

"The management of severe psoriasis has been transformed in the last 10 years. Atopic eczema is a chronic, disabling and for some a lifelong condition.

Is the management of severe atopic eczema about to be transformed in a similar way?"

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## ‘Tis but a scratch:

Discussing the future of eczema treatment in the wake of a psoriasis revolution

Psoriasis and eczema are both common chronic dermatological conditions in New Zealand. The treatment of these two conditions, however, are vastly different. Over the past 10 years, research breakthroughs in psoriasis have given doctors more targeted and effective treatment, and psoriasis sufferers hope in the face of a long-term condition. Those suffering from eczema seem to have not yet been afforded the same treatment revolution. Could our future eczema patients soon see a transformation in their treatment and their symptom load? Through an understanding of the pathophysiology of each disease, alongside the remarkable revolution of biologics in psoriasis treatment, those with eczema may yet soon see an era where their chronic disease is “but a scratch” in their lives.

Eczema and psoriasis are common dermatological conditions in New Zealand. Eczema, also known as atopic dermatitis, is more common and has a high incidence in children, with around 15% of children under 5 experiencing symptoms (Dermnet NZ, 2004). Psoriasis in its many forms is also common, with an estimated 3% of adults in New Zealand experiencing symptoms (bpac NZ, 2017). The impact of dermatological disorders on patients can be huge, and their quality of life can suffer immensely. Rashes are often seen as unsightly and patients can experience psychological distress. Eczema in particular can be very itchy, a source of great anguish for those who suffer from it (Cather and Young, 2017). In medical school, our exposure to the medical specialties is fleeting and for Dermatology, my clinical introduction was in the form of two morning clinics. During these clinics, I met many of the New Zealanders suffering from psoriasis and eczema and I experienced first-hand the disparity between the two populations. Patients with severe psoriasis seemed to be given a smorgasbord of effective targeted treatments such as tablets, injections and light therapy. Equivalent eczema patients sat in itchy incredulosity as they were offered treatments with less certain efficacy.

Why is psoriasis easier to treat than eczema? The answer begins at the pathophysiology. While a comprehensive understanding of both diseases has yet to be fully elucidated, research has shown some key differences. Psoriasis is fundamentally an autoimmune disorder, with leukocytes, dendritic cells, neutrophils and cytokines identified as key immunological players interacting with the skin to cause inflammation (Blauvelt et al, 2019). Accordingly, psoriasis is associated with the immunological HLA-Cw6 gene and appears alongside other autoimmune

diseases such as psoriatic arthritis (Blauvelt et al., 2019). Eczema on the other hand is seen as a disorder of the skin as a barrier. Filaggrin, a protein produced by keratinocytes, is an important part of the skin's natural moisturiser and its deficiency is implicated in the pathogenesis of eczema (Weston et al., 2019). Eczema commonly occurs in patients with other atopic conditions such as asthma and hay fever, where there is abnormal IgE production post-allergen exposure. This gives another clue to its pathogenesis (Weston et al., 2019). Other important players in eczema include abnormal T helper cell responses and the release of inappropriate inflammatory molecules (Weston et al., 2019). In essence, psoriasis is thought to be an overreactive immune response against the skin, whereas eczema is thought to be a disordered barrier aided and abetted by abnormal immune responses to allergens.

The remarkable revolution of psoriasis treatment may give us clues on how to best revolutionise eczema treatment, too. Van Voorhees and Weinberg (2017) summarise the history of psoriasis treatment. The 1950s heralded an exciting era for dermatology with the introduction of synthesized hydrocortisone cream. In the 1970s, anti-folate agent methotrexate was found to reduce psoriasis in patients taking the medication for their rheumatoid arthritis. PUVA (psoralens and UVA) was found to be effective against psoriasis in the 1970s, and UVB treatment a safer alternative in the 1980s. Vitamin D, retinoids, and ciclosporins were all accepted as psoriasis treatments by the end of the 20th century (Van Voorhees and Weinberg, 2017). However, the era of biologics has been the real revolution. In the past 10 years, systemic biologics such as adalimumab, etanercept, infliximab and secukinumab have been shown to dampen an overactive immune system and suppress symptoms of psoriasis (Florek and Gordon, 2017). As a consequence, these four medications have been subsidised under special authority through New Zealand's pharmaceutical funding agency, PHARMAC (PHARMAC, 2018). While a small portion of patients do not respond, experience adverse effects, or find their response weakens over time, most patients find biologics a safe and effective drug to manage their psoriasis (Florek and Gordon, 2017).

The current eczema treatment guidelines are evidence of the comparative lack of pharmaceutical options available for patients. First-line therapy for mild to very severe eczema is emollients to moisturise and reinforce the skin barrier, and steroid creams to reduce inflammation (Giam et al., 2016). Topical calcineurin inhibitors can improve mild to moderate eczema without the same side effects as steroids (Solman et al., 2019). However, this medication is not subsidised by PHARMAC (PHARMAC, 2019). If these medications are not

effective, some oral medications are approved for eczema. First-line oral therapy are cyclosporines, followed by azathioprine. After this, Hajar, Hill and Simpson (2017) assert that other medications commonly used for psoriasis are not indicated in the literature as safe and efficacious treatment for eczema. The use of methotrexate is common in practice, but not officially endorsed. Short-term oral steroid courses have been used, but in fact may potentiate an eczema flare later on (Hajar et al., 2017). UVB treatment can also be effective for eczema sufferers (Hajar et al., 2017). There is no biologic in New Zealand funded for the treatment of eczema (PHARMAC, 2019).

