : 1 to three different, four-weekly dosing schedules of nemolizumab, one eight-weekly dose and a placebo. The primary efficacy endpoint was the percentage improvement between baseline and week 12 in the score on the pruritus visual-analogue scale. In total, 216 completed the study and a significant reduction in pruritus occurred in all those who were on the four-weekly dosing schedule. There was also an improvement in the dermatitis and sleep measures versus the placebo.[35]

In a 52-week, double-blind extension of the same study, 191/216 continued with their original randomisation schedule and 131 completed the entire 64 weeks. The improvement was maintained or progressively increased with long-term treatment for the 64 weeks. During the extension, the use of topical corticosteroids was permitted and there was a trend towards a lower duration and cumulative dose of concomitant TCS in those receiving higher doses of nemolizumab.

Overall, nemolizumab was well tolerated over the 64 weeks.[63] the exacerbation of AD, nasopharyngitis, upper respiratory-tract infection, peripheral oedema and increased creatine kinase levels were the most common adverse events associated with nemolizumab.[35]

Tralokinumab is a fully human monoclonal antibody against IL-13. IL-13 levels are not only increased in the lesional and non-lesional skin of AD patients, they are proportional to disease severity and response to treatment. In a phase 2, double-blind, placebo-controlled 12-week RCT, 204 adults with moderate to severe AD were assigned 1 : 1 : 1 : 1 to receive 45, 150 or 300 mg of subcutaneous tralokinumab or a placebo every two weeks for 12 weeks with concomitant topical glucocorticoids. Co-primary efficacy endpoints were the change in EASI score from baseline to week 12 and the percentage of participants achieving an Investigator's Global Assessment response of 0 (clear) or 1 (almost clear), with a reduction of two grades or more from baseline to week 12. An exploratory analysis for biomarkers of IL-13 activity was performed on the responders. An early (week 4) and sustained response was seen with a 300 mg dose and patients with higher IL-13 activity were the best responders. Tralokinumab had an acceptable safety and tolerability profile similar to those of the previous studies.[32] The most frequent are injection-site reactions, exacerbation of asthma, headache, nasopharyngitis, diarrhoea and urinary tract infections (UTIs).[64]

Lebrikizumab is an anti-IL-13 monoclonal antibody. Recently, a proof-of-concept phase 2 RCT that enrolled 209 patients with moderate to severe AD was published. The patients were randomised 1 : 1 : 1 : 1 to receive lebrikizumab 125 mg single dose, lebrikizumab 250 mg single dose, lebrikizumab 125 mg every four weeks for 12 weeks, or a placebo every four weeks for 12 weeks, after a protocol-mandated, two-week, medium-potency topical corticosteroid run-in. A statistically significant greater proportion of patients in the lebrikizumab 125 mg every four weeks group achieved the primary endpoint of an EASI-50 response compared to the placebo grade. The lower doses of lebrikizumab showed a trend towards an improvement, suggesting a dose–response relationship. The limitations of the study were the protocol-mandated use of topical steroids twice a day for two weeks and the short duration.[33] The only adverse events associated with lebrikizumab not seen in the placebo group are musculoskeletal. These include arthralgia, body pain, myalgia and arthritis.[64]

Fezakinumab is a human monoclonal antibody against IL-22. IL-22 plays a role in the epidermal barrier dysfunction associated with AD, and also seems to be responsible for the characteristic epidermal hyperplasia of AD.[43] A phase 2a RCT of 60 cases with moderate to severe AD, 40 of whom received intravenous fezakinumab as monotherapy every two weeks for ten weeks and 20 of whom received a placebo, has recently been reported. There was a significantly higher improvement in the fezakinumab group that was progressive beyond the last dosing (ten weeks) until end of the study at 20 weeks and was well tolerated.[40] The only reported adverse events with fezakinumab that vary significantly from those in placebo groups are upper respiratory-tract infections.[40]

Rituximab is a monoclonal antibody against CD20, a protein found primarily on the surface of B-lymphocytes and inducing their lysis and subsequent B-depletion. This has an inhibitory effect on antibody production, T-cell- dependent B-cell activation and antigen presentation.[43] A small open-label study of six patients using two doses of 1 000 mg by intravenous infusion for two weeks showed significant improvement. This was associated with a reduction in the number of B-lymphocytes in both lesional and non-lesional skin as well as IL-5, IL-1 and total serum IgE levels.[27] However, two other patients treated with a 500 mg intravenous infusion over two weeks actually worsened on rituximab.[28] Another, more recent, series of treatment of three consecutive patients with AD who were treated with rituximab failed to show an improvement.[65] Promising results have been seen when combining rituximab with omalizumab, a monoclonal antibody against IgE, in six patients with AD.[66] Current data are insufficient to reach definite conclusions and larger studies are therefore necessary to determine the efficacy and optimal dosing of rituximab in AD. Adverse events with the use of rituximab include infusion reactions, progressive hypogammaglobulinemia, thrombocytopenia, non-infectious interstitial lung disease, psoriasis, cutaneous vasculitis, Stevens–Johnson syndrome and liver failure in patients with hepatitis-B virus infection.[64]

Omalizumab is a recombinant, humanised monoclonal antibody against the high-affinity Fc receptor of human IgE. The drug is

FDA approved for chronic spontaneous urticaria and has proved to be very effective.[67] The use of omalizumab in AD has yielded mixed results. A recent systematic review found that fewer than half of the patients treated with omalizumab achieved significant clinical improvement.[68] However, there seems to be a subset of AD cases that is responsive to the drug, including those with the wild-type FLG gene and low serum IgE levels.[55,68-70] If this proves to be true on further investigation, it would improve patient selection and the overall efficacy of the drug. Omalizumab is safe and well tolerated. Adverse events are usually mild and include injection-site reaction, headache and pharyngitis. Anaphylaxis is a rare association.[64]

Janus kinase (JAK) inhibitors block IL-4 signalling through the JAK 1/3-STAT6 pathway. The pathway moderates inflammation and the activation of STAT3, which is responsible for the abnormal keratinocyte differentiation and epidermal-barrier dysfunction seen in AD. Baricitinib, upadacitinib and F-04965842 are systemic JAK inhibitors that have shown promising results in treating AD and they are currently in phase 2 clinical trials. Another JAK inhibitor, itacitinib, is on trial for pruritus.[43,44]

Tezepelumab is a novel human monoclonal antibody that prevents the interaction of thymic stromal lymphopoietin (TSLP) with its receptor. TSLP is a cytokine that is secreted by keratinocytes and is thought to play an important role in the pathogenesis of AD. It is highly expressed in acute and chronic lesions of AD and promotes the activation of myeloid dendritic cells; it favours lymphocyte activation and a Th2-polarised response with the consequent release of pro-inflammatory cytokines. The results from a phase 1 trial of tezepelumab in patients are pending.[43]

BIOLOGICS TRIALLED FOR AD FOUND NOT BE EFFICACIOUS

TNF-α blockers, *infliximab*, a chimeric monoclonal TNF-α antibody, and *etanercept*, a human-recombinant fusion protein that blocks the TNF-α receptor, have been evaluated for treatment of AD in both children and adults have shown limited efficacy. Their use is also associated with an increased frequency of infections and a rapid loss of efficacy.[71-73] Another deterrent to the use of TNF-α blockers is the development of AD in patients with psoriasis who are treated with the drugs.[74-76]

Mepolizumab is a monoclonal antibody against IL-5, a cytokine that drives eosinophil growth, differentiation and migration. Considering the frequently elevated eosinophil levels in AD and its significant glucocorticoid-sparing effect in patients with severe eosinophilic asthma, mepolizumab has been trialled in the management of AD.[77,78] Despite effecting a reduction in blood and tissue eosinophils, the clinical improvement of AD was not achieved in small randomised-controlled trials of short duration.[34]

Ustekinumab is a fully human monoclonal antibody that binds to the shared p40 sub-unit of IL-12 and IL-23 to inhibit the differentiation and clonal expansion of naive cells into Th1 or Th17 responses respectively. IL-17, a Th17 cytokine, is highly expressed in both the lesional skin and the circulation of patients with AD and it is thought to play a role in the pathogenesis of the disease.[79] Two well-designed randomised-controlled trials have shown the drug to be ineffective in treating AD.[36,37,80]

Anakinra is a recombinant human-receptor antagonist against interleukin IL-1, a pro-inflammatory cytokine that plays a role in the initiation and maintenance of Th2 response. A study evaluating the efficacy of anakinra in AD was terminated for unknown reasons.[81]

BIOLOGICS TRIALLED FOR AD BUT SINCE WITHDRAWN FROM THE MARKET

Efalizumab was a humanised monoclonal antibody that prevented lymphocyte function-associated antigen 1 from binding to ICAM-1 on endothelial and antigen-presenting cells. This reduced T-lymphocyte recruitment and activation at sites of inflammation. Its use in AD produced conflicting results before the drug was withdrawn after being associated with progressive multifocal leukoencephalopathy.[43]

Alefacept was a human-dimeric fusion protein that blocked the interaction of lymphocyte function-associated antigen 3 and CD2, expressed on antigen-presenting cells and T-lymphocytes respectively. This interaction provided co-stimulatory signals for the activation of T-lymphocytes. The drug showed promising results before it was withdrawn owing to a lack of demand.[43,64]

Pitrakinra was a recombinant human IL-4 protein that blocked the alpha sub-unit of the IL-4 receptor, inhibiting the downstream signalling pathways of IL-4 and IL-13. The trial to assess its efficacy in AD was not published after clinical development of the drug was terminated.[31,82]

USE OF BIOLOGICS IN COMBINATION WITH OTHER BIOLOGICS OR TRADITIONAL THERAPIES

Limited data exist on the use of a combination of two or more biologics in general, not only in AD. Biologics are highly selective and as used in other diseases they seem to demonstrate the required efficacy to be administered as monotherapy. In other diseases, the rationale for combination therapy with other drugs includes:

- the prevention of antibody formation to the biologic;
- an inadequate response to the biologic;
- efficacy synergies for a more complete response;
- a quicker response, and
- a broader response to treatment including extra-cutaneous complications such as cardiovascular disease that may not be targeted by the highly selective biologic.[83,84]

USE OF BIOLOGICS IN PREGNANCY AND LACTATION

The largest repository on the use of biologics in pregnancy and lactation involves TNF-α blockers. There are no controlled studies and the total number of pregnant or lactating women exposed to biologics is still too small to make definitive conclusions on their safety profile in these situations. This is further complicated by use of multiple drugs in most patients included in current reports

of biologics in pregnancy and breastfeeding. Currently, it seems that the benefits of TNF-α blockers to the foetus and to breastfed children outweigh the risks. This cannot be generalised to other biologics, however.[85,86]

USE OF BIOLOGICS IN CHILDREN

The safety and efficacy of biologics in children with AD, the most commonly affected population, is not clear, since almost all the published studies excluded patients under the age of 18. Currently, no biologics are approved for use in children with AD. Following the success of dupilumab in adult patients with severe AD, a number of clinical trials on children with AD are in progress. These include an open-label study (R668-AD-1434); a double-blind, placebo-controlled RCT investigating the efficacy and safety of dupilumab administered concomitantly with TCS in patients over six years but younger than 12 years of age with severe AD (R668-AD-1652), and phase 2 and 3 studies. These last two studies are investigating the pharmacokinetics, safety and efficacy of dupilumab in patients aged between six months and six years with severe AD (R668-AD-1539 and 0456-0107, respectively). Preliminary data from these studies suggest outcomes that are even better than those observed in adults (personal communication).

Omalizumab has been approved for asthma in children <12 years of age. There is an ongoing trial of omalizumab for severe childhood eczema.[87] Etanercept, adalimumab, abatacept and tocilizumab all have no significant role in AD but have been approved for use in juvenile arthritis. Concerns over their use in children are controversial, reported adverse events including malignancies, infections and autoimmune diseases.[88] The available data are mainly derived from case reports.

NEUTRALISING ANTIBODIES AGAINST BIOLOGICS

The formation of antibodies against monoclonal antibodies has a significant impact on their efficacy. This has been linked to a reduction in serum levels of the drug and an increase in antibody clearance correlating to a reduced clinical response.[89] Infliximab and adalimumab are known to be associated with anti-drug-neutralising antibodies that decrease their efficacy.[90] Non-neutralising antibodies against nemolizumab have been reported.[35]

LIMITATIONS OF THE USE OF BIOLOGICS IN AD

The use of biologics in AD is still in its infancy and data on their efficacy, patient selection, interchangeability with biosimilars and other molecules with similar targets, and unknown long-term risk are limited at this stage. Most data are derived from rheumatology. A major challenge is the cost of the drugs, being out of reach of most people, particularly those in developing countries.[91]

FUTURE DIRECTIONS

It is becoming increasingly clear that AD is just one disease of many for which biologics may be an appropriate intervention. The differing responses to biologics point towards differences in disease pathogenesis. Current and future studies need to focus on delineating AD phenotypes based on variables such as age of onset, ethnicity, severity, biomarkers and genetics. Pharmacogenomics will further the determine response to specific drugs.[11-75]

The next generation of biologicals is small proteins that may either:

- have an antibody or novel binding domains;
- have diverse specificity;
- be able to be engineered to bind more than one target;
- be able to be produced in bacteria at a lower cost;
- be relatively stable, or
- because of their small size, be able to penetrate diseased tissues more effectively than antibodies.[92]

Oral JAK kinase inhibitors fall into this category.

CONCLUSIONS

The use of biologics in the treatment of AD is still in its infancy, but promising new and repurposed drugs are in the pipeline.

DECLARATION OF CONFLICT OF INTEREST
The authors declare not conflict of interest.

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Review Article

CHRONIC SPONTANEOUS URTICARIA IN THE ERA OF BIOLOGIC THERAPY: A NEW HOPE

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ABSTRACT
Chronic spontaneous urticaria (CSU) is a morbid condition associated with spontaneous urticaria, angioedema, or both for at least six weeks. CSU may persist for years, and until recently, the lack of effective disease-modifying therapies has been a disapointment for both patient and physician alike. A new hope has been provided with the registration of omalizumab – a targeted anti-IgE therapy which can be effective in up to 80% of CSU patients not adequately controlled with high-dose antihistamine therapy. Access to omalizumab remains an obstacle; however, its increasing use as standard-of-care in the public sector is encouraging. It is heartening that an improved understanding of the heterogeneous pathogenesis of CSU means there is a growing pipeline of new therapies, including biologics, under investigation. This article outlines novel therapies, either already registered or under investigation for CSU, with detailed discussion of omalizumab use – at present the only registered biologic available in South Africa.

BACKGROUND

Urticaria is an oedema involving the superficial portion of the dermis only – appearing as well-circumscribed wheals with raised erythematous serpiginous borders and blanched centres that sometimes coalesce to form large to giant wheals. Angioedema, on the other hand, is a well-circumscribed area of oedema involving deeper layers of the skin and the subcutaneous tissue. Urticaria and angioedema can appear either together or separately.[1]

Clinically, the temporal classification includes acute urticaria (less than six weeks) – usually a result of a specific triggering allergen or infection; and chronic urticaria (persists for more than six weeks) – where the likelihood of identifying specific offending triggers is significantly lower. Chronic urticarias are spontaneous, inducible or both. Chronic inducible urticarias (CIndU) can be secondary to friction (dermographism), deep pressure, cholinergic stimuli, for example exercise, temperature (cold or hot), water and sun.[2]

Chronic spontaneous urticaria (CSU), also known as chronic idiopathic or autoimmune urticaria, is characterised by urticarial lesions, with or without associated angioedema for an overall period of more than six weeks. No identifiable trigger is found and symptoms are present most days of the week.[3] In this brief article we will outline novel CSU therapies, either already registered or under investigation, presented in the context of the developing understanding of pathogenesis. A more detailed discussion of anti-IgE therapy with omalizumab is provided, as at present it is the only registered biologic available for CSU treatment in South Africa.

CURRENT UNDERSTANDING OF PATHOPHYSIOLOGY

A complete pathophysiological picture of CSU remains elusive. Figure 1 provides an overview of the current major pathological drivers of a likely heterogeneous disease. The final common pathway driving the leakage of fluid into the cutaneous tissues involves a combination of site-of-disease mast-cell, basophil and eosinophil activation, either through IgE or IgG autoantibodies. IgG autoantibodies against the FCεR1 and IgE have been long established in patients with CSU (type II hypersensitivity/autoimmunity), whereas IgE autoantibodies (type 1 hypersensitivity/autoallergy) against >200 cutaneous autoantigens has recently been demonstrated.[4]

The presence of autoantibodies suggests roles for T- and B-lymphocytes, as well as plasma cells in the immune pathogenesis. Other lines of evidence indicate the contributory roles of the extrinsic coagulation cascade and systemic inflammation.[5] D-dimer has been proposed as a biomarker for CSU; increased d-dimer levels indicate turnover in the coagulation cascade. The extrinsic coagulation system is activated by increased expression of tissue factor on both activated site-of-disease eosinophils, and local endothelium with coagulation components having downstream effects through their protease-activated receptors (PARs) (see Figure 1).[6]

In fact, warfarin therapy has even been studied as a therapy for CSU.[7] Non-specific systemic inflammation has been identified as a driver of CSU; for instance, both infection with *helicobacter pylori*[8] and the metabolic syndrome have been associated with CSU and disease severity.[5] A more detailed discussion of the

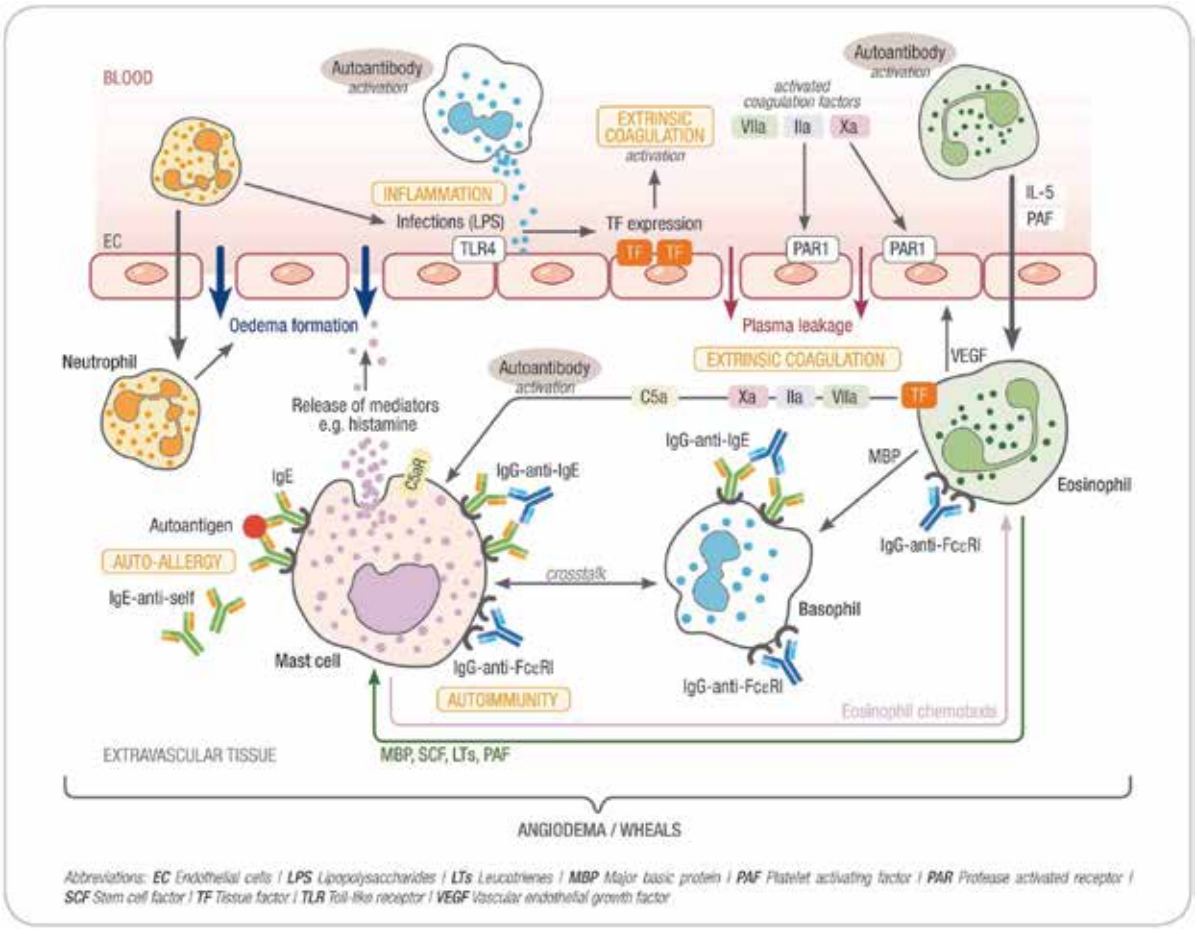

Figure 1: Intersecting components underlying CSU pathophysiology

Mast cells, basophil and eosinophils are the effector immune cells involved in CSU pathology. Current understanding groups four major upstream contributors to mast-cell degranulation, basopenia and eosinophilic activation. These are: i) auto-allergy – IgE antibodies directed against cutaneous autoantigens (>200), such as IL-24 (Schmetzer et al 2017); ii) auto-immunity – IgG antibodies directed against IgE and FCεR1; iii) inflammation – elevated cytokines, eg IL-6 & TNF-α or inflammatory molecules, eg lipocalin-1 are produced in response to either metabolic or infective stimuli and lead to endothelial activation and signalling through innate pattern recognition receptors, eg TLR4; iv) coagulation – activation of the extrinsic coagulation cascade predominantly via increased TF expression on activated eosinophils with downstream signalling through protease-activated receptors (PARs). These mechanisms are suggested to work synergistically to differing extents in individuals.

aetiopathogenesis of CSU is beyond the scope of this article and readers are referred to other recent focused reviews by Kolkhir et al in 2016 and Asero et al in 2017. Undoubtedly, increasing insights into the multiple activated cells and pathways continue to open up novel therapeutic targets.[9]

EXISTING THERAPIES AND CURRENT RECOMMENDATIONS

All registered non-sedating antihistamines are first-line treatment for urticaria. The second line is high-dose antihistamine therapy: up to 4 × normal daily dosing. Safety and efficacy studies of high-dose antihistamine therapy are available for Cetirizine, Levocetirizine, Loratidine, Desloratidine, Fexofenadine, Rupatadine and Bilastine, with use for prolonged periods.[7] Up- and down-titrating, as well as split- and single-dosing strategies are driven by provider preference in the absence of a solid evidence base justifying a particular approach.

The *European Academy of Allergy and Clinical Immunology* (EAACI) 2018 guideline lists omalizumab as the only evidence-based, third-line therapy and the fourth line is Cyclosporine A (an immunosuppressant) at a recommended dose of six months at a 1.5–2 mg/kg dosing, but risk–benefits require consideration given the many adverse effects (strong recommendation/high level of evidence).[7]

A number of other therapies are used in difference healthcare settings, but all have low level of evidence and hence weak recommendations in the guideline, including:

- Leucotriene receptor antagonists (eg Montelukast);
- H_2-antihistamines (eg Cimetidine), and
- pseudoallergen-free diets.

Short-course corticosteroids are also used widely for acute exacerbations (weak recommendation/low level of evidence); but long-term therapy is contraindicated due to adverse effects (strong recommendation/high level of evidence).[7]

The evidence is too low for current EAACI guidelines to make favourable recommendations concerning multiple other

agents which have been attempted for the treatment of CSU, including: Dapsone, sulfasalazine, methotrexate, interferon, plasmapheresis, high-dose immunoglobulins, tranexamic acid, anti-TNF-α agents and phototherapy. However, in some of these responses to therapy have been promising.[7]

BIOLOGIC THERAPY FOR CSU

There are a number of novel biologic-based approaches to the treatment of CSU; these include:

- registered biologic therapy (eg Omalizumab);
- off-licence exploratory use of available biologics targeting applicable pathways (eg Canakinumab (IL-1 blockade));
- clinical trials of new targeted biologic and small-molecule drugs (eg Ligelizumab (anti-IgE)) or DP2 (CRTH2) receptor blockers (eg Fevipiprant).

A list of current and possible biologic therapies and their targeted pathway is provided in Table I.

Some other interesting therapeutic targets are also under evaluation for novel drug approaches. Substance P (SP), a neuropeptide that binds mainly to neurokinin receptor 1 (NKR1), is a mast-cell degranulator associated with itch and wheal formation. Recent case series show SP antagonists to have significant anti-pruritic effect in acute and chronic pruritus. DARPins (designed ankyrin repeat protein) are small oligonucleotides that exhibit highly specific and high-affinity target-protein binding; an IgE-specific DARPin has been reported to bind IgE and suppress mast-cell activation. Further details on these novel therapeutic approaches are available in an excellent recent review by Kocaturk and Zuberbier in 2018. The remainder of this article focuses on the use of omaluzimab, the only biologic registered for use in CSU in South Africa.

THE WHEN, HOW MUCH AND HOW LONG OF OMALIZUMAB

Omaluzimab is a recombinant humanised anti-IgE monoclonal antibody licensed to Novartis, and registered in 2015 for use by South African CSU patients. Omalizumab targets the C3 domain of the Fc region of IgE, reducing levels of free IgE by sequestration. Postulated mechanisms include:

- raising degranulation thresholds of mast cells and basophils;
- reducing pro-inflammatory mediator release and cell recruitment (eg eosinophils), and
- reducing free IgE.

See Chang et al for a detailed report on the proposed mechanisms of action.[10]

The evidence base for the use of omalizumab in patients with antihistamine refractory CSU is high quality, with a series of randomised, placebo-controlled, multicentre studies including the proof-of-concept study X-CUSITE, a phase II study MYSTIQUE, and then three pivotal phase III studies ASTERIA I, ASTERIA II and GLACIAL.[11] In all studies, omalizumab provided rapid and sustained improvement in symptoms of CSU. The studies met all primary and secondary efficacy end points at week 12 and exploratory efficacy end points at week 24 in ASTERIA I and GLACIAL (300 mg dose only) – end points included itch severity score, urticaria activity score 7 (UAS7) and the dermatology life quality index.

Three doses (75 mg, 150 mg and 300 mg) administered subcutaneously every four weeks were studied, with only the 300 mg dose meeting all efficacy end points across all the studies. Notably, only the GLACIAL study enrolled patients with CSU refractory to high-dose antihistamines and adjunctive

TABLE I: BIOLOGIC THERAPIES FOR CSU

DRUG	TYPE OF DRUG	PATHWAY TARGET
REGISTERED IN SOUTH AFRICA FOR CSU		
Omaluzimab	Humanised anti-IgE	Suppression of free IgE, preventing basophil degranulation
ACTIVE IN CLINICAL TRIALS FOR CSU/CINDU		
Ligelizumab	Humanised anti-IgE (binds Cε3 domain of IgE)	Suppression of free IgE, preventing degranulation of basophils
Quilizumab	Humanised anti-IgE (binds M1 prime segment of membrane expressed IgE on IgE-switched B cells/ plasmablasts)	Suppression of free IgE, preventing degranulation of basophils
Canakinumab (or Rilonacept)	Humanised anti-IL1	Suppression of Interleukin 1 beta, preventing innate inflammation
FUTURE BIOLOGICS TO CONSIDER IN CSU		
Rituximab	Chimeric Anti-CD20	Antibody producing memory B-lymphocytes depletion
Adalimumab (or Infliximab or Etanercept)	Anti-TNF alpha	Suppression of TNF alpha, preventing inflammation
Eculizumab	Humanised anti-C5 inhibitor	Suppression of complement, preventing inflammation
Natalizumab (or vedolizumab)	Adhesion molecule inhibitor (alpha-4 integrin)	Inhibits cellular adhesion molecules, preventing a sustained late phase of CSU.
Benralizumab (or Mepolizumab, Reslizumab)	Anti-IL-5	Inhibits eosinophil activation and downstream inflammation
Dupilumab	Anti-IL-4	Reduction of IgE production

Abbreviations: *IgE – Immunoglobulin E; CD20 – Cluster Differentiation 20; IL – Interleukin; TNF alpha – Tumor Necrosis Factor alpha; CSU – Chronic spontaneous urticaria; SA – South Africa; HUS – Hemolytic uremic syndrome; PNH – paroxysmal nocturnal hemoglobinuria; CIndU – Chronic inducible urticaria.*

therapies, for example H2-antagonists and LRTA, thus more closely resembling difficult-to-control patients in clinical practice.[11] Omalizumab is safe; across allergic asthma and CSU programmes there are an estimated 5 890 patient treatment years with very few adverse effects. Common minor side-effects include headache, arthralgia, injection-site reactions and upper respiratory-tract infections.[11] It is important to note that the safety profile is better than the only other guideline recommended for step 3 treatment – cyclosporine A. Real-life efficacy studies suggest that omalizumab is effective in between 60–80% of CSU patients. Studies are ongoing for CIndU and other unusual conditions such as urticarial vasculitis.[11]

Considerable interest is now focused on early identification of biomarkers that predict responses to omalizumab; as well as variables to predict relapse following discontinuation of omalizumab after 24 weeks. Regression models applied to the three phase III RCTs indicate that higher baseline disease severity (as measured by UAS7) and slower response to therapy (low UAS7 area above the curve, AAC determined by plotting the UAS7 scores across time-points) predicted relapse.[12] Promising proposed biomarkers of poor treatment response include:

- low pre-treatment levels of FCεR1 expression on basophils;[13]
- lower d-dimer levels,[14] and
- lower pre-treatment total IgE, and perhaps more importantly limited increase in total IgE at week four after treatment initiation.[15]

Easily accessible biomarkers are urgently required to predict treatment response to anti-IgE therapy.

PRESCRIBING IN THE SOUTH AFRICAN CONTEXT

Omalizumab is registered and available to patients at a monthly cost for 300 mg of ~R10 000. CSU is, unfortunately, not a prescribed minimum benefit condition meaning that with such a high price tag, many medical schemes continue to decline funding motivations. Fortunately, certain schemes have put in place funding policies of omalizumab in CSU that include:

- refractory to second-line guideline therapy (high-dose antihistamines);
- UAS7≥16, and
- dermatology quality of life (QoL) index score ≥11.

In addition, specialist allergy centres have successfully motivated in the public sector for omalizumab on a named patient basis indicating that this is guideline-driven standard of care for CSU patients.

Patient advocacy around the severe morbidity of CSU, continued efforts for price reductions from Novartis, and ongoing motivation by allergy specialist and centres of excellence to individual schemes is required to ensure that our CSU patients are able to access this and other future targeted therapies. Finally, three centres in South Africa have been identified as clinical trial sites for the next generation anti-IgE therapy – Ligelizumab (see Table I), and this remains a method for severe patients to access biologic treatments.

CONCLUSION

An estimated one in five people will experience urticaria in their lifetime; it is a debilitating symptom. CSU carries serious morbidity, impact on QoL and indirect costs. The condition has a complex aetiopathogenesis that we are slowly unravelling; and our improved understanding together with an exploding array of immune-targeting biologics heralds a new hope for diverse treatments. A robust evidence base supports the efficacy and safety of omalizumab and it is being accessed for CSU patients in South Africa. Allergy and dermatology specialists should be encouraged and feel comfortable to prescribe omalizumab, especially given the support available for its use. However, ongoing efforts are required to raise CSU-awareness, and continue to encourage lower prices and wider access through private and public health funders.

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DECLARATION OF CONFLICT OF INTERESTS

The authors declare no conflict of interests.

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Case Report

TREATMENT OF URTICARIAL VASCULITIS WITH OMALIZUMAB

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CASE REPORT

A 45-year-old woman with an eight-year history of chronic urticaria was reviewed in our multidisciplinary allergy and dermatology clinic for worsening symptomatology. The evolution of her chronic urticaria included: initial typical urticarial plaques on trunk and limbs (lasting less than 48 hours) with intermittent angioedema of her lips. She experienced flaring of urticaria prior to menstruation; flare-up after a trial of medroxyprogesterone acetate for worsening menorrhagia; progressively increasing size and duration (up to 96 hours) of the urticarial plaques with associated blistering; and resolution with post-inflammatory hyperpigmentation (see Figures 1–3).

She had no known co-morbid medical conditions, and a three-pack-year smoking history. Family history included breast cancer in both grandmothers. Relevant gynaecological history included two normal pregnancies, a tubal ligation after the second pregnancy and menorrhagia ten years after the last pregnancy.

On examination she was overweight with a body mass index (BMI) of 44. She had tender, large indurated erythematous plaques with areas of coalescing blisters. The largest plaque was over the upper back with smaller ones scattered on the upper body and to a lesser extent lower limbs (see Figures 1 and 2). The plaques were noted to resolve with post-inflammatory hyperpigmentation (see Figure 3). Laboratory results included a normal full blood count, liver profile, C3 and C4 complement levels and appropriate follicle-stimulating, luteinising and oestrogen hormone levels. An autoimmune screen was negative.

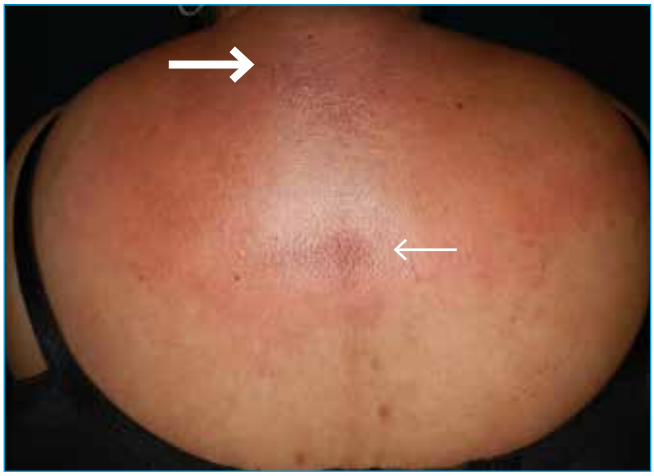

Figure 1: Large urticarial plaque on the mid back with peau d'orange (small arrow) and vesicles (large arrow) on the upper back.

We considered progesterone-associated urticaria, due to the history of worsening symptoms with menstruation and flaring

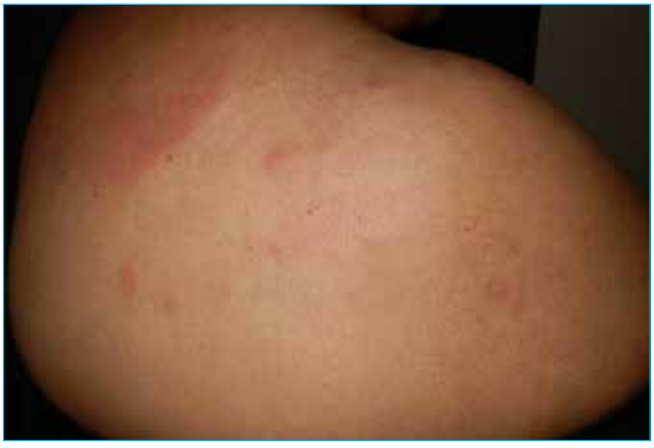

Figure 2: Large indurated urticarial plaque surrounded by smaller erythematous plaques.

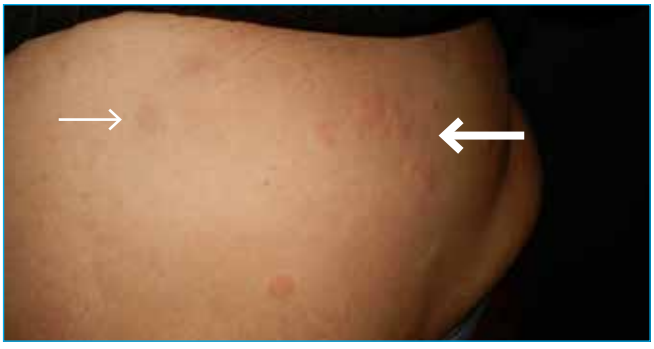

Figure 3: Urticarial plaques in different stages of evolution. Larger arrow highlights fresh lesions and the smaller arrows those that have resolved with post-inflammatory hyperpigmentation.

during medroxyprogesterone acetate treatment. Patch testing using 30% dilutions of medroxyprogesterone acetate in two vehicles (sterile water and petroleum jelly) was negative both at 20 minutes and 48 hours. Persistence of the plaques and resolution with post-inflammatory hyperpigmentation prompted us to perform another skin biopsy. A skin biopsy performed during her initial presentation, seven years prior, showed mild superficial oedema in the papillary dermis, ecctatic vessels and no vasculitis – features consistent with urticaria. In contrast, the second biopsy showed epidermal spongiosis with intracorneal blister formation and papillary dermal oedema. Abundant eosinophils with admixed neutrophils and lymphocytes were present within the superficial and deep dermis in a perivascular and periadnexal distribution. Leucocytoclasis and dermal flame figures were noted. In addition, there was evidence of vascular damage, manifested by focal fibrinoid necrosis of vessels and erythrocyte extravasation (see Figure 4). These features were consistent with leucocytoclastic vasculitis and our final diagnosis was urticarial vasculitis (UV).

Over the preceding eight years her chronic urticaria had been managed with different classes of high-dose antihistamines, including cetirizine, desloratadine, and fexofenadine; adjunctive H2-receptor antagonist ranitidine; and low-dose oral prednisone with only partial resolution. We considered the risk–benefit of:

- attempting more aggressive progesterone suppression with gonadotropin-releasing hormone agonists;
- immunosuppression with cyclosporine, or
- anti-IgE therapy.

We decided on a trial of anti-IgE therapy with omalizumab, a humanised anti-IgE monoclonal antibody. A dose of 300 mg was administered subcutaneously. The response was a complete resolution of her urticarial plaques within days following the injection. Two weeks after the injection she developed shortness of breath and an increased blood pressure requiring hospitalisation. She was diagnosed with a pulmonary embolus. She recovered fully and is now on lifelong warfarin therapy and antihypertensives. In consultation with haematologists and pharmacologists we decided to recommence omalizumab therapy as the test dose had resulted in a dramatic improvement of her symptoms and quality of life. She has since received four doses of omalizumab, four weeks apart, with no recurrence of her urticarial plaques.

In parallel to our diagnosis of UV, gynaecological work-up for menorrhagia found a left ovarian cyst measuring 50 × 40 × 30 mm. Initial management was conservative, but due to persistent heavy bleeding she elected to have a left oophorectomy. Histology confirmed this to be a benign cystic teratoma. In the three months following the removal of the teratoma and off omalizumab, she had continued to have cyclical urticaria. This resolved on reinitiating of omalizumab.