Why have biologics not had the same revolutionary effect for eczema? The pathophysiology of eczema gives us a clue. The biologics funded for plaque psoriasis in New Zealand, according to bpac NZ (2013) and PHARMAC (2018), are etanercept, infliximab, adalimumab and secukinumab. All three work by reducing the inflammatory protein Tumour Necrosis Factor alpha (TNF $\alpha$ ), thereby reducing harmful inflammation and tissue destruction in the skin. Biologics work well for plaque psoriasis, where the main postulated mechanism of action is autoimmunity. Eczema is thought to be borne from the interactions of an imperfect skin barrier, inappropriate IgE and T helper cell activity, and environmental antigens. When TNF $\alpha$  antagonists are used in those with eczema, patients in the literature have had a poor response or sometimes worsening of their eczema (Hajar et al., 2017).

The field of biologics is exploding, and many novel biologics have been developed in recent years. Similarly to how psoriasis treatment followed the treatment of other pathologically similar conditions, some new eczema medications were modelled after existing treatments for other diseases. Omalizumab reduces the activity of IgE and is funded in the United States of America for severe asthma in children (Hajar et al., 2017). Rituximab binds to the CD40 receptor on B cells, reducing their frequency in the lymphocyte population. It is already a treatment for other dermatological treatments such as bullous pemphigoid (Hajar et al., 2017). Unfortunately, omalizumab failed to show efficacy in randomised controlled trials and rituximab's small body of literature is not promising (Hajar et al., 2017).

One new biologic, however, has sparked interest in the search for an effective eczema treatment. Hajar et al. (2017) two years ago observed that eczema researchers had begun to look for specific immunological targets present in eczema, to exciting results. There are many biologics targeting interleukin proteins such as dupilumab, which reduces the inflammatory cytokines

IL-4 and IL-13. Blocking these cytokines reduces T helper cell activity, and reduces inflammation (Hajar et al., 2017). Dupilumab has performed well in randomised controlled trials and the adverse effects were similar in both the placebo and treatment groups (Gooderham et al., 2018). A systematic review published in 2018 evaluated six randomised controlled trials and confirmed that dupilumab was a safe biologic that significantly improved eczema symptoms and quality of life (Wang et al., 2018). Dupilumab has been accepted for use in patients with moderate to severe eczema by the Food and Drug Administration of the United States, Therapeutic Goods Administration of Australia, and MedSafe in New Zealand (Dermnet NZ, 2017). However, it has not been funded by PHARMAC and is not readily available for New Zealand consumers (PHARMAC, 2019).

There is hope that the breakthrough efficacy of dupilumab will usher in a new era of biologic medication for eczema, just like etanercept and infliximab for psoriasis in the mid-2000s (Hajar et al., 2019; Van Voorhees and Weinberg, 2017). The most promising sign of this change is the research effort around new eczema treatments. Solman et al. (2019) periodically publish a review of the literature around eczema treatments and noted that each year more and more systematic reviews are published on novel treatments and new regimes. Each biologic medication like dupilumab that has found success is one of hundreds of medications devised and tested by pharmaceutical companies. In addition, many biologics can target the same inflammatory cascade in different ways. For example, etanercept, infliximab and adalimumab all target the TNF $\alpha$  molecule. It is conceivable that at this moment, alternative IL-4 and IL-13 blockers are being developed. Finally, as technology advances, more insights can be gained into the multifactorial pathophysiology of eczema and possible targets for treatment.

There are a few important cautions to this hopeful transformation. Many of the medications discussed above have failed to revolutionise eczema treatment because of their limited overall efficacy and their side effect profile. The perfect eczema medication, which is easy to use, fast-acting, long-lasting, effective and safe for the patient, has not yet been uncovered. All medications have side effects, and medications such as biologics that interfere with the immune system can be devastating. A pertinent example is Efalizumab, which inhibited T cells. While it was effective in preventing eczema flares, it also caused serious and highly unusual infections in patients and has since been taken off the market (Hajar et al., 2017). In addition, New Zealand is unlikely to be on the forefront of novel eczema treatments. The national funding body for medications, PHARMAC, has recently been in the media once again for its slow

uptake of cutting-edge treatments (RNZ, 2019). It is likely revolutionary eczema medication like dupilumab will be commonly used elsewhere in the world for years before New Zealanders will have access.

In the past decade psoriasis has experienced a treatment revolution, much to the delight and relief of patients and dermatologists alike. The same cannot be said about those suffering from a similarly common condition, eczema. The multifactorial pathophysiology of eczema means it has been difficult to find equivalent medication for eczema management with the appropriate efficacy and safety. However, pharmacological lessons learned from the psoriasis revolution have gone on to contribute to novel treatments currently showing promise, and more research than ever is underway looking at eczema treatment. I hope that in 10 years from now, I will be able to explain to medical students the stories of the psoriasis and eczema treatment revolutions.

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