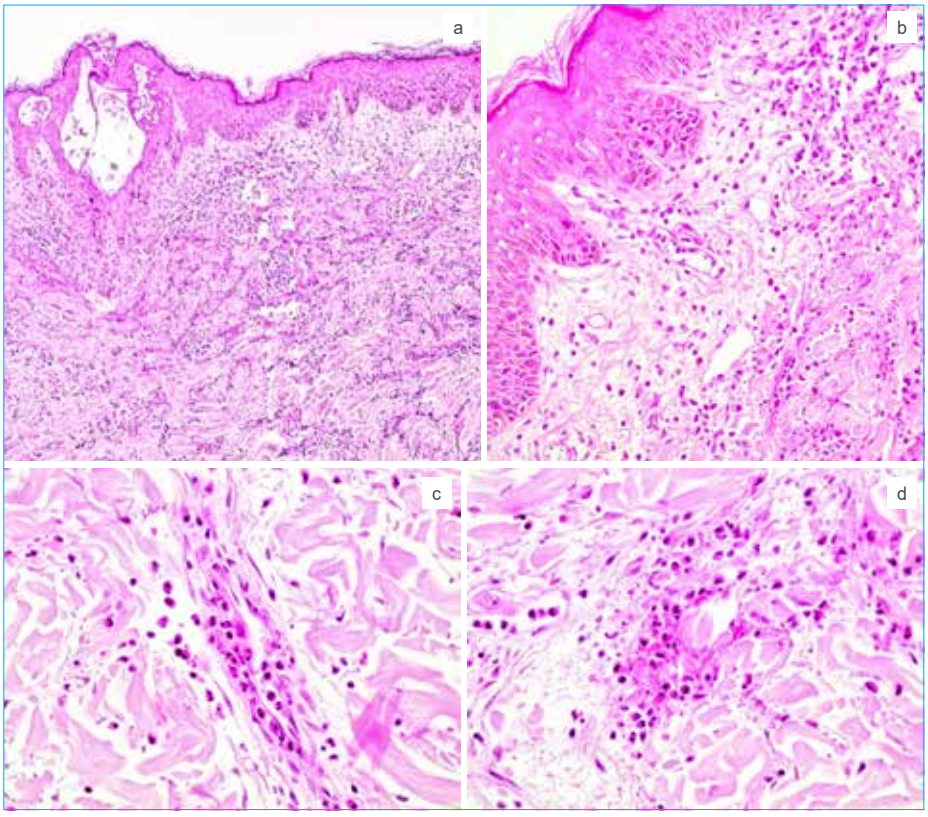

Figure 4: Haematoxilin and eosin stains of sections of the skin punch biopsy shows: ***a)*** *an intracorneal blister, with epidermal spongiosis, papillary dermal oedema and moderately dense superficial and deep dermal inflammation,* ***b)*** *numerous eosinophils, neutrophils and lymphocytes are noted in the dermis, with evidence of leucocytoclasis and red blood cell extravasation,* ***c)*** *prominent perivascular eosinophils,* ***d)*** *a conspicuous flame figure and fribrinoid necrosis*

DISCUSSION

Chronic urticaria is the occurrence of wheals and/or angioedema lasting longer than six weeks.[1] UV is a clinico-pathologic entity characterised by recurrent episodes of wheals that have the histopathologic features of leukocytoclastic vasculitis.[2] Neutrophilic urticaria has been proposed to represent a type of urticarial reaction pattern in between ordinary urticaria and urticarial vasculitis, although this is still debated.[3] UV is classified as normocomplementaemic or hypocomplementaemic based on the presence of complement consumption (decreased C3, C4 and C1q).[4] In both subtypes, urticaria and angioedema are often accompanied by other symptoms including chest or abdominal pain, fever and joint pain. These extra-cutaneous features are most prominent in the hypo-complementaemic subtype, most frequently associated with systemic

lupus erythematous.[4] UV can be associated with infections, drug reactions or part of paraneoplastic syndrome.[2]

UV is immune-complex mediated, where circulating antigen-antibody complexes are deposited in cutaneous vascular walls activating complement, generating anaphylatoxins, which in turn causes mast cell degranulation and neutrophil chemotaxis.[2] It is interesting to postulate a connection between our patient's UV and her ovarian teratoma. A teratoma derives from all three embryonic tissue types – ectoderm, mesoderm and endoderm.[5] Thus, it is possible that auto-reactive antibodies directed against tumour antigens (paraneoplastic) led to the development of UV. The persistence of symptoms post-resection argue against the teratoma as the disease driver, although circulating antibodies may persist for up to six months post-removal and close follow-up will be required.[6]

Efficacious off-label use of omalizumab for UV treatment has been reported in case series and case reports.[4,7] The specific mechanism of action in UV remains uncertain. Omalizumab inhibits IgE by binding to the IgE C3 domain.[7] It also produces immunomodulatory effects, including a decrease in IgE cell receptors in mast cells and basophils as well as reducing B-cell activation and homing.[7] Dosing in UV is similar to that in chronic urticaria (150–300 mg/month).[4,7] The maintenance dose of omalizumab in UV, duration of treatment and tapering protocols are still unclear. No adverse effects were reported in the previous cases of UV treated with omalizumab.[4,7]

We were concerned by the temporal relationship between omalizumab administration and pulmonary embolus in our patient. A prospective real world epidemiologic study that evaluated clinical efficacy and long-term safety of omalizumab in asthma showed omalizumab to increase the risk of pulmonary embolisms/venous thrombosis with an incidence event rate of 3.2 (95% CI 2.4–4.3) per 1 000 patient years versus 1.5 (95% CI 0.8–2.5) in non-omalizumab group.[8] However, the adjusted hazard ratio was 1.32 (95% CI 0.91–1.91) thus suggesting no significance between the two groups.[8] Narukonda et al reported on a 53-year-old male patient with severe asthma on omalizumab for two years who developed an acute pulmonary embolism.[9] They attributed the pulmonary embolism to omalizumab as they could not find any other identifiable cause.[9] Our patient had other thromboembolic risk factors including obesity (BMI 44), recent surgery, and undiagnosed hypertension; her elevated d-dimer also indicated excess turnover of her coagulation pathway. Thus the contribution of omalizumab to her pulmonary emboli is uncertain; nevertheless, clinicians using omalizumab should be aware of this data in similar patients with high thromboembolic risk.

CONCLUSION

This complex case highlights the spectrum of severe chronic urticaria and important clinical role of histology in the management of such patients. The link to a benign ovarian teratoma is a rare association that may drive a paraneoplastic aetiology of UV. The case adds to the literature on the successful use of omalizumab in UV, as well as highlighting for clinicians the possible link of omalizumab with thromboembolic events. Further studies are required to understand the role, adverse effects and long-term outcomes of UV treatment with omalizumab.

INFORMED CONSENT

Written informed consent was provided by the patient for this case report and pictures to be published.

DECLARATION OF CONFLICT OF INTERESTS

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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Case Report

HEREDITARY ANGIOEDEMA – HOW IS THIS MANAGED IN PREPARATION FOR PREGNANCY?

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INTRODUCTION AND CLASSIFICATION OF HEREDITARY IDIOPATHIC ANGIOEDEMA

Hereditary angioedema (HAE) is a rare disease that is inherited in an autosomal dominant fashion. The hallmark of the disease is the development of spontaneous and recurrent episodes of angioedema. Importantly, these episodes of angioedema occur in isolation, without urticaria or pruritis. The disease has no gender predominance. Left untreated, the mortality can be as high as 30 per cent.

In low- to middle-income countries (LMICs) such as South Africa, the treatment modalities include therapeutic fresh frozen plasma (FFP), anti-fibrinolytics and androgens. The more expensive and effective treatments available internationally are not readily available in South Africa. Danazol (an androgen) is teratogenic and cannot be used during the period of conception or during pregnancy.

We present a case of a young woman with HAE who desires to fall pregnant and have a baby of her own. In our discussion, the authors describe HAE and the pathogenesis of this condition. Treatment strategies are explored with specific reference to conception and pregnancy.

CASE PRESENTATION

Patient AZ is a young woman who lives in Johannesburg. She has inherited a terrible and strange disease from her mother. She develops spontaneous swellings of parts of her body in an asymmetric fashion that last 3–5 days before spontaneously resolving. During these episodes of swelling she often suffers from agonising abdominal pain. On two occasions, she developed life-threatening laryngeal oedema and almost required ventilation for upper-airway obstruction. In the past, she had previously witnessed her mother suffocate to death from the same disease. Figures 1 and 2 illustrate the angioedema attacks that patient AZ has endured previously.

The medical professionals from whom she sought help previously thought that she had severe allergies; however, no obvious trigger was identifiable. She was finally diagnosed with HAE after referral to an allergy unit in a tertiary centre. The diagnosis was confirmed with low levels of Complement 4 and low levels of C1 esterase inhibitor. She was finally diagnosed with HAE type 1, the most common type. After confirmation of the diagnosis, treatment with Danazol was initiated. Unfortunately, because of the risk of teratogenicity, she was advised against falling pregnant.

Figure 1: Angioedema of the face during a period of severe life-threatening laryngeal oedema

Figure 2: Asymmetric swelling of the hands during a period of cutaneous angioedema

Then she met her partner and wanted to marry. Her culture prohibits marriage if she cannot have children. She had a fervent desire to have a baby and live a normal life; but because of the teratogenicity of Danazol, this was not an option.

After many years of exploring different possibilities, her doctors finally received a breakthrough. After consulting with an international company that supplies C1-INH, patient AZ was given the opportunity to use the plasma-derived preparation during the period of conception and pregnancy. This occurred after approval was obtained from the South African Health Products Regulatory Authority (SAHPRA).

Patient AZ is trained in the self-administration of C1-INH. She has had six attacks in 12 months that required C1-INH administration. She eagerly awaits falling pregnant and having a baby of her own.

DISCUSSION

HAE is thought to occur at a prevalence of 1 : 50 000, with no gender or racial predilection.[1,2] Up to 40 per cent of patients will experience their first attack before five years of age, and up to 75 per cent by the age of 15. However, the diagnosis is made only by the second or third decade of life.[3]

Angioedema on its own can result from either a histamine or a bradykinin. Bradykinin-mediated angioedema can be either hereditary or acquired. The acquired forms are usually the result of the use of angiotensin-converting enzyme inhibitor (ACEi).[4]

There are a number of subtypes of HAE. The most common are types 1 and 2; with type 1 being the most common subtype, occurring in 85 per cent of patients.[3] Types 1 and 2 are inherited in an autosomal dominant pattern of inheritance; however, *de novo* mutations do occur in a small percentage of patients. Rare forms of the disorder exist due to mutations of the Factor X11 or plasminogen gene. The rare forms of the disease are associated with normal C4, normal C1-INH levels and function. This article concentrates specifically on types 1 and 2, the other subtypes being beyond the scope of this article. The distinguishing features from a laboratory perspective are illustrated in the table below:[3,4]

TABLE I: DISTINGUISHING FEATURES OF HAE-1 AND HAE-2

	C1-INH FUNCTION	C1-INH LEVELS	C4
HAE-1	Low	Low	Low
HAE-2	Low	Normal or high	Low

HAE generally affects three anatomical areas:[3]

1. *The skin (cutaneous attacks):* these are by far the most common. The oedema associated with this manifestation is non-pitting in nature. The affected sites are usually the face, the genitals and the extremities, although any site can be affected. The swelling is usually asymmetric and it is not associated with pruritis and urticaria. The swelling spontaneously resolves within 3–5 days.
2. *The gastrointestinal tract (GIT):* symptoms of abdominal pain, diarrhoea, abdominal bloatedness, nausea and vomiting all arise as a result of bowel-wall oedema. Gastrointestinal symptoms can occur in isolation and, in a minority of patients, this can be the only presenting feature.
3. *The upper airway (laryngeal attacks):* these attacks are by far the most concerning. Left untreated, they can result in fatal asphyxiation. Laryngeal swelling can occur either in isolation or in association with swelling of the lips, tongue, uvula and soft palate. Up to 50 per cent of patients with HAE will experience one episode of laryngeal oedema in their lifetime, and some may experience recurrent symptoms.

Identifiable triggers of attacks include:[3]

- minor trauma;
- oral and dental procedures preceding laryngeal attacks;
- medications including oestrogen-containing drugs such as the combined oral contraceptive, hormone-replacement therapy and tamoxifen;
- *H pylori* infections;
- hormonal changes, including puberty and pregnancy.

The diagnosis of HAE rests on a good history and examination and relevant laboratory confirmation. The diagnosis should be suspected when patients present with recurrent episodes of angioedema. The following support the diagnosis:[4,5]

- A positive family history – this may not be present in 25 per cent of cases.
- The occurrence of symptoms in childhood or adolescence.
- Recurrent painful abdominal symptoms.
- Failure to respond to the conventional methods of managing allergy or anaphylaxis, including glucocorticoids, antihistamines or adrenaline.
- An attack of laryngeal oedema.
- The absence of urticaria with symptoms.

Laboratory testing based on clinical suspicion involves C4 levels, C1-inhibitor (C1-INH) protein levels and C1-INH-function studies (see Table I above). C1-INH-function studies are not readily available in South Africa, especially in the public sector.

In December 2017, the World Allergy Organisation/*European Academy of Allergy and Clinical Immunology (WAO/*EAACI) published a position statement on the management of HAE.[4] Treatment should ensue in all patients in which a diagnosis is confirmed. Therapy can be based either on an 'on-demand' strategy or on 'long-term prophylaxis'. For an on-demand strategy, the following classes of drug can be used:

- *C1-INH concentrate:* this is available in two preparations – plasma-derived or recombinant. The two plasma-derived drugs approved for on-demand use are Berinert and Cynrize. Both of these are well tolerated and adverse events are minimal. Ruconest is the only recombinant human C1-INH available.
- *A kallikrein inhibitor:* the only obtainable kallikrein inhibitor is Ecallantide, which is available in the United States for use in patients above 12 years of age. Hypersensitivity is a risk and, because of this, this drug is not licensed for self-administration. It therefore has to be administered by a healthcare professional.[6]
- *Bradykinin-receptor antagonist:* Icatibant is available internationally for use in adults above 18 years of age. The risk of hypersensitivity is low as compared to Ecallantide and the drug is accordingly registered for on-demand self-use.[7]

Long-term prophylaxis should be considered in all patients exhibiting a high disease activity in order to reduce the number of attacks. Suggested strategies include:[4]

- *Twice-weekly C1-INH concentrate:* this is the preferred choice of treatment. However, this is expensive and not readily available in all countries, especially not in South Africa.
- *Androgens:* these are suggested when C1-INH is not available.
- *Anti-fibronyltics:* these are not readily suggested for long-term prophylaxis as their efficacy has not been adequately demonstrated.

In South Africa, the agents suggested for on-demand use are not easily available. They are imported after SAHPRA approval on a patient-to-patient basis. These drugs are exceptionally expensive; and funding for them is also challenging. Danazol is the only available option for long-term prophylaxis in South Africa. However, the use of the drug comes with side-effects that include virilisation and interaction with other drugs, especially statins. It is absolutely contra-indicated during pregnancy because of its potentially teratogenic effects.

As this is an autosomal dominant condition, patients should be referred to a genetic counsellor. Genetic counsellors are available in both the public and the private sectors in South Africa.

HAE DURING PREGNANCY AND LACTATION[4,8,9]

The hormonal, anatomical and physiological changes that accompany pregnancy may alter the course of the disease in HAE. Pregnancy itself can either mitigate or aggravate the disease, or have no effect at all. It is very rare that the first attacks of the disease happen during pregnancy.

Internationally, C1-INH concentrate is the suggested treatment. Ecallantide, however, is not suggested. There are case reports for the use of Icatibant in pregnancy. An on-demand strategy can be employed in patients with a low attack frequency. However, in patients who have a higher attack frequency, long-term prophylaxis with C1-INH concentrate may be needed. If nothing else is available, FFP can be used on demand during severe attacks.

Vaginal delivery is the preferred method of delivery. Avoiding surgery and/or intubation is essential to avoid exacerbation. If surgery is necessary, however, then pre-procedural C1-INH concentrate is necessary prior to anaesthesia.

As with all other patient groups, anti-fibrinolytics may be used, but their efficacy is not proven. Androgens cross the placenta. The side-effects include masculinisation of the female foetus, intra-uterine growth restriction and placental insufficiency. As a result, the use of androgens during pregnancy is contra-indicated.

In summary:

- During the conception phase, it is advised that all androgens be discontinued two months prior.
- During pregnancy, androgens are completely contra-indicated for the reasons mentioned above. The options available in South Africa include on-demand FFP; unless one is able to gain access to C1-INH concentrate.
- During breastfeeding, androgens have been shown to be excreted in breastmilk and they are therefore contra-indicated during lactation. Lactation should be discontinued prior to commencing androgens again. In contrast to androgens, anti-fibrinolytics are safe during breastfeeding and remain an option for those living in South Africa (although their efficacy in preventing attacks has not been proven).
- The newborn should be watched closely for the development of spontaneous swellings of the body and the paediatrician should be made aware of the mother's diagnosis.

CONCLUSION

HAE is in itself a rare disease. Its diagnosis is missed very often, owing largely to a lack of awareness of the disease. Patients are commonly misdiagnosed as having severe allergies.

The available therapies in South Africa favour a long-term prophylaxis strategy to prevent angioedema attacks. The most commonly used and most effective agent is Danazol, but it is unfortunately contra-indicated during conception, pregnancy and lactation. International guidelines suggest the use of C1-INH during pregnancy and breastfeeding; however, it is not easily available is South Africa. A special motivation and funding are necessary to support patients of childbearing age who wish to lead a normal life and have a family of their own.

Patients should be managed by a multidisciplinary team, including obstetricians, immunologists/allergists, paediatricians, geneticists and genetic counsellors.

DECLARATION OF CONFLICT OF INTEREST

The authors declare no conflict of interest.

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OBITUARY

BONGANI MAYOSI – GIANT, FRIEND AND CHAMPION

We are deeply saddened by the untimely death of Professor Bongani Mayosi – an academic giant, personal mentor, colleague, friend and champion.

Bongani was born in the Eastern Cape and studied medicine at the University of Natal. He did his internship at Livingstone Hospital in Port Elizabeth and then specialised in internal medicine at the University of Cape Town. He became a sub-specialist cardiologist.

Bongani's life was marked by a great energy and enthusiasm for all he did, his mind invariably open and enquiring.

His research focused on the diseases of poverty such as tuberculosis and rheumatic fever. These research contributions led to the improved management of constrictive pericarditis and rheumatic fever, and are of global importance. He was also involved in ground-breaking research into our understanding of the genetic basis of sudden cardiac death in young adults. His extraordinary clinical ability and research were highly regarded by both local and international faculty. The recipient of numerous prizes and awards, Professor Mayosi also received an A rating from the National Research Foundation: as a scientist, he was nothing short of an academic and research giant.

After serving as head of the Department of Medicine at the University of Cape Town for several years, he was then appointed Dean of the Faculty of Health Sciences. During this era, we spent time with him in different capacities; our stories relate snippets of his personal impact and latest legacy.

Jonny: he was my most significant mentor. His style of mentorship was like that of a shepherd … I always felt he knew where I was, and where I should be heading, right from the moment he offered me a training post. My interests in immunology, clinical medicine and research didn't always follow a cogent path, but Bongani seemed to know the best route for me – co-supervising my PhD and then encouraging me to apply for an Oxford Nuffield fellowship. Needless to say, he was chair of that selection committee. He remained in regular contact while I was at Oxford, always asking me about my plans to return to South Africa, and outlining his vision that Allergy and Clinical Immunology should expand, both at UCT and nationally. I shall miss his guidance, enthusiastic encouragement and wisdom.

In fact, Bongani was very supportive of the development of our discipline at all levels. In his positions at the Health Professions Council of South Africa (HPCSA) and in the College of Medicine of South Africa he was a champion for the recognition of Allergology as a sub-speciality of Medicine and Paediatrics. He facilitated and strongly supported the Adult Allergology training programme initiated at Groote Schuur Hospital once the sub-speciality had been recognised by the HPCSA.

Paul: he was a wonderful and trusted personal friend and, after hours, we often discussed confidential and difficult matters on the telephone. Bongani knew how to listen. He had immense interpersonal skills. He also knew how to have fun and enjoy himself, though much of his enjoyment was derived from helping and encouraging his colleagues and students. We kept in touch regularly by telephone and via WhatsApp, even into my retirement. He remained interested in the Aerobiology work done by Dilys Berman as a PhD student in the department.

A characteristic example of his penchant for impish fun occurred one evening, after a long day at the Department of Medicine's post-graduate refresher courses at the International Conference Centre in Cape Town. We happened to find ourselves in separate cars on Nelson Mandela Boulevard, driving towards the southern suburbs. Bongani rolled down the driver's-side window of his Audi TT and gave me a wink and a nod to have some fun on the freeway. The road being very quiet, it was his signal to dice each other to hospital bend. Needless to say, with his usual enthusiasm for a challenge, Bongani soon sped ahead of me and disappeared in his car around hospital bend as I reached the top of the hill. It is a fun moment I shall never forget.

In addition to his outstanding clinical and research contributions, mentorship and friendship, Bongani was an extraordinary human being, and a beloved family man. He was a strong champion of social justice, particularly for the disadvantaged. He was also a role model for excellence and integrity.

With Bongani's departure, the South African medical profession has suffered an enormous and irreplaceable loss.

Our sympathies and prayers go out to his family, whom he loved dearly.

Sincerely

Associate Professor Jonny G Peter

Emeritus Professor Paul Potter

Ethics Article

STRATEGIES AND ETHICS TO ENSURE EQUITABLE ACCESS TO BIOLOGICAL MEDICINES IN THE TREATMENT OF AUTOIMMUNE INFLAMMATORY DISEASES

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ABSTRACT
Because of substantial differences in access to medical care, not all patients with refractory autoimmune inflammatory diseases have benefitted from the improved outcomes offered by biologic therapies. Resource constraints, together with the drug regulatory environment, access to private medical insurance, and the availability of specialist services influence access to biologics. 'Biologic-sparing' approaches include early diagnosis and aggressive treatment with available therapies. Improved availability of biologics in low- and middle-income countries might entail better access to specialist healthcare services; selection of the most cost-efficient biologic available; and development of patient selection criteria to guide allocation. In addition, biosimilars may offer similar efficacy and side-effect profiles, at a greatly reduced price. Lessons learnt from the past ten years of civil campaigning for access to antiretroviral therapies show what can be achieved by mobilising patient advocacy groups together with healthcare providers, researchers and funders both in state and private sectors.

Keywords: strategies; ethics; equitable access; biological medicines; autoimmune inflammatory diseases

INTRODUCTION

The licensing of the first biologic disease-modifying drug over two decades ago has revolutionised the treatment of autoimmune inflammatory diseases (AIID). Since then, many biologic therapies have been developed, each targeting specific immune cells or cytokines implicated in systemic inflammation. Biologics are now used to treat a wide range of AIID, including rheumatological, gastrointestinal, dermatological and other systemic diseases. Nine biologic drugs are currently registered in South Africa. These include four tumour necrosis factor inhibitors (TNFi) (etanercept, infliximab, adalimumab, golimumab); a B-lymphocyte inhibitor (rituximab); T-cell co-stimulation inhibitor (abatacept), IL-12/23 inhibitor (ustekinumab), IL-17 inhibitor (secukinumab), and an IL-6 inhibitor (tocilizumab). Meta-analyses of randomised control trials, together with registry data, have confirmed the efficacy of biologic therapies – by controlling inflammation and reducing disease activity, they prevent damage, disability, comorbidities and restore health-related quality of life (QoL).[1–4] They are widely used, and in 2017, four of the five top-selling global therapies were biologics used to treat AIID.[5]

Autoimmune inflammatory conditions lead to significant direct and indirect medical costs, in terms of medication, outpatient visits, hospitalisations, rehabilitation and surgery. Furthermore, these diseases frequently result in work disability; loss of productivity and poor QoL. Biologics are moderately cost-effective in terms of quality-adjusted life-years (QALYs) in treating patients with active disease compared with conventional therapy; however; data for South Africa are lacking.[6–10]

One important point for consideration is that most studies of cost-effectiveness have been conducted in high-income countries. In South Africa and other low- and middle-income countries (LMICs), the value of labour is low, and the majority of patients in the state healthcare system are employed as labourers, factory workers, or domestic workers, or are unemployed due to socio-economic rather than health reasons. From an economic perspective, offering biologic therapy to protect against job loss to such patients may offer unconvincing cost-effectiveness returns. However, the gains to a patient's QoL, and that of their immediate family and community are considerable.

Two major factors limit the widespread use of biologics, particularly in LMICs: their exorbitant cost and the risk of serious opportunistic infections associated with their use.

Biologics in South Africa public sector cost between R50 000 and R120 000 per annum. Pharmaceutical companies offer explanations for the high cost of biologics, citing the high price of novel drug research and development, with very few medicines making it through from drug discovery to licensing and marketing. In addition, the manufacturing process is complex; adding to their costs. However, we believe that the industry should develop innovative ways to decrease these costs or restructure their pricing for LMICs.

Biologic therapy confers a risk of serious and opportunistic infections, and tuberculosis (TB) is of particular concern in TB-endemic South Africa. Registry data show rates of TB infection among patients using TNFi therapy of 106–172/100 000 person-years in Europe and North America compared to of 1 387/100 000 in South Africa.[11] Thus, biologics must be used with caution, and prescribed by experienced and vigilant practitioners to motivated patients exposed to excellent support programmes. It is imperative to rule out latent TB in all patients and consider the prescription of isonicotinylhydrazide (INH) prevention therapy in those at risk.

Research has explored the optimal timing of biologic drug prescription, and an approach favouring treatment of early disease, before irreversible damage has occurred, seems appealing. However, many patients respond adequately to traditional therapies. For example, in the case of rheumatoid arthritis (RA), approximately 20%–25% of patients respond to traditional synthetic disease-modifying antirheumatic drugs (tsDMARDS).[12,13] Given the high cost of biologic therapy, together with the increased risk of infection, they are recommended only for patients with insufficient response or intolerance to standard drug therapies.[14–18] In South Africa, guidelines or recommendations for AIIDs, recommend biologics for patients with refractory disease.[19–21]

INEQUITIES IN ACCESS TO BIOLOGICS

Health inequity refers to the availability of health services and treatment based on individuals' personal, financial and socio-economic characteristics rather than their health status.[22] Resource constraints underlie the poor availability of biologics in LMICs. In 2009, the QUEST-RA study, conducted in 25 countries across Europe and the United States, demonstrated a significant association between gross domestic product (GDP) per capita and disease activity scores of RA patients, with higher disease scores among patients in low GDP per capita countries compared to those in the high GDP per capita countries.[23] A more recent study across 46 European countries showed that access to biologics was dependent on a country's socio-economic status, with some low-income countries having no or almost no access to reimbursed biologic therapy.[24] A recent registry-based study of RA patients spanning 12 countries worldwide, showed that use of biologics is particularly low in South Africa (0.9% of patients) compared to Ireland (75%).[25] This study highlighted that average annual biologic prices differ substantially between countries, with the highest cost in the United States (US$80 000 per year), and the lowest in France (US$15 000), with South Africa in the middle range (US$25 000). However, when understood from the perspective of the cost of biologics per year as a function of GDP per capita, South Africa scores high at 1.93 versus European countries, including 0.69 (United Kingdom) and 0.37 (France). Factors beyond GDP account for some of the differences in access to biologics. These might include the drug regulatory environment, reimbursement policies, access to private medical insurance, and the availability of specialist services.

In South Africa, most patients using biologic drugs are in the private sector with medical insurance funding. Most patients are required to be on the highest medical aid plan, frequently with a substantial co-payment. Very few patients in the state sector are able to access biologics, and do so via access to biologics via either hospital provision, self-funding or through participation in clinical trials. In the Western Cape state healthcare system, serving approximately 10 000 adult and paediatric patients with rheumatic diseases, only 30 patients are offered a biologic per year for RA. Currently, 80 patients at Groote Schuur, Tygerberg and Red Cross War Memorial Children's Hospitals have refractory uncontrolled disease that meet the standard of care recommendations for biologic therapy. Similar numbers of patients are seen in dermatology and gastroenterology clinics, where there is limited access based on strong motivation.

The promulgated prescribed minimum benefits include RA in the private sector; and despite this being celebrated, the divide between access for patients within the private and public sectors has widened. The authors note that patients in private are often required to be on high-end options with significant co-payments. With recession-related worsening constraints placed on health budgets by government health authorities, the outlook for the next decade is bleak for these patient groups.

STRATEGIES TO SOLVE INEQUITIES

BETTER ACCESS TO SPECIALIST HEALTHCARE SERVICES

Because AIID tend to be complex, they frequently require treatment at secondary or tertiary care level, particularly for patients with aggressive or refractory disease. As mentioned above, not all patients with AIID require biologic therapy. In the case of RA, for example, early diagnosis, rapid escalation of tsDMARD therapy using a goal-directed approach, and combination tsDMARD including leflunomide are 'biologic-sparing' approaches that should be adopted.[26–28] Such strategies to optimise available and relatively affordable therapies require concerted efforts to enable early diagnosis and referral, requiring improved awareness of AIID by healthcare workers at all levels.

Biologics are prescribed by specialists and sub-specialists, with support from pharmacists, and specialist nurses. Unfortunately, there is a critical shortage of these professionals in LMICs, particularly on the African continent. For example, South Africa has only 85 adult and paediatric rheumatologists for nearly 58 million people.[29] Other sub-Saharan African countries have a few or even no rheumatologists or rheumatology services. The situation is similarly dire in other specialties. This scarcity limits

the number of patients who have their AIID correctly diagnosed and optimally managed, with biologic therapy in the case of refractory disease, and underscores the urgent need to train more specialists and offer more specialised services.

Patient knowledge about their disease is an essential component of self-management, allowing for shared decision-making between patient and physician. Patient motivation is an under-recognised but vital pre-requisite to successful outcomes and adherence to any treatment strategy, with particularly relevance to biologic therapy.[30] Patients with a language barrier, frequently encountered in LMICs, have severely limited access to disease information and resources. Using trained patient volunteers to provide peer support and education is an excellent example of a successful intervention of delivering information and encouraging patients to become more involved in their disease management.[31]

In South Africa, access to biologic drugs is currently largely dependent on having medical insurance coverage through employers. For patients with severe diseases, disability can jeopardise their ability to continue working. Thus, interventions aimed at rapidly controlling disease activity and maintaining patients' function and work productivity are vital. Occupational therapy together with training in ability to cope with the disease has been shown to protect against work loss and disability.[32]

PATIENT SELECTION; LESSONS FROM OTHER SPECIALTIES

The need to ration expensive medical services is a reality in most LMICs. Orthopaedic surgeons are faced with increasing number of patients requiring large joint replacement surgery. This procedure is expensive, requiring a costly prosthetic device, specialist surgeons, anaesthetists, theatre staff, theatre time, hospital and sometimes intensive-care admission, and rehabilitation. The solution in New Zealand, recently adopted by orthopaedic clinics at Groote Schuur Hospital, is to calculate a prioritisation score which is based on patient's pain, functional disability, physical abnormalities, radiographic severity, independence in society, and threat to patient role (such as the ability to work or care for dependents).[33] Patients are ranked according to this score and offered surgery as places become available.

Similarly, renal replacement therapy (RRT) is expensive, and in sub-Saharan Africa only about 1.5% of hypertensive or diabetic patients requiring RRT receive it.[34] Prioritised selection is based on medical and psychosocial factors, including mental illness, employment, living circumstances, insight into illness, education or illiteracy, criminal record, substance abuse, adherence to treatment, and ability to travel to hospital.[35] However, Moosa et al raise concerns about the ethics of these selection criteria, demonstrating that almost 60% of patients were denied RRT because of social factors related to poverty.[36] The authors advocate the need for fair transparent prioritisation policies that are presented as accurate and unambiguous information to patients. Furthermore, they promote developing national guidelines which are uniform across the country, with selection decisions made by a team rather than by a single clinician with the burden of moral choice complicating an already complex work environment in state-sector institutions.

In the AIID, selection criteria for access to biologic therapy have not yet been explored. However, the possibility of developing evidence-based scoring as well as the documentation of a transparent and unambiguous prioritisation policy should be investigated and incorporated into the process of defining selection criteria for biologic therapy in AIID patients.

CHOOSING THERAPY WISELY

Careful consideration of the cost-effectiveness of the available biologics may allow better use of limited resources. For example, rituximab had lower costs per QALY than TNFi inhibitors in patients with RA in a UK study.[37] Adding to this, low dose rituximab is almost as effective as high dose, meaning twice the number of patients can benefit from this therapy.[38] One further benefit of rituximab is the lower risk of TB compared to TNFi therapy.[39]

BIOSIMILARS

As patents on biologics expire, biosimilar versions of these drugs have been developed and have the potential to substantially increase patient access to treatment. Biosimilars must demonstrate no clinically meaningful differences in terms of structure and function, efficacy, safety, and immunogenicity compared with an existing licensed, originator biologic.[40] It is hoped that biosimilars will offer significant cost reduction, without compromising efficacy or safety. In a European study, the annual cost savings from the use of an infliximab biosimilar were between 10% and 30%.[41] Biosimilars are now the preferred biologic, based on cost, in many European countries, and many patients on a biologic are switched to a biosimilar. Although strict regulatory approval guidelines have been developed, pharmacovigilance needs to be continued after marketing approval to monitor long-term safety of these therapies.[42] The pharmaceutical industry must be provided with the appropriate regulatory framework, which will encourage them to license and market their biosimilars in South African and other LMICs to provide increased access for our patients.

ACTIVISM FOR EQUITY OF ACCESS

Access to medicines is a fundamental human right.[43] New approaches to achieving innovation and access to medicines are possible today because of the previous decade of activism that demanded health equity in provision of antiretroviral therapy (ART) for people living with HIV. The Treatment Action Campaign mobilised people living with HIV/AIDS, doctors and nurses, ministries of health, developing country and donor governments, intergovernmental organisations, and pharmaceutical companies to achieve access to ARVs for more than five million people in the developing world.[44] Three steps were needed to realise this: research confirming that ART was effective, safe and thus feasible in resource-poor settings; placing access to treatment on the global political agenda; and thirdly, the price of ART had to come down.

In the case of AIID, patient advocacy groups together with healthcare providers and funders both in state and private sectors as well as relevant health authorities can continue to work with pharmaceutical companies to find solutions for patients requiring biologic therapy. There is already a call to revise the drug pricing of biologics in LMICs, and this needs to be amplified as high prices cannot be legitimate grounds for withholding lifesaving and life-changing therapies.

RESEARCH

Health inequities associated with AIID conditions are under-estimated and under-investigated in LMICs. Future studies to allow better understanding of patients' unmet health and healthcare needs, and to identify determinants of access to resources are urgently needed. Further research is needed to explore the impact of refractory AIID on work, productivity and HRQoL of patients and their communities in LMIC.

Regular review, ideally via clinical registries, of outcomes and adverse events of patients receiving biologic and biosimilar therapy is essential. If a selection or prioritisation strategy is in operation, this needs regular monitoring and evaluation to ensure ethical decisions of inclusion and exclusion are followed, with appropriate outcomes.

In conclusion, health authorities, funders and health practitioners must realise that chronic refractory AIID are as much social, economic, and ethical problems as they are medical ones. Improved access to biologic therapies for patients with AIID will require concerted effort to increase the number of specialist clinics, optimise available therapies, consider prioritisation scores, explore innovative ways to utilise biologic or biosimilar therapies, and to campaign for lower prices and better availability for all. We require successful campaigns for better health (and other socio-economic rights) that are driven by human rights demands and that take advantage of legal systems and the law.

DECLARATION OF CONFLICT OF INTEREST

The authors have no conflict of interest to declare.

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THE USE OF BIOLOGICS IN THE MANAGEMENT OF SEVERE ASTHMA

1. *True or false:* All biological treatments require an eosinophil level prior to starting therapy.
2. *True or false:* Omalizumab is the only biological that requires a body weight calculation for dosing.
3. *True or false:* Roughly 15% of all asthmatics could be considered severe.
4. *Choose the correct answer:* Which of the following statements is false:
   a. Underlying thyroid disease may affect asthma control.
   b. Certain biological treatments work best in those with high eosinophils.
   c. Severe asthma and uncontrolled asthma are synonymous terms.
   d. Once on a biological treatment patients can stop inhaled steroids.
   e. Inhaler adherence should be reviewed before starting biological treatment.

BIOLOGICS FOR MANAGEMENT OF ATOPIC DERMATITIS

5. *True or false:* IL-1 and IL-6 are some of the cytokines thought to play a pivotal role in inflammatory lesions of AD.
6. *True or false:* The pathogenesis behind the development of AD includes dysregulation of the immune system.
7. *True or false:* Biologics work by targeting a specific immune pathway; in that way they are immunosuppressive.
8. *Choose the correct answer:* Biologicals currently approved for use in treating AD in children include:
   a. Ustekunimab
   b. Omalizumab
   c. Tralokuzimab
   d. Dupilumab
   e. All of the above

CHRONIC SPONTANEOUS URTICARIA (CSU) IN THE ERA OF BIOLOGIC THERAPY: A NEW HOPE

9. *True or false:* There is currently a low level of evidence to support the usage of Cyclosporin A as an alternative disease modifying agent in the management of CSU refractory to high dose antihistamine therapy.
10. *True or false:* CSU with poor response to high dose antihistamine therapy is an indication for Omaluzimab therapy which is currently licensed for use and available in South Africa.
11. *True or false:* Current evidence supports the Omaluzimab dosage of 75 mg over the 150 mg and the 300 mg every 8 weeks for the management of CSU refractory to high dose antihistamine.
12. *Choose the correct answer:* Other biologic agents currently on clinical trials for use in the management of CSU refractory to high dose antihistamine therapy include:
    a. Omaluzimab and Rituximab
    b. Ligelizumab and Quilizumab
    c. Adalimumab and Natalizumab
    d. Dupilumab and Reslizumab

HEREDITARY ANGIOEDEMA – HOW IS THIS MANAGED IN PREPARATION FOR PREGNANCY?

13. *True or false:* Hereditary Idiopathic angioedema is characterised by development of urticaria/pruritis together with the spontaneous swellings of the body.
14. *True or false:* C1-INH concentrate such as Berinert or Cynrize is an effective therapy in the acute management of attacks in HAE.
15. *True or false:* With regards to management of HAE during pregnancy and lactation, the use of Danazol is contraindicated due to the risk of teratogenicity.
16. *Choose the correct answer:*
    a. A low complement 4 level is suggestive of the diagnosis of HAE.
    b. C1-INH concentrate is easily available in South Africa.
    c. Androgens can be used safely during the phase of conception and lactation.
    d. All of the above.
    e. None of the above.

ETHICS ARTICLE: STRATEGIES AND ETHICS TO ENSURE EQUITABLE ACCESS TO BIOLOGICAL MEDICINES IN THE TREATMENT OF AUTOIMMUNE INFLAMMATORY DISEASES

17. *True or false:* Health inequity refers to the availability of health services and treatment based on individuals' personal, financial and socioeconomic characteristics rather than their health status.
18. *True or false:* Biologic drugs are exorbitantly expensive and therefore careful selection criteria are required in a resource limited environment.
19. *True or false:* Poverty constitutes an ethically justifiable reason to limit access to expensive therapies.
20. *True or false:* Access to medicines is a fundamental human right.
21. *Choose the correct answer:* It is ethically acceptable to use a biosimilar drug in the treatment of autoimmune inflammatory diseases (AIID) for the following reason(s):
    a. It is a therapy that is an exact copy of an original drug, with identical dosage, intended use, effects, side effects, route of administration, risks, safety, and strength as the original drug.
    b. It is a therapy without clinically meaningful differences in terms of structure and function, efficacy, safety, and immunogenicity compared with its originator drug.
    c. It is used in high income countries.
    d. All of the above.
    e. None of the above.

Short Review Article

THE SKIN AS AN ENTRY POINT FOR ALLERGENS: EVIDENCE AND INTERVENTIONS

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INTRODUCTION

Atopic dermatitis ('eczema') is a common skin disorder characterised by a dry, itchy, inflamed skin in an age-typical distribution. Atopic dermatitis is very often the first 'step' in the allergic march, preceding food allergy and respiratory allergy manifestations.[1] A defective skin barrier has been recognised as being central to the pathogenesis of atopic dermatitis.[2] Evidence is mounting to support the hypothesis that such a defective skin barrier could play an important role in the development of sensitisation to food and aeroallergens, via the epicutaneous route, with the subsequent development of food allergies and/or allergic respiratory disease.[3,4] In a similar vein, the 'dual allergen hypothesis', as described by Gideon Lack,[5] hypothesises that exposure to environmental food allergens in early life can lead to an increase in food allergies if skin-barrier function is poor, but that early oral ingestion of food allergens may abrogate this risk by promoting immune tolerance to foods.[6,7]

This article explores some of the evidence for epicutaneous sensitisation and the importance of restoring and maintaining the skin barrier in the quest to reduce further allergic manifestations.

THE SKIN BARRIER IN HEALTH AND DISEASE

The epidermis of the skin is the first line of defence between the body and the environment.[1] The epidermis prevents environmental irritants, allergens and microbes from entering the body, and also excessive water loss.

The barrier function of the epidermis is primarily located in the stratum corneum at the surface of the skin. The permeability of the epidermis is determined by complex interactions between:

- terminal differentiated keratinocytes in the stratum corneum;
- groups of structural proteins such as filaggrin, regulatory enzymes, and lipids such as ceramides in between the cells;[8]
- tight junctions in the stratum granulosum (see Figure 1).

Therefore, based on the constituents of the barrier, possible causes of skin-barrier abnormalities are listed in Table I.[9]

The skin barrier is more permeable in infancy and matures over time as the ceramide concentrations in the stratum corneum increase.[10,11]

Eczematous skin is characterised by decreased ceramide levels as well as increased transcutaneous water loss. Increased

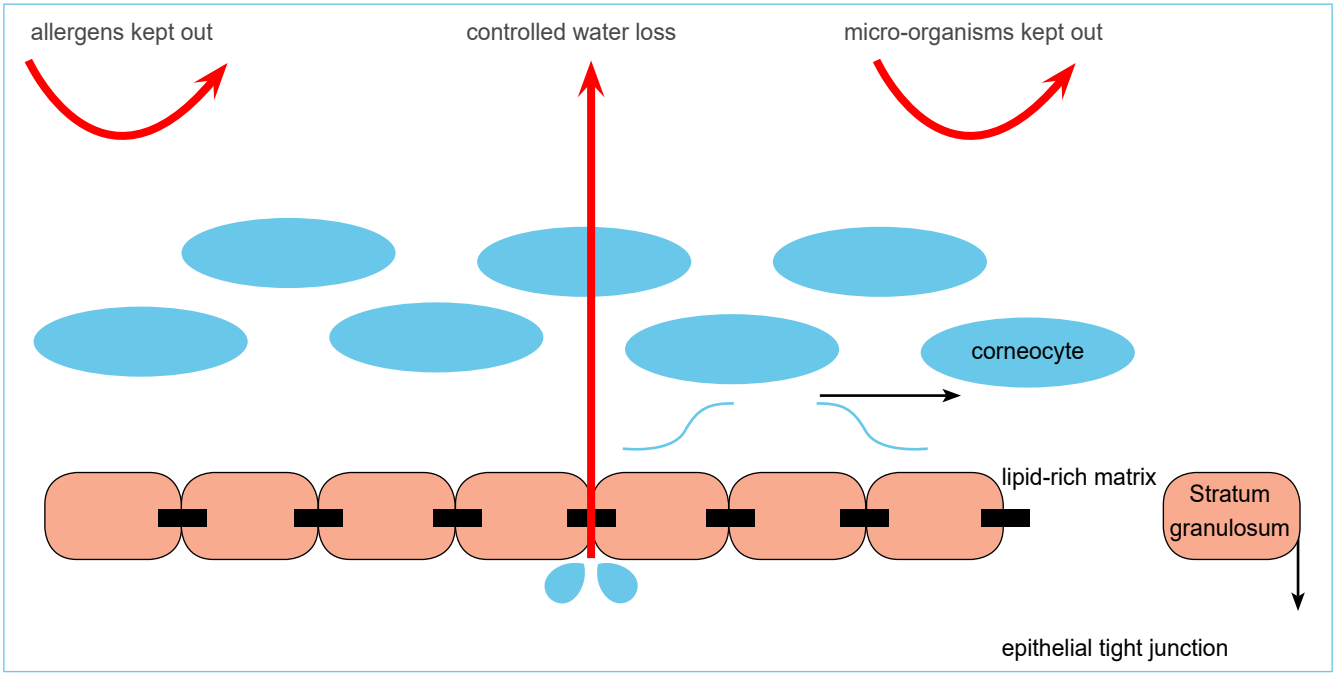

Figure 1: Components of the skin barrier

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- Aveeno® DERMEXA cream is uniquely formulated with Triple Oat formula + Ceramides to soothe skin, reduce itch and help strengthen the skin barrier
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- Improves transepidermal water loss (TEWL) by 30% at 4-9 days of use[2]
- Helps prevent sensation of itch and redness, leaving skin looking healthy
- High patient satisfaction[1]

A complete emollient therapy to help strengthen the skin barrier function

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TABLE I: CAUSES OF AN ABNORMAL SKIN BARRIER

- Imbalance between stratum corneum protease and antiprotease activity.
- Abnormalities in lipid synthesis and metabolism.
- Genetic variants, including filaggrin mutations.
- Abnormalities in epithelial tight junctions.
- Immune activation, especially type 2 responses, that decrease epithelial differentiation.
- Microbial dysbiosis, for example, staphylococcus aureus overgrowth.

transcutaneous water loss has been detected in the first few days of life in infants who develop eczema by 12 months of age.[12] An important concept in eczema is that the skin barrier is impaired even in asymptomatic skin.[8] The impaired skin barrier can lead to localised immune activation in the skin, skin inflammation, and a dysregulated response to environmental allergens which should usually be harmless to an intact skin barrier.

WHAT IS THE EVIDENCE FOR THE SKIN AS AN ENTRY POINT FOR ALLERGENS?

1. There is a significant co-existence between eczema and food allergen/aeroallergen-related diseases, with more severe eczema leading to an even higher probability of co-existent allergies.

Some 30–40% of children with moderate to severe eczema have at least one food allergy.[13,14] In a South African study on children with atopic dermatitis, 42% of children under the age of ten years had at least one IgE-mediated food allergy;[15] this is far higher than the food-allergy prevalence in the general population of 2–10%. Some 70-80% of children with atopic dermatitis develop respiratory atopic disorders (asthma and/or allergic rhinitis (AR)). The severity of atopic dermatitis and the co-morbidity of atopic dermatitis and food allergy are particular risk factors for asthma and AR.[16] In a South African study on children with atopic dermatitis, 39% of children under the age of ten years had asthma symptoms and 53% had AR symptoms.[17]

Aeroallergen sensitisation is common in atopic dermatitis and is positively correlated with the occurrence of asthma (see Figure 2). Epicutaneous sensitisation to aeroallergens via a defective skin barrier can lead to the subsequent migration of sensitised T-cells into the nose and airways, causing upper and lower airway disease.

Early-onset eczma (particularly less than six months) and more severe eczema have been associated in various studies with an increase in food allergy.[16,18]

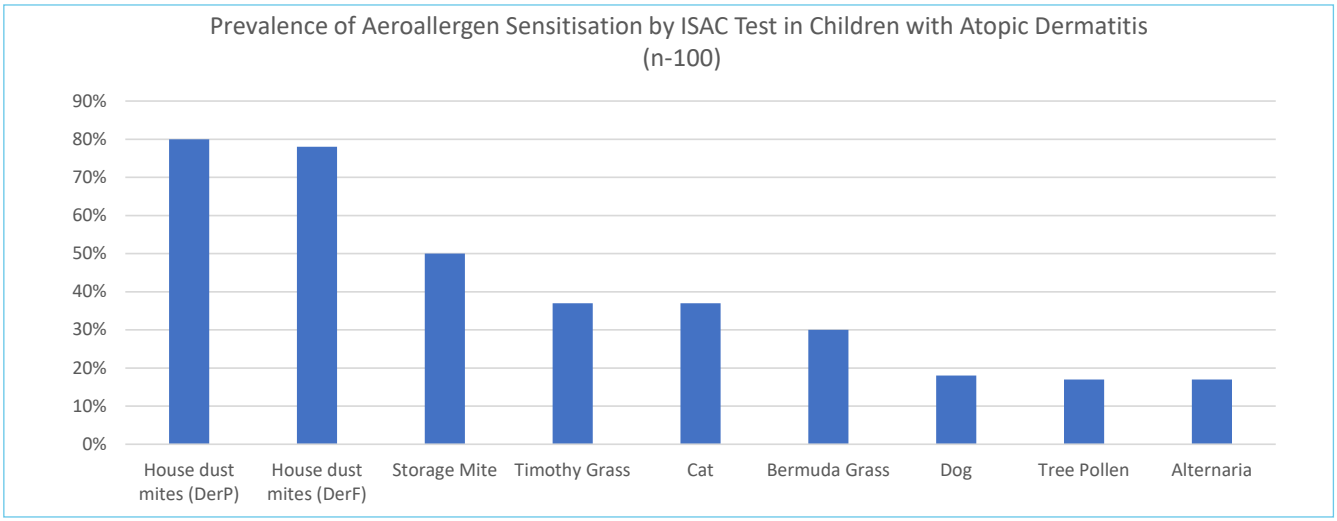

Figure 2: Aeroallergen sensitisation in South African children with moderate to severe atopic dermatitis[17]

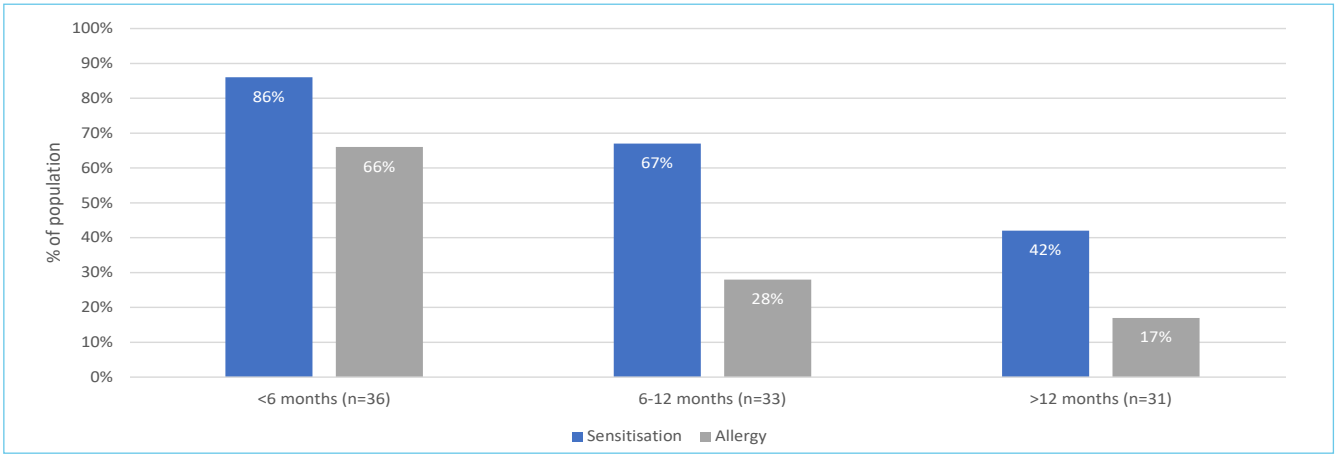

Figure 3: Age of onset of eczema and its effect on food sensitisation and allergy in 100 South African children with atopic dermatitis[15]

This was also demonstrated in the South African context in which a study of 100 children with atopic dermatitis showed a markedly increased risk of food allergy in early-onset as opposed to later-onset eczema (see Figure 3).[17]

2. In the AVON study, published in 2003, the use of peanut-oil-containing topical creams for treating nappy rashes was associated with an increased risk of peanut allergy.[19]
3. Helen Brough's group in the United Kingdom showed that higher environmental peanut allergen levels in a household increased the risk of peanut sensitisation and allergy in high-risk infants (those with AD or filaggrin gene mutation).[20-22]
4. Further studies have shown that filaggrin gene mutations which impair skin-barrier functions have been associated with an increased risk of atopic dermatitis, asthma and food allergy.[23,24]
5. At a molecular level, studies have shed some light on the role of various cytokines in epicutaneous sensitisation.[25] Over-expression of IL21 and the IL21 receptor have been shown to play a role in epicutaneous allergic sensitisation in mice.[26] Mouse studies have shown that epicutaneous allergic sensitisation may even promote eosinophilic oesophagitis by the IL33–ST2 basophils axis. [27]

CAN MAINTENANCE OR RESTORATION OF THE SKIN BARRIER LEAD TO A REDUCTION IN OTHER ALLERGIC MANIFESTATIONS?

EVIDENCE THAT EARLY-ONSET EMOLLIENT USE CAN REDUCE ECZEMA

Initial studies by Horimukai[28] and Simpson,[29] published in 2014, showed a 50% reduction in the risk of developing atopic dermatitis by using a daily standard emollient, started within the first few weeks of life and continued until 6–8 months of life. A more recent study by Lowe using a ceramide-rich formulation showed a similar reduction in eczema and a promising trend towards the persistent decrease in atopic dermatitis at 12 months (six months after stopping treatment).[30] Larger and longer-lasting studies need to explore this further to investigate whether the reduction in atopic dermatitis is sustained or temporary.

Head-to-head trials of the ideal emollient have not been performed, but from studies thus far it would seem that a more frequent application of emollients has better benefits.[30]

EVIDENCE THAT EARLY-ONSET EMOLLIENTS CAN RESULT IN A LOWER INCIDENCE OF FOOD ALLERGY AND RESPIRATORY ALLERGIES

The pilot study of PEBBLES (Prevention of Eczema by a Barrier Lipid Equilibrium Strategy) showed a trend for decreased food sensitisation at six and 12 months, especially when emollients were started at less than two weeks of age and were used at least five days a week.[30] The larger PEBBLES phase 3 study is now underway in Australia. Other studies include the United Kingdom-based BEEP study (Barrier Enhancement for Eczema Prevention, n = 1 400),[31] and the Norwegian PREVENTADELL study (Preventing Atopic Dermatitis and Allergies in children, n = 2 500).

EVIDENCE THAT EARLIER AND BETTER TREATMENT OF ATOPIC DERMATITIS CAN REDUCE SUBSEQUENT ALLERGIES

Secondary prevention means the prevention of later allergic disease through better and more aggressive management of established atopic dermatitis.

A small Italian study published in 2010 showed that the early diagnosis and management of atopic dermatitis led to a reduction in the evolution to asthma from 29% to 15%.[32]

The Japanese PACI study (Japanese Prevention of Allergy via Cutaneous Intervention, n = 650) is currently looking at aggressive management in infants with atopic dermatitis at 7–13 weeks of age and the prevalence of food allergy at 28 weeks.[8]

CONCLUSIONS

There is now strong evidence that atopic dermatitis may increase the risk of other allergic diseases because of epicutaneous sensitisation via a defective skin barrier. Studies have shown that the regular use of emollients from infancy substantially reduces the risk of developing atopic dermatitis. Further research is ongoing as to whether emollient use from an early age may also reduce the risk for food allergy and asthma. As childhood allergic diseases are on the increase without a 'cure' being available, the possibility of preventing or reducing allergic disease by maintaining a good skin barrier is attractive at both the individual and the public health levels.

HOW CAN WE APPLY THIS EVIDENCE IN THE CLINICAL SETTING?

- Based on a better understanding of epicutaneous sensitisation, the old notion of 'allergies as the cause of eczema' has now been superseded the notion that 'eczema is the cause of allergies'. This can help clinicians and patients alike to understand eczema as a skin-barrier disease, and management strategies to be prioritised accordingly.
- Restoring the skin barrier aggressively by frequent emollient application and appropriate topical anti-inflammatories is central to the management of eczema, and possibly to minimising further allergic manifestations.
- Applying appropriate emollients to the infant early and frequently may reduce the development of atopic dermatitis and is worth advising on a large scale.
- Using appropriate emollients that restore the skin barrier and do not irritate the skin, is essential.

DECLARATION OF CONFLICT OF INTEREST

The author declares no conflict on interest.

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OCCUPATIONAL CONTACT URTICARIA AND EARLY-ONSET WORK-RELATED ASTHMA IN A LATEX-ALLERGIC WOODWORKER EXPOSED TO OBECHE WOOD

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ABSTRACT

Exposure to wood dust has been shown to cause allergic skin and respiratory symptoms in woodworkers. We describe a case of a 53-year-old latex-allergic woodworker presenting with work-related contact urticaria and subsequent upper and lower airway symptoms associated with obeche wood (*Triplochiton scleroxylon*) exposure. Clinical evaluation of the patient was suggestive of an early-onset, work-related asthma and latex allergy with possible cross-reactivity to obeche wood. The difficulties associated with investigating and managing workers with occupational allergy and asthma related to wood dust exposure are illustrated. It is recommended that workers with wood dust-related airway and skin symptoms should be investigated thoroughly using a more extensive repertoire of immunological and pulmonological tests in order to confirm the diagnosis and institute appropriate management of these patients.

Keywords: occupations contact urticaria; early-onset work-related asthma; latex-allergic woodworker; obeche wood

INTRODUCTION

Work in the furniture and wood-processing industries is associated with an increased prevalence of respiratory and skin symptoms and asthma.[1,2] The evidence for a greater risk of impaired lung function with increasing exposure to wood dust is conflicting. Despite this clear link being reported in case reports and epidemiological studies, the underlying pathophysiological mechanisms remain poorly understood, although IgE-mediated reactions have been reported with some woods. Wood dust has been shown to cause irritation to mucous membranes, allergic sensitisation and asthma as a result of exposure to inhalable particles as low as 1 mg/m^3.[3] This report highlights the case of a woodworker who presented with work-related urticarial symptoms due to latex gloves and subsequently developed upper and lower airway symptoms associated with obeche wood exposure.

CASE PRESENTATION

A 53-year-old woman presented to the Occupational Medicine Clinic of Groote Schuur Hospital in Cape Town with a three-year history of contact urticaria affecting her hands. This condition was initially associated with her use of latex gloves at work, but this was subsequently triggered by handling obeche wood. Handling other species of wood used in the factory had no effect (see Table I). A few months following urticarial symptoms the patient developed work-related intermittent itchy, blocked or runny nose, chest tightness, wheezing and cough. She reported significant improvement of her symptoms during weekends and during annual leave, with a recurrence on returning to work. She had no history of childhood asthma, eczema or hay fever. She was a smoker with a ten pack-year smoking history. When she presented to the clinic, the patient had been on treatment with Budesonide inhaler 400 mcg twice daily (BD) and Salbutamol inhaler 200 mcg whenever required.

The occupational history revealed that for five years she had been working as a woodsander and stainer at a wooden shutter-making factory. The patient worked an eight-hour day for five days a week. She used oil-based wood stains (containing maleinised

linseed oil, medium aliphatic solvent naphtha, namely, petroleum and kerosene) and polyurethane varnishes (containing 1, 2, 4-Trimethylbenzene, cobalt carboxylate, ethylbenzene, white spirit, mesitylene, petroleum and xylene) for staining wood. She used powdered latex gloves while staining the wood. She sanded mainly meranti and obeche woods and was provided with respiratory protection (FFP2 respirators) while performing these tasks. Her previous work included clerical work for a plastics factory (three years) and woodsanding at a furniture-making factory (five years), but denied having any respiratory symptoms at the time. She could not recall the types of wood she had worked with in her previous position.

On clinical examination she was comfortable and not in respiratory distress. Her body mass index (BMI) was 25.30 kg/m^2. Her nasal turbinates were only 25% patent, but the rest of the ear and throat examination revealed no abnormality. On chest examination, she had no features of hyperinflation and no wheezing on auscultation. Her blood pressure was 120/80 mmHg and there was no evidence of cardiac failure. Examination of the other systems was unremarkable.

The spirometry results showed moderate airway obstruction with no significant reversibility of FEV_1 following bronchodilator administration. Her serial peak expiratory flow (PEFR) measurements showed a diurnal variation greater than 20% and the Occupational Asthma Expert System (OASYS) work-effect index (WEI) computed was borderline with a value of 2.00 (a value >2.5 denotes a high probability of occupational asthma).[4] The fractional exhaled nitric oxide (FeNO) level was 9 ppb, which was within normal limits (>50 is considered high – indicative of probable allergic-airway inflammation), while the chest radiograph did not reveal any underlying lung disease.

Skin-prick testing (SPT) with a standard panel of common aeroallergens was negative but the patient demonstrated a positive SPT to latex (see Table I). This was also demonstrated on specific immunoglobulin E (sIgE) testing showing mildly elevated sIgE to latex (k82) (0.54 kUA/L) but very low levels of recombinant latex allergen Hev b 6.02 and rHev b5. The levels of sIgE to obeche wood (sIgE = 0.19 kUA/L) was very low but relatively higher than meranti wood. The IgE to cross-reactive carbohydrate determinant (CCD) was below reliably detectable limits.

WORKPLACE WALKTHROUGH INSPECTION

A walkthrough inspection of the patient's factory (see Figure 2) revealed poor occupational hygiene measures in that settled wood dust was visible on the floor and on fixed surfaces. The wood dust easily became airborne during sweeping or dusting of the surfaces. Tasks associated with excessive wood dust generation in the factory included wood cutting, thicknessing,

TABLE I: SUMMARY OF THE PATIENT'S CLINICAL, PULMONOLOGICAL AND IMMUNOLOGICAL PROFILE

Demographic characteristics	Age	53 years
	Gender	Female
	Smoking status	Smoker
Exposure history	Exposure duration	Five years
	Job type	Wood sanding and staining
	Wood species causing symptoms	Obeche
Work-related symptoms	Urticaria	Yes (associated with obeche wood or NRL gloves)
	Ocular-nasal	Yes
	Asthma	Yes (three years duration)
Pulmonological assessment	Chest radiograph	NAD
	Spirometry	
	FEV_1 pre-BD/post-BD, mL FVC pre-BD/post-BD, mL FEV_1/FVC pre-BD/post-BD, % FEV_1 increase post- BD, mL (%)	1340/1470 2140/2190 63/67 130 (10% increase)
	Work-related changes on serial PEFR- OASYS Score	2.00
	FeNO (away from work, at clinic)	9 ppb
Immunological assessment (*in vivo*)	SPT to common aeroallergens SPT to occupational allergens	Negative Positive (Latex extract)
	Allergen-specific IgE, kUA/L	
	Meranti	0.01
	Obeche	0.19
	CCD	0.00
	Latex (K82)	0.54
	Latex (K220- rHev b 6.02)	0.28
	Latex (K218- rHev b 5)	0.00

NAD: No abnormality detected; BD: bronchodilator; FEV_1: Forced expiratory flow in one second; FVC: Forced vital capacity; FeNO: Fractional exhaled nitric oxide; SPT: skin-prick test; CCD: cross-reactive carbohydrate determinant – horse radish peroxidase

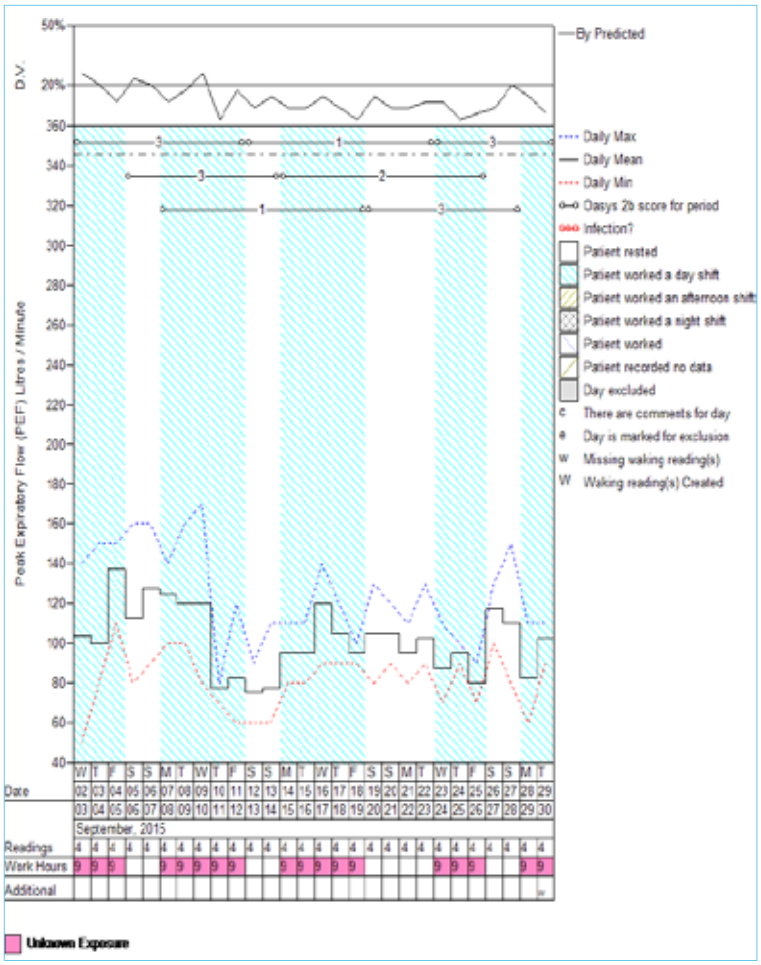

Figure 1: Serial expiratory flow recording of the patient over a four-week period (at work and away from work)

Figure 2a: A schematic layout of the factory floor

Figure 2b: Wood receiving section

Figure 2c: Wood cutting section

planing, moulding and sanding (see Figures 2a–d). Wood-staining used non-isocyanate polyurethane varnishes as well as oil-based wood stains that potentially had respiratory and skin-irritant properties. According to the report of an occupational hygiene survey conducted in the factory, the wood dust concentrations in the machining and sanding sections of the factory were found to be below the South African occupational exposure limit for wood dust (5 mg/m^3) but nevertheless the machine operators (2.81 mg/m^3) and sanders (1.26 mg/m^3 and 1.65 mg/m^3) experienced relatively higher levels of inhalable wood dust than other jobs.

CLINICAL AND WORKPLACE MANAGEMENT

Since the patient was not optimally managed with budesonide and salbutamol inhaler treatment, a long-acting β-agonist

Figure 2d: Wood-planing and thicknessing section

(Formoterol 12 mcg twice daily) was added to her treatment regimen. Attempts to accommodate her in another section of the factory were unsuccessful since the factory was conducting wood machining, staining or spray painting in one open area. The patient was counselled on the importance of seeking alternative employment without exposures to the offending wood dust in addition to taking up a smoking cessation programme. However, since there were no alternative jobs available to the patient she chose to continue working in her current job despite experiencing intermittent work-related respiratory and skin symptoms that resulted in significant absenteeism. She was concerned that she would not be able to find alternative employment due to her age and level of education. The company was advised to provide her with powder-free non-latex gloves, which they duly implemented. This resulted in intermittent alleviation of her skin symptoms. A worker's compensation claim was initially submitted to the Worker's Compensation Fund in the Department of Labour according to the Compensation for Occupational Injuries and Diseases Act of 1993.[5]

DISCUSSION

This report highlights a case of a non-atopic woodworker with latex-allergic contact urticaria and features suggestive of early-onset asthma associated with obeche wood dust exposure.

Obeche is a softwood widely used for all purposes for which durability and strength are not very important but stamina is needed, such as windows and door frames.[6] Inhalation of dust from obeche wood, is known to cause allergic sensitisation and asthma in exposed workers. It has been demonstrated that this dust has a higher protein content[7] and therefore possesses greater allergic sensitisation potential resulting in contact urticaria, rhinitis and occupational asthma (OA).[6,8–11] A 38 kDa class I chitinase obeche wood allergen, Trip s 1, has been identified as the major allergen of this wood with a large proportion (70%) of symptomatic workers demonstrating sensitisation to this allergen.[7] Other extractable protein patterns identified for obeche wood are in the range of 5–70 kDa with dominant bands present at 7, 12, 26, 28, 29, 30, 38 and 62–65 kDa.[7,12]

Since no standardised wood allergen test solutions for assessing wood sensitisation exist, individual wood allergen extracts must be prepared and tested for each wood species. However, the protein content of the prepared extracts has been shown to vary depending on the tree growing conditions, geographical origin as well as drying and storage methods used.[13] These limitations mean that it is difficult to assess sIgE-mediated wood sensitisation using the conventional SPTs. Adding to this complexity, recent studies have recommended that *in vitro* tests, particularly those involving plant allergens, should be evaluated for clinically irrelevant results caused by CCDs.[13,14] These are asparagine-linked carbohydrate moieties of plant and insect glycoproteins found abundantly in the environment.[15] Therefore, in order to confirm work-related wood sensitisation it is important to exclude sensitisation to these compounds. In this current study, the patient did not demonstrate sIgE sensitisation to CCDs (sIgE = 0 kUA/L) confirming that her sIgE to the latex and obeche wood allergens were not due to clinically irrelevant glycogenic sensitisation.

The extent to which wood dust exposure causes allergic sensitisation and work-related asthma depends on the presence of environmental risk factors such as increased job duration and high wood dust exposures as well as host-associated risk factors such as genetic susceptibility, atopy, smoking and presence of upper airway symptoms.[16] In this case study, the patient had worked in the wood industry for more than ten years, which included five years of exposure to obeche wood dust. She was involved in wood-machining and sanding tasks, which were demonstrated to produce excessive wood dust exposures of >1 mg/m^3 according to the industrial hygiene report. Furthermore, the patient had an appreciable smoking history, which has been associated with increased risk of work-related asthma symptoms (OR 3.6, CI 1.7–7.6) and symptomatic bronchial hyper-responsiveness (OR 2.3, CI 1.0–5.4) in woodworkers.[17] All these factors provide additional evidence for an increased risk of sensitisation and asthma.

In this case report, the patient presented with upper airway symptoms for several months prior to developing asthma. Rhinitis has consistently been reported as an independent risk factor for asthma development in atopic and non-atopic individuals.[18] Workers with allergic rhinitis (AR) may therefore form an important population for secondary intervention to interrupt the natural history of allergic respiratory disease.[19]

Despite the strong history of work-related asthma symptoms, the spirometry showed mild airway obstruction with no significant reversibility. However, the serial PEFR measurements revealed a maximum single-day variability of 26%, consistent with a clinical picture of asthma (see Figure 1). Although the OASYS

WEI was borderline negative, this score does not rule out the presence of occupational asthma, because an analysis of data collected showed that 26% of patients with score of 2.0 and a suggestive history have OA.[20] FeNO has been shown to be useful in detecting eosinophilic airway inflammation and determining the likelihood of corticosteroid responsiveness.[21] The fact that FeNO levels were within normal limits in this patient suggests that other mechanisms may also be present.

The patient also reported urticarial reactions associated with using powdered latex gloves. Interestingly, she subsequently developed urticaria and respiratory symptoms when working with obeche wood despite having very low sIgE to this wood. It is likely that these reactions could be due to possible cross-reactivity between natural rubber latex (NRL) and obeche wood. It is well known that many NRL-sensitised individuals show allergic reactions to a wide range of allergens originating from different plant families.[22] The existence of cross-reactivity between proteins in NRL and obeche wood has been demonstrated to be largely due to a 38 kDa protein (Trip s 1), a chitinase, which is the most important cross-reacting obeche allergen. This allergen has been reported to share some IgE-binding epitopes with Hevein (Hev b 6.02), the major latex allergen from *Hevea brasilensis*.[6,7] A study conducted to identify obeche wood allergen and determine possible cross-reactivity reported that, while co-recognition or cross-reactivity of obeche chitinase was observed in individuals with primary latex sensitisation, the latex Hev b 6.02 allergen did not cause cross-reactivity in obeche wood sensitised patients.[7] The natural history of urticarial symptoms, an elevated sIgE to latex (k82) (0.54 kUA/L) and relatively lower IgE to obeche wood (0.19 kUA/L) in this patient may suggest that primary sensitisation was due to NRL followed by cross-reactivity to obeche wood. Furthermore, component-resolved analysis of the latex sensitisation using individual recombinant latex allergens revealed that sIgE to Hev b 6.02 (0.28 kUA/L) were comparable to obeche wood sIgE (0.19 kUA/L). This may indicate possible cross-reactivity between obeche wood and Hev b 6.02 latex allergen, as previously suggested in the literature.[6] Specific IgE-inhibition tests would need to be conducted with these allergens to objectively confirm this cross-reactivity.

The occupational hygiene survey conducted in the patient's workplace revealed that the total dust particulate concentrations in the machining and sanding sections were below the South African Occupational Exposure Limit (OEL) for wood dust of 5 mg/m³ as contained in the Hazardous Chemical Substances Regulations.[23] However, it is evident that this exposure limit is not protective since symptoms were reported by the patient at levels below this limit. A similar observation was reported in a previous study of spice-mill workers in South Africa.[24] The American Conference of Governmental Industrial Hygienists (ACGIH) guideline (2013) recommends that the threshold limit value (TLV) for wood dust, other than western red cedar, of 1 mg/m³ should be used.[25] Using this limit, the wood dust concentrations measured during machining (2.81 mg/m³) and sanding (1.26 mg/m³ and 1.65 mg/m³) tasks were above this TLV. Furthermore, it has been recommended that apart from measuring the concentration of airborne wood dust, the allergen content of wood should also be quantified in order to determine the risk of sensitisation[26] since the total dust particulate may not be a good reflection of allergenic exposures. This was demonstrated in a study, which reported that the total obeche wood dust concentration in workplaces did not correspond to the assessed airborne allergen concentration despite the assay being highly sensitive. The assay was able to quantify obeche wood-allergen concentrations from 30 to 300 ng/mL.[27]

This case study has demonstrated the difficulties associated with managing workers with OA in the South African setting. The patient opted to continue working despite intermittent asthma symptoms due to daily exposures to wood dust and other respiratory irritants at work. Early and complete removal from occupational exposure is an important factor in the management of OA and its prognosis.[28] However, removal from exposure seems to benefit only those who continue to be employed in alternative employment. Woodworkers exposed to western red cedar with OA who remained employed, particularly without any wood dust exposure, were shown to have better quality of life (QOL) scores compared to those quitting work, especially for OA-related reasons.[29]

CONCLUSION

This report demonstrates a case of a latex-allergic woodworker with features of work-related contact urticaria, rhinitis and early asthma symptoms due to possible cross-reactivity with obeche wood. It illustrates the point that workers with wood dust-related airway and skin symptoms should be investigated thoroughly using a more extensive repertoire of immunological and pulmonological tests to confirm the diagnosis and institute appropriate management.

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DECLARATION OF CONFLICT OF INTEREST

The authors declare no conflict of interest.

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Research Article

HEREDITARY ANGIOEDEMA TYPE 1 EXPERIENCE IN KWAZULU-NATAL

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ABSTRACT

Introduction: Hereditary angioedema type 1 (HAE1) is a rare autosomal-dominant genetic disorder caused by a mutation of the SERPIN 1 gene on chromosome 11 (11q12.1) that codes for the synthesis of the enzyme C1 esterase inhibitor (C1INH). E Moran et al first reported HAE1 among members of a Zulu family in rural northern KwaZulu-Natal (the NM family) in 2008. We studied four consecutive generations of this family in order to:

- determine the genetic burden;
- identify the common clinical manifestations of HAE1 acute episodes;
- review the therapeutic challenges in this rural setting in comparison to world standards, and
- evaluate the socio-economic burden inflicted by the disease.

Methods: Twenty-nine NM family members with possible HAE1 were collectively identified by the family, and those unable to attend at least one of the three booked Medical Outpatients Department appointments were excluded, which resulted in a final study sample of 13. An interview was conducted and a family tree was drawn identifying the affected individuals in four consecutive generations. Information concerning acute clinical presentations in the past year (2017) was documented. A questionnaire was used to obtain the relevant HAE1-associated socio-economic burdens. A chart review was done to identify the prophylactic and acute therapeutic strategies used by doctors in this region. Blood samples for C1INH levels, complement C3 and C4, were taken to make a diagnosis of HAE1, and C-Reactive protein (CRP) was taken to rule out an acute episode.

Results: Polygamy as a local practice was found to be an important factor that perpetuated the genetic burden of the disease. When compared to the laboratories' normal value indices, C1INH levels were significantly lower than that of the population mean (30 mg/dL), with a mean of 5.45 mg/dL (CI: 3.97–6.92, SD–1.65, $p<0.01$) and a variance of 2.71. C4 levels were also significantly lower than that of the population mean (0.25 g/L), with a mean of 0.03 g/L (CI: 0.0087–0.0513, SD–0.0252, $p<0.01$) and a variance of 0.0006. The findings were suggestive of HAE1 in all the participants individually.

Clinical features during acute attacks included angioedema of the extremities (100%), face (69%), neck (23%) and larynx (8%). Therapeutic strategies for acute attacks included fresh frozen plasma (FFP) or fresh dried plasma (FDP) depending upon the availability of FFP. Danazol was the prophylactic drug of choice despite its potentially deleterious side-effects, including virilisation, which occurred in one of the female participants. These treatment strategies were due to the unavailability of newer agents in this region. HAE1 has had a significant negative impact upon the socio-economic status of the NM family.

Conclusion: HAE1 is a newly identified disorder in the broad spectrum of allergy medicine in KwaZulu-Natal. The diagnosis is simple to confirm, but it requires a high index of suspicion. Therapeutic management still poses a challenge in this region owing to a lack of resources. Genetic counselling is of paramount importance, bearing in mind the nature of the disease (autosomal dominant) and the local practice of polygamy. A support structure such as HAE1 (Hereditary Angioedema International Organization) is highly recommended in raising awareness, improving therapeutic options via international liaisons and alleviating the socio-economic challenges posed by the disease.

Hereditary angioedema (HAE) is a disease characterised by recurrent episodes of angioedema without urticaria or pruritus that lasts for about two to five days. It is caused by a non-histamine, bradykinin-mediated allergic reaction associated with low levels of C1 esterase inhibitor (type 1), or normal levels but dysfunctional C1 esterase inhibitor (type 2), or normal levels and function of C1 esterase inhibitor (C1INH) with a mutation of factor XII of coagulation (type 3) or, lastly, with an unknown genetic or biochemical association (type 4).[1,2]

The South African context of HAE includes 60 cases identified in the Western Cape province by KM Coovadia et al in 2017 over a period of 35 years. These were identified in Cape Town between the Groote Schuur Allergy Clinic and the Allergy Diagnostic and Clinical Research Unit at the University of Cape Town's Lung Institute.[3] Ten years ago, six cases of HAE type 1 (HAE1) were identified by E Moran et al at Hlabisa District Hospital in 'kwaZulu-Natal', the so-called 'NM' family members.[4] This publication is geared towards sharing experiences of HAE1 in KwaZulu-Natal in view of the increasing awareness among medical professionals, affected families and other interested stakeholders.

OBJECTIVES

In 2008, the initial cohort identified in KwaZulu-Natal with clinical and serological manifestations of HAE1 included only six members of the NM family (NM1, NM2, NM3, DM, SS, SM). We have studied the NM family further in order to:

- review the current prevalence of HAE1 among members of the NM family;
- identify common clinical manifestations of HAE1 during attacks;
- compare therapeutic interventions against world standards;
- evaluate the socio-economic burden inflicted by HAE1 on this family.

METHODS

A total of 29 NM family members with possible HAE1 were collectively identified by the family members, and those unable to attend at least one of the three booked Medical Outpatients Department appointments were excluded because during these visits consents were signed, blood tests taken, questionnaires distributed and individual interviews conducted. As a result, the final study sample comprised 13 individuals.

Blood samples for C1INH levels, complement C3 and C4, and C-reactive protein (CRP) were taken to confirm the diagnosis and exclude the possibility of an acute event at the time of obtaining samples. C4 can be lowered by an acute angioedema event; hence CRP samples were taken to exclude such a possibility.[5]

Interviews were conducted and a family tree was drawn up identifying affected individuals in four consecutive generations. Information was gathered concerning the acute clinical presentations during attacks in the past year (2016–2017). A chart review was conducted to identify the prophylactic and acute therapeutic strategies used by doctors in this region. Lastly, a questionnaire was designed to obtain the relevant information regarding HAE1-associated socio-economic burdens.

The questionnaire included the following:

1. How many times have you missed school/work due to an acute flare of HAE1 in the past 12 months? <3 times (1 point), 3–5 times (3 points), >5 times (5 points).
2. Have you repeated a grade at school or been suspended or demoted at work due to absenteeism at school/work secondary to hospital admissions or prolonged HAE1-related illness? YES (3 points), NO (0 points).
3. Have you ever been unable to participate in sports, trips, or any other social activity that has a potential to positively influence your future endeavours, but had to forfeit due to HAE1-related illness? YES (3 points), NO (0 points).

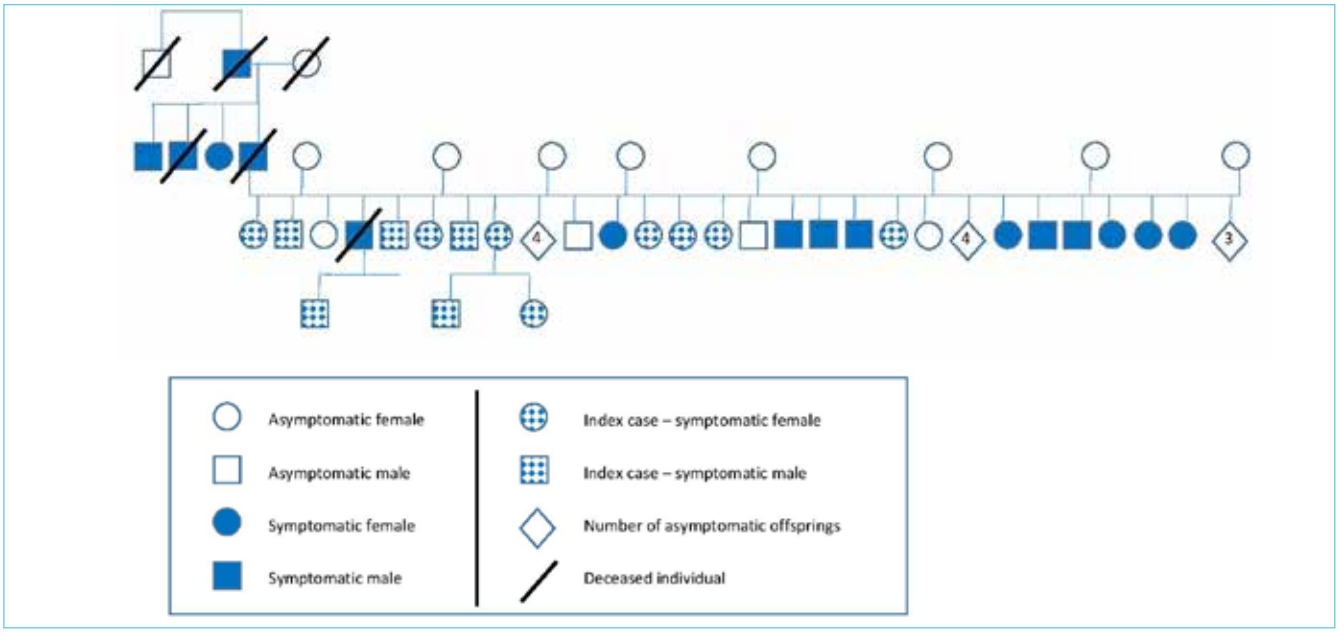

Figure 1: Genealogy of the NM family

TABLE I: CLINICAL AND LABORATORY SCREENING DATA

PATIENT, AGE, GENDER	CLINICAL DATA (2016–2017)	C1INH (21–39 mg/dL)	C3 (0.90–1.80 g/L)	C4 (0.10–0.40 g/L)	CRP (<10 mg/L)
DM1, 28 F	Face and extremities	7.4 L	1.23 N	0.03 L	<1
DM2, 7 M	Face and extremities	5.5 L	1.23 N	0.04 L	<1
DM3, 12 F	Neck and extremities	3.0 L	1.08 N	0.01 L	<1
DM4, 10 F	Face and extremities	5.6 L	1.10 N	0.07 L	<1
DM5, 14 F	Face and extremities	5.7 L	0.85 L	0.03 L	5
DM6, 8 F	Extremities	<2.8 L	1.44 N	0.00 L	Unavailable
DM7, 2 F	Face and extremities	5.0 L	0.82 L	0.03 L	<1
DM8, 6 M	Neck and extremities	Unavailable	1.17 N	0.01 L	<1
DM9, 9 F	Neck and extremities.	4.3 L	1.29 N	0.02 L	1
DM10, 11 M	Face and extremities	4.9 L	Unavailable	0.03 L	<1
DM11, 10 F	Face and extremities	7.8 L	1.32 N	0.01 L	2
DM12, 17 M	Face, extremities and larynx	7.8 L	1.26 N	0.02 L	5
DM13, 22 M	Face and extremities	5.6 L	1.04 N	0.09 L	6

Abbreviations: *C1INH (C1 esterase inhibitor), CRP (C-reactive protein)*

4. Have you ever been discriminated against taking up a position at school (eg prefect, etc) or at work (promotion) due to your background of having HAE1? YES (3 points), NO (0 points).
5. Do you consider your current socio-economic status to have been negatively affected by your illness (HAE1)? YES (3 points), NO (0 points).

RESULTS

Out of 29 NM family members with clinical features suggestive of HAE1, four demised and 12 were lost to follow-up. Thirteen family members were followed up on in this study. Their demographics included ages ranging between two and 28 (mean age 12); eight were females and five males (M:F ratio – 1:1.6); and all the participants were black Africans in ethnicity. The partial genogram of the NM family (see Figure 1) demonstrates a geometric increase in the prevalence of the disease. The factor seen to be responsible is the culture of polygamy.

As per regional laboratory normal value indices (see Table I), the C1INH levels of all the results received were significantly lower than that of the population mean (30 mg/dL), with a mean value of 5.45 mg/dL (CI: 3.97–6.92, SD–1.65, p<0.01) and a variance of 2.71 among family members. Similarly, C4 levels were also significantly lower than that of the population mean (0.25 g/L), with a mean value of 0.03 g/L (CI: 0.0087–0.0513, SD–0.0252, p<0.01) and a variance of 0.0006 among family members. CRP levels were within the normal range.

A history of angioedema in association with decreased levels of C1INH, C4 and normal CRP levels is suggestive of the HAE1 diagnosis. C3 was normal except for one individual, where it was borderline low. Usually, C3 is normal in HAE since it is not affected by low levels of C1INH, unlike C4.[1,6]

The most common symptom during acute attacks was the swelling of the extremities (100%), followed by facial swelling (69%), neck swelling (23%) and, lastly, laryngeal swelling (8%).

TABLE II: ACUTE AND PROPHYLACTIC THERAPEUTIC STRATEGIES (2016–2017)

Emergency therapy	FFP – 3 occasions FDP – 1 occasion (FFP was unavailable) Antihistamines & steroids – 4 occasions cited above Adrenaline – 0
Prophylactic therapy	Danazol – 10 participants Tranexamic acid – 1 participant (features of virilisation while on Danazol) No therapy – 2

TABLE III: QUESTIONNAIRE RESULTS

SOCIO-ECONOMIC BURDEN SECONDARY TO HAE1
(10 participants/5 identical questions each)

QUESTIONS	ANSWERS ON AVERAGE
Question 1 (0–5 points)	3
Question 2 (0–3 points)	2
Question 3 (0–3 points)	1
Question 4 (0–3 points)	1
Question 5 (0–1 point)	1
TOTAL	8/15

Interpretation: Total of 15 points
Category 1 (Mildly affected): <5 points
Category 2 (Moderately affected): 5–10 points
Category 3 (Severely affected): >10 points

There has been no historical report of abdominal and genital manifestations of acute HAE1 in this family.

Symptomatic NM family members are currently receiving Danazol as prophylactic therapy with all its potentially deleterious side-effects such as virilisation, identified in one of the female participants who is currently on Tranexamic acid (see Table II). Choosing this particular therapeutic agent is because of the present unavailability and the cost of novel therapeutic options in South Africa. Acute attacks were mostly managed with FFP or FDP, depending on the availability of FFP, which was the first choice.

Out of the 13 participants, only 10 participated on the questionnaire, because three participants were too young to comprehend some of the questions (see Table III). Five questions were asked, and the answers were rated in a scale of 0 to 5 according to the severity of the response given. The results demonstrated in Table 3 suggest that the socio-economic status of the participants has been affected moderately by the disease.

DISCUSSION

HAE is a fairly new clinical entity in South Africa, having been identified for the first time less than 40 years ago. HAE1 is secondary to a mutation of the SERPIN 1 gene on chromosome 11 (11q12.1); it causes decreased levels of C1INH responsible for the inhibition of various proteases, among which complement proteases such as C1r, C1s, MASP1 and MASP2 are included. The decreased levels of this protease inhibitor lead to a cascade of events that culminate in increased bradykinin that results in angioedema, the herald feature of HAE, with the potential to affect multiple organs.[3,7]

The complete pathophysiology that leads to the release of bradykinin is still unclear, but heat shock protein 90, activated factor XII, and kallikrein are implicated among the initial steps. C1INH is responsible for the regulation of the levels of bradykinin among other functions such as the regulation of the complement classical pathway via the inhibition of C1 complex, which cleaves C4. C1INH deficiency leads to a dysregulation of bradykinin production, with excess bradykinin causing the manifestations of angioedema by increasing vascular permeability, and the exaggerated C4 cleavage by C1 complex as a result of failure to inhibit the C1 complex.[8,9,10]

The clinical presentation of an acute attack of HAE1 typically includes swelling of the face, tongue, larynx, neck, extremities, genitals and intra-abdominal organs. These clinical features are associated with a low C1INH and a low complement C4. In making a diagnosis of HAE1, it is important to note that 25% of HAE1 is due to *de novo* mutations, and that the presence of normal C4 levels does not exclude the diagnosis in approximately 10% of cases; a negative family history and a normal C4 level do not therefore exclude the possibility of HAE1. Genetic testing is not necessary to establish the diagnosis of HAE1. It is also important to differentiate between hereditary and acquired angioedema since some modalities of the latter can be prevented by simply restricting exposure to the trigger factor, as in the case of ACE inhibitors.[1,6]

Success in the management of acute attacks is highly reliant upon early detection and early initiation of treatment, preferably at home.[11] First-line therapies in First World countries include a plasma-derived C1INH concentrate (Cinryze, Berinert),[12] recombinant human C1 inhibitor (Conestat alfa, Rocunest),[13] synthetic bradykinin beta-2 receptor antagonist (Icatibant),[14] and a recombinant plasma kallikrein inhibitor (Ecallantide),[15] among other agents. The use of adrenalin, corticosteroids and antihistamine is not effective during the acute attacks of HAE1. FFP is the alternative of choice in the absence of these novel therapeutic options.[16]

Short- or long-term prophylaxis should be given to all HAE1 patients, since there is a more than 50% chance of developing an acute laryngeal attack in all HAE1 patients at least once in their lifetime, and these episodes can be fatal. Attenuated androgen (Danazol) used to be the drug of choice for prophylaxis, but is neither inexpensive nor convenient due to its long-term side-effects, such as virilisation in females and liver cancer. Tranexamic acid has also been used for long-term prophylaxis.[17,18] Head-to-head studies are still to be done to evaluate and compare the efficacy of Danazol and tranexamic acid.[19] The prophylactic agents used in Europe and America include kallikrein inhibitor,[20] recombinant C1INH.[21]

European studies havendemonstrated HAE to have a significant socio-economic burden upon affected individuals and their immediate families in terms of direct medical costs and indirect costs related to lost productivity.[22,23] This socio-economic burden can only be expected to be exponential in a family that is situated in a rural area of a Third World country such as South Africa, already with a background of socio-economic challenges.

CONCLUSION

HAE1 is a newly identified disorder in KwaZulu-Natal and falls within the broad spectrum of allergy medicine. The diagnosis is simple to confirm but requires a high index of suspicion. Therapeutic management still poses a challenge in this region, mainly due to a lack of resources. Genetic counselling is of paramount importance, bearing in mind the nature of the disease (autosomal dominant) and the local practice of polygamy. A support structure such as HAEi (Hereditary Angioedema International Organization) is highly recommended in raising awareness, improving therapeutic options via international liaisons, and alleviating the socio-economic challenges posed by the disease in this region.

DECLARATION OF CONFLICT OF INTEREST
The authors declare no conflict of interest.

This article has been peer reviewed.

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PID123

Primary Immunodeficiency

ATAXIA TELANGIECTASIA

Emily, a five-year-old girl, was referred by her family practitioner (GP) to the nearby hospital into the care of Dr Goodheart, a paediatrician, for the treatment of severe pneumonia.

Emily's history at the time was as follows: she was born by normal delivery and she has two older half-siblings. The rest of the family are all healthy. Emily was exclusively breastfed until approximately two-and-a-half years of age, when the infections started. Emily did not attend a creche. There were no significant childhood infections in early infancy. The GP, however, informed Dr Goodheart about recurrent otitis media which required grommets, sinusitis episodes and three documented episodes of pneumonia. He had already noted a pronounced hypogammaglobulinaemia.

On clinical examination at initial referral, Dr Goodheart had noted that height and weight were on the 10th centile for age. No dysmorphic or syndromic features were observed. The third set of grommets were still in situ. Crepitations in both lungs were recorded.

A full and differential blood count including platelets, serum immunoglobulins and a sweat test were done. Of note, although IgM levels were normal, IgG and IGA were low, although not absent. All lymphocytes were below reference range, with markedly low B-cell and NK-cell counts.

The differential diagnosis at this stage included various disorders such as Common Variable Immune Deficiency, Ig class-switching syndromes or still undefined hypogammaglobulinaemia.

Dr Goodheart then contacted her friend, the immunology specialist Dr Bala, asking her to guide further investigation.

This included tetanus and pneumococcal vaccine antibodies titres, which turned out to be protective. Lymphocyte stimulation to mitogens was low when compared to a normal control. Dr Bala explained that in a male patient, CD40L expression could have been done, a test for X-linked antibody class-switching defects seen in Hyper IgM Syndrome.

Based on the clinical picture and the laboratory results, Dr Bala suggested a preliminary diagnosis of hypogammaglobulinaemia with low but not absent B cells. For the extremely low IgG levels and the severity and recurrence of infections, Dr Bala recommended that Emily should immediately be started on IgG supplementation with regular follow-ups including monitoring of serum IgG levels and further infection frequency by Dr Goodheart.

During one of the follow-up visits, her mother reported that Emily started to have balance difficulties, which included frequent falling and 'head bobbing'. Emily was therefore referred to a paediatric neurologist for an urgent assessment. The neurologist diagnosed ataxia and requested alpha foetoprotein measurement which turned out to be elevated. This suggested a new diagnosis of ataxia telangiectasia syndrome – without telangiectasia (A-T), which Emily never developed [see BOX].

Emily falls frequently when she is playing

BOX

Ataxia telangiectasia (A-T) is an autosomal recessive disorder caused by mutations in the **ATM** (Ataxia Telangiectasia Mutated) **gene** which encodes the **ATM protein**. The primary role of this protein is the coordination of cellular pathways in response to DNA damage, oxidative stress and other genotoxic stress.

A-T is a complex disorder with **substantial variability** in the severity of features between affected individuals ('classic' to 'mild' forms of A-T). **Clinical features** may include:

- Neurological – Cerebellar ataxia with progressive neurological deterioration
- Radiation sensitivity
- Malignancies – chromosomal abnormalities; predisposition for cancers, particularly of lymphoid origin
- Immunological – since ATM is involved in somatic recombination of immunoglobulins; a/ß chain recombination (T-cell receptors); class switching in B cells; T-cell proliferation and survival – ATM deficiency leads to:
  - low immunoglobulin levels (particularly IgA, IgG subclasses and IgE)
  - lymphopenia (particularly T cells)
  - decreased immune repertoire diversity resulting in:
  - infections – recurrent infections (especially sinopulmonary); may lead to chronic lung disease
  - autoimmune or chronic inflammatory diseases.

DIAGNOSIS

A combination of neurologic clinical features (above) with one or more of the following:

- telangiectasia
- frequent sinopulmonary infections
- specific laboratory abnormalities (eg IgA deficiency, lymphopenia, increased alpha-fetoprotein levels, radio-sensitivity).

Genetic counselling is advised for family members and the patient to confirm a diagnosis. 'Gene panels' are available for testing.

Over time, Emily's neurological features worsened. Apart from balance difficulties, she also developed visual impairment and a speech impediment. This necessitated special schooling.

Her infections, on the other hand, were well controlled on Intravenous immunoglobulin (IVIG) therapy and she gained height and weight normally.

Meanwhile, Dr Bala contacted an overseas laboratory to confirm the diagnosis of A-T. With the technology available at the time, the absence of ATM kinase protein was confirmed by Western Blot. The laboratory also noticed radio-sensitivity in EBV immortalised lymphoblastoid cells.

This confirmed the diagnosis of a variant (ie milder) form of A-T. The differential diagnosis of chromosomal breakage included Nijmegen and Bloom Syndrome, for which Emily had no clinical features.

A-T leads to chromosomal abnormalities

Emily is now permanently confined to a wheelchair as there is still no treatment for the neurological decline, but she remains infection-free on IVIG treatment. All X-rays and radioactive exposures are limited in her follow-up because of her radiosensitivity.

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VARIABLE EXPRESSION IN SAMHD1-ASSOCIATED FAMILIAL AICARDI-GOUTIÈRES SYNDROME

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ABSTRACT

Aicardi-Goutières syndrome (AGS) is an encephalopathy of early childhood. This disorder is genetically heterogeneous, with mutations in seven genes having been identified to be disease-causing. Most patients with AGS present with poor developmental outcome and reduced survival in the neonatal period or early infancy. Significant variability can be found in the onset and phenotypic severity of the condition, sometimes even within the same family. Here we describe two sisters of mixed ancestry from the Western Cape province of South Africa presenting with skin manifestations of autoimmune disease resembling those of systemic lupus erythematosus (SLE) on histology but with negative serology. The two affected individuals carried a homozygous c.1681_1682delAG; p. Ser561Phefs*61 mutation in exon 15 of *SAMHD1* on chromosome 20. Both parents and the unaffected brother are heterozygous for this variant. The molecular investigation yielded a unifying diagnosis for an unusual combination of physical findings and differential phenotypic expression in the sisters. A confirmed diagnosis allowed for informed genetic counselling and targeted investigation and screening for complications such as glaucoma in the older sister.

Keywords: Aicardi-Goutières syndrome; intra-familial variability; *SAMHD1*; South Africa

INTRODUCTION

Aicardi-Goutières syndrome (AGS) is a Mendelian, autosomal recessive, neuro-inflammatory disorder that typically manifests in infancy, and is associated with severe developmental consequences.[1] Later onset and milder forms of the disease are also recognised. AGS encephalopathy is characterised by chronic cerebrospinal fluid (CSF) lymphocytosis, calcification of the basal ganglia, abnormalities of the white matter and cerebral atrophy.[2] There is an increased risk of early childhood death, and clinical manifestations include psychomotor retardation, dystonia, spasticity and microcephaly.[3] The combination of intra-cranial calcification, spasticity and microcephaly means that AGS may be mistaken clinically for congenital infection with cytomegalovirus or toxoplasmosis. AGS is genetically heterogeneous and mutations in seven genes, namely *TREX1*,[4] the three nonallelic components of the RNase H2 endonuclease complex (*RNASEH2B*, *RNASEH2C*, and *RNASEH2A*),[5] the deoxynucleoside triphosphate triphosphohydrolase *SAMHD1*,[6] the adenosine deaminase-1 *ADAR1*,[7] and the cytosolic dsRNA sensor *MDA5*[8] have been associated with the disease.

Mutations in *SAMHD1* are postulated to lead to the accumulation of nucleic acids in cells, mirroring a viral infection and subsequently leading to immune system activation.[6] This

activation of the immune system is considered to be the cause of the enhanced production of interferon-alpha (IFN-α) in the serum and CSF of AGS patients, which is considered a hallmark of the disease.[9] It is well documented that IFN-α levels are higher in the CSF than in the serum, thus indicating intrathecal production,[9,10] and astrocytes have been identified as a source of IFN-α and IFN-driven cytokines such as CXCL10.[10,11] AGS patients can also demonstrate elevated CSF levels of FMS-related tyrosine kinase 3 ligand, IL-12p40, IL-15, TNF-α and soluble IL-2 receptor.[12] It has been noted that most cytokines in the CSF decrease with age, but CXCL10 levels are continuously increased beyond early childhood.[12] Similar observations have been described for IFN-stimulated genes (ISGs) such as *IFI27*, *IFI44L*, *IFIT1*, *ISG15*, *RSAD2* and *SIGLEC1,*[13] with the presence of an 'interferon signature' representing a highly reliable disease biomarker. Here we describe two sisters of mixed racial ancestry from the Western Cape, South Africa, presenting to the Paediatric Rheumatology Clinic at Tygerberg Hospital. Subsequent molecular investigation established a diagnosis and allowed for appropriate screening for complications.

MATERIALS AND METHODS

The study was approved by the Health Research Ethics Committee of Stellenbosch University (study no N13/05/075). The parents granted their informed consent, which included the genetic evaluation of the siblings. The study adhered to the ethical guidelines as set out in the 'Declaration of Helsinki, 2013'.[14] Venous blood required for DNA extraction was drawn from both patients (1 mL), an unaffected brother and both parents (5 mL). DNA was purified from blood using the Nucleon BACC3 Kit (Amersham Biosciences, Buckinghamshire, UK).

PATIENT 1

The index patient was born at term to non-consanguineous parents. She presented at age three years with dysmorphic but not distinctive features of a syndrome, a history of idiopathic infantile hemiplegia, complex partial seizures in infancy and delayed milestones. Imaging of the brain was consistent with moyamoya disease (see Figure 1). At four years of age she was referred to the Dermatology and the Paediatric Rheumatology Services with interface dermatitis, vasculitic lesions on her ears and fingertips with threatened gangrene and recent onset of deteriorating gait. On examination, she had generalised signs of hypertonicity and global developmental delay and was unable to walk as a result of ankle contractures. She tested negative for human immune deficiency (HIV) disease, antinuclear antibody (ANA), anti-SM antibody and anti-double-stranded DNA (dsDNA) antibody, but tested positive for anti-beta2 glycoprotein 1 antibody. Treatment was started with Chloroquine, Azathioprine and Nifedipine to control extensive vasculitic and necrotic lesions of the extremities and sodium valproate was continued for seizure control. As a result of a poor response to treatment, and the finding of positive antiphospholipid antibody (anti-beta2 glycoprotein), she was anti-coagulated with Warfarin, which was associated with an improvement of her gait. However, she again deteriorated at age nine years and presented as unable to walk, with draining

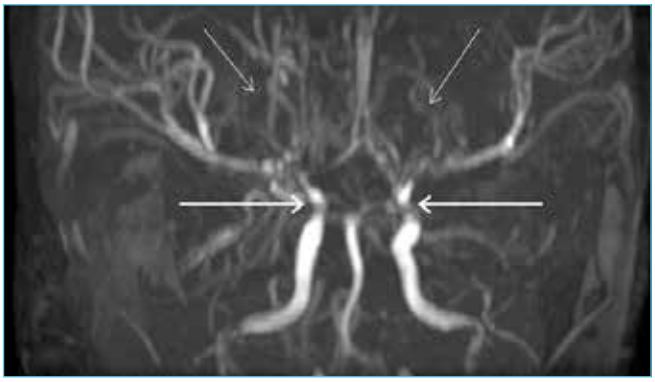

Figure 1: Three-dimensional time of flight (TOF) reconstruction demonstrating narrowed distal internal carotid arteries (ICA) bilaterally (thick white arrows) and lenticulo-striate collaterals (thin white arrows).

lesions of the spine as a presentation of extrapulmonary tuberculosis (TB). Multidrug-resistant tuberculosis (MDR TB) and *Staphylococcus aureus* were isolated from swabs of pus drained from the incision and drainage of lesions of the spine. Chest X-ray and sputa, including examination by GeneXpert, remained negative for TB. The patient responded well to MDR TB and antibacterial treatment, regaining the ability to walk. She is currently maintained on isoniazid prophylaxis and Warfarin.

PATIENT 2

The older sister of the index patient was brought to the attention of the Paediatric Rheumatology Clinic by her mother at age 14 years. She had a longstanding history of Raynaud's phenomenon, vasculitic skin lesions of the nose and auricles similar to her sister's and threatened gangrene of the fingertips on presentation. She was severely stunted, with a weight of 30.5 kg (less than the third centile for age) and height of 128.3 cm (less than the third centile for age), with delayed puberty, a feature not typically described in AGS. Her intellectual development appeared delayed but was not formally assessed. As in the case of her sister, a skin biopsy showed perivascular-interface dermatitis. On investigation she was HIV-negative and screening for autoimmune diseases, including SLE or antiphospholipid syndrome, was negative. She was diagnosed with glaucoma, a recognised feature of AGS. Further imaging for suspected orbital vascular malformations was refused by this patient She subsequently developed progressive contractures of her distal interphalangeal joints without bone resorption on X-ray. She responded well to Nifedipine, Chloroquine and low-dose Aspirin. TB prophylaxis with isoniazid was initiated in view of her sister's status. The presence of two similarly affected siblings suggested the possibility of a genetic disorder, and at this stage AGS was suspected.

Prompted by similar case descriptions, oligonucleotide primers were designed to polymerase chain reaction (PCR)-amplify the exons of *SAMHD1*. Purified PCR amplification products were sequenced using BigDye terminator chemistry and an ABI 3130 DNA Sequencer.[6] Mutation description is based on the reference cDNA sequence NM_015474. A 303-base pair fragment containing the candidate variant was polymerase chain reaction (PCR)-amplified from genomic DNA from the patients,

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Figure 2: Vasculitic skin lesions

an unaffected brother and both parents using the following primers: *SAMHD1*-F- 5'-AGTTAGGAGCCTAGGGACCAG-3' and *SAMHD1*-R- 5'-TGGGAACTTTTCAGCAGATAGAC-3'. Each amplicon was bi-directionally sequenced using the BigDye® Terminator v3.1 Cycle Sequencing Kit (Perkin-Elmer, Applied Biosystems Inc, Foster City, California, USA), followed by electrophoresis on an ABI 3130XL Genetic Analyzer (Perkin-Elmer, Applied Biosystems Inc, Foster City, California, USA). All the automated DNA-sequencing reactions were performed at the Central Analytical Facility (CAF) at Stellenbosch University, Stellenbosch, South Africa. Following the positive identification of the variant in the affected family, a total of 322 ethnically matched controls were screened for the variant.

RESULTS

A homozygous single base pair deletion (c.1681_1682delAG; p. Ser561Phefs*61) was identified in exon 15 of *SAMHD1* in both affected siblings. The details of the variant are summarised in Table I. The variant leads to a frameshift, resulting in a premature stop codon 61 base pairs downstream, and *in silico* predictions of the variant (SIFT and Polyphen2) indicated that this variant is probably damaging (see Table I). The deletion was found in the heterozygous state in both parents and an unaffected brother (see Figure 3). The variant was absent from all 322 ethnically matched controls that were screened.

TABLE I: DETAILS OF THE CANDIDATE VARIANT IDENTIFIED IN EXON 15 OF *SAMHD1*

Chromosome	Chr 20
Position	35526290
Gene name	*SAMHD1*
RefSeq	NM_05474
Reference sequence	A
Mutation type	Frameshift
Mutation: DNA (HGVS nomenclature _c)	1681_1682del
Mutation: protein (HGVS nomenclature _p)	Ser 561Phe fs*61
Prediction <SIFT	Damaging
Prediction <PolyPhen-2	Probably damaging
Sanger verification	Yes

DISCUSSION

AGS is a rare genetic disorder in which mutations in seven genes have been associated with the autoinflammatory phenotype.[5,13,15] Here we identified a novel variant (c.1681_1682del p. Ser 561Phe fs*61) in *SAMHD1* in two sisters. Moreover, we documented marked intra-familial phenotypic variability associated with the same homozygous variant, where the index patient presented with early onset features of AGS, while her older sister presented incidentally with features of the disease that had not been recognised earlier. Certain genes that are mutated in AGS, namely *TREX1*, *SAMHD1* and *RNASEH2*, encode proteins that function as cellular nucleases,[13,15,16] mutations in which are hypothesised to result in a failure of cellular processing of endogenous nucleic acids and the subsequent induction of type I IFN-driven immune activation.[7] Mutations in *SAMHD1* have been associated with different forms of the AGS clinical phenotype, with later onset, increased survival and better intellectual preservation.[3,17,18] It has been suggested that *SAMHD1* might have a specific role in cerebral vascular homeostasis and blood-vessel integrity.[19,20,21] The marked phenotypic variability seen in this family may be as a result of the effect of environmental or genetic modifiers, which might be explained by cell-specific IFN-stimulated gene and cytokine responses.[10]

Mapping of the breadth of presentation and features of AGS raises the possibility that the disease may go undiagnosed in patients with a later onset or a milder course, or in those individuals who present with non-specific inflammatory features.[22] The genetic diagnosis of AGS related to *SAMHD1* mutations is important for affected families due to the 25% recurrence risk. Genetic counselling is essential for the family on prognosis, intra-familial variability, recurrence risks and risks for other family members. Careful clinical monitoring is indicated to evaluate for the presence or evolution of complications, including glaucoma or endocrine dysfunctions such as insulin-dependent diabetes mellitus (IDDM) or hypothyroidism. The observation of such intra-familial differences is highlighted in the family presented

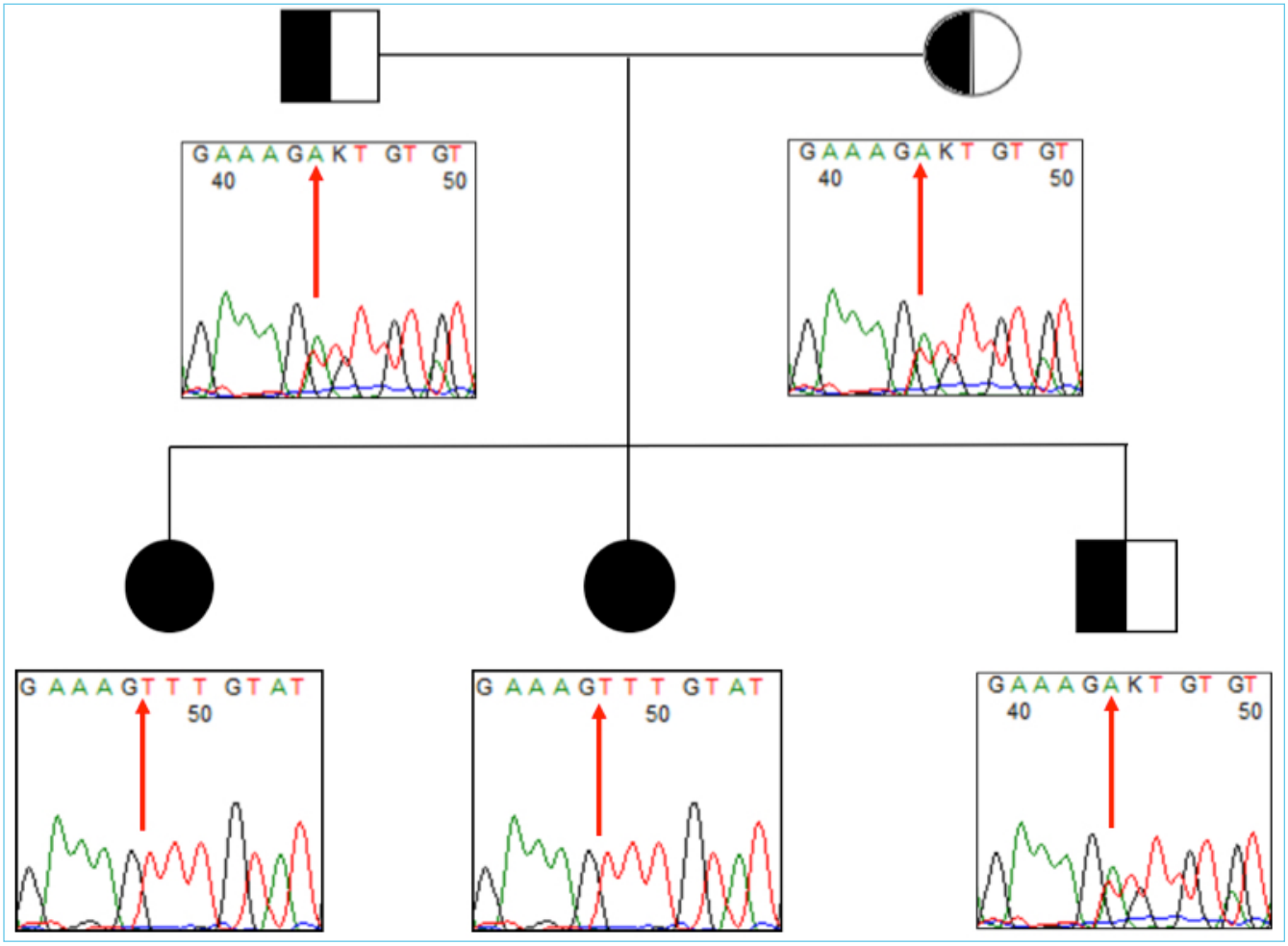

Figure 3: Sanger sequencing of Exon 15 of SAMHD1. Pedigree and sequence chromatograms of affected family. (The red arrow indicates the position of AG deletion.)

here, with an expanding range of clinical phenotypes being reported in this innate immune defect and other primary immune deficits. Whether patients with the *SAMHD1* mutation are also more susceptible to TB, as observed in our index patient, or whether carriers may be at increased risk for autoimmune disease, remains to be investigated on follow-up.

CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

This article has been peer reviewed.

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CONGRESS REPORT

The 27th Annual ALLSA Congress was held in Cape Town from 29th August to 2nd September, at the popular Century City Conference Centre. This year ALLSA joined forces with SAPA, and it was a privilege to work together with our paediatric colleagues from Tygerberg Hospital to give you a programme filled with topics that appealed to all.

A big thank you to all of the trade exhibitors. The stands looked fantastic, and between the coffee and chocolates we were also treated to useful information by knowledgeable representatives.

Professor Robin Green gave a superb opening lecture tying allergy to PID. ALLSA and PIDSSA had speakers at all of the combined plenaries, as well as focussed in-congress workshops.

The Gala dinner was generously sponsored by Cipla, and was an evening to remember, with superb food from Around the World. The venue and entertainment were incredible and great fun was had by all. Thanks Cipla!

We have included just a few photographs of this most enjoyable event, but you may view the rest on our website. See you all next year in Pretoria.






















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