Biologics

New therapy for atopic dermatitis

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The recent TGA approval of dupilumab, a biologic therapy aimed at targeting specific immune markers, provides new hope in the treatment of adults with moderate-to-severe atopic dermatitis.

Atopic dermatitis (AD) can be burdensome to the individual and the healthcare system.[1] Although 30% of the population are susceptible to AD, of this cohort less than 1% have severe AD. However, the condition is chronic and relapsing and can be debilitating.[2] In various forms of severity (i.e. mild, moderate or severe), AD can greatly affect daily function and activities, carrying with it the burden of symptoms such as itch and pain (especially if superimposed infection occurs), which subsequently adversely affect quality of life, with negative psychological impact.[3] There is a wide spectrum of clinical presentations and combinations of symptoms in AD. Figures 1 to 3 illustrate severe AD. GPs are often at the forefront of managing AD in the community, with dermatology expertise required for severe and refractory disease.

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Pathophysiology

AD is influenced by a complex interplay between immunoglobulin E (IgE) mediated sensitisation, the immune system and environmental factors. Epithelial barrier dysfunction involving filaggrin gene defects could be a consequence of both genetic mutations and local inflammation.[3-6] Four cells play a key role in its physiopathology:

- dendritic cells
- T-helper cells
- activated eosinophils
- keratinocytes.[7]

First, dendritic cells polarise T cells, which results in IgE mediation and non-IgE mediated sensitisation.[8] This then stimulates T-helper 2 (Th2) cells to release pro-inflammatory cytokines interleukin (IL) 4, IL-5 and IL-13. The next category of cells, T-helper cells, consists of T-helper 1 (Th1) and Th2 cells. Th1 cells secrete cytokines in acute, exudative lesions, whereas Th2 cells secrete interferon gamma in chronic lesions.[9] The third group of cells are the activated eosinophils, which play a role in local inflammation. The fourth group are keratinocytes, which express high levels of Th2 polarising cytokine (thymic stromal lymphopoeitin), which amplify or sustain the allergic response.[10-12] A greater understanding of this underlying immune pathway has paved the way for new research into, and treatments for, AD.

Current treatment

Current treatment revolves around topical therapies and, less commonly, systemic therapies. Topical therapies involve emollients, topical corticosteroids of varying potencies and topical calcineurin inhibitors such as pimecrolimus and tacrolimus.[13]

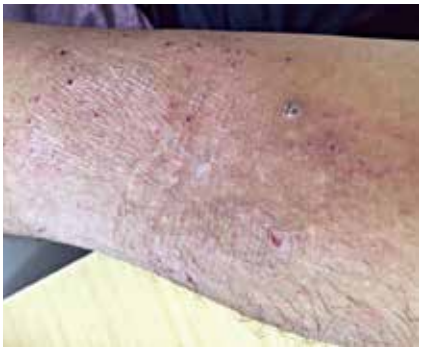

Figure 1. Flexural atopic dermatitis.

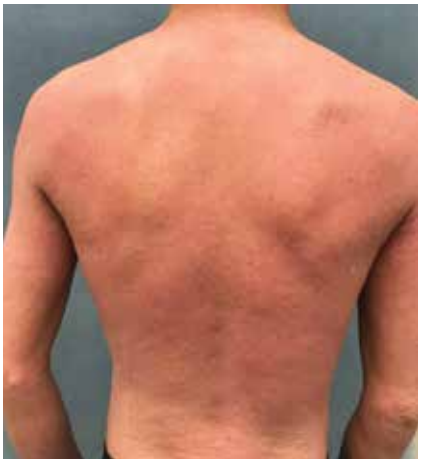

Figure 2. Widespread atopic dermatitis involving on back and arms.

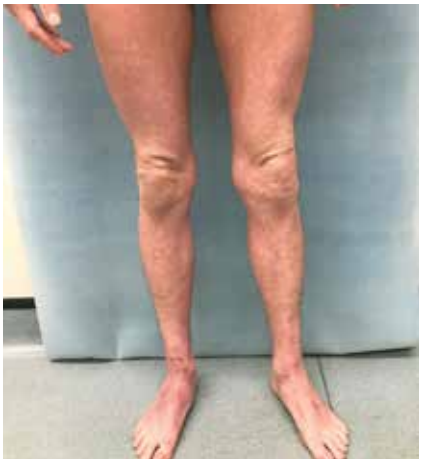

Figure 3. Widespread atopic dermatitis involving lower limbs.

Phototherapy may also be effective in a number of patients, but this requires regular treatment and is therefore time consuming to the patient. Some patients require hospital admissions for wet dressings, and this is a significant burden on both the patient and the healthcare system.

Systemic treatment options include immunosuppressants (cyclosporin has been the mainstay of treatment for many years), along with the off-label use of methotrexate, azathioprine and mycophenolate. Systemic glucocorticoids are occasionally utilised in acute exacerbations but rarely have a place in the long-term management of patients with AD.

For many years the treatments outlined above have remained the only options available for the management of patients with AD. However, the scope of treatment is now expanding with the addition of targeted biologic therapies.

Biologic therapy for atopic dermatitis

In recent times, biologics have been investigated as a potentially safer and more effective alternative to current treatment therapies. This type of therapy is focused on trying to control T-helper response through the blockade of IL-4, IL-13 and IL-31 targets.

What are some of the benefits of biologic therapy? Many patients struggle with the strict regimen required with topical treatments, which necessitates correct technique and frequent application. This can impact patient compliance and have a detrimental effect on quality of life. In addition, some patients are unnecessarily worried about the use of topical corticosteroids – referred to as 'steroid phobia' – and may refuse treatment.[14-16] Biologics may offer a favourable alternative to these arduous and continuing treatments. Their safety and efficacy have been shown in clinical trials, and it is expected they may also offer a favourable cost-benefit ratio given the severity of refractory disease and use of resources, including hospitalisations.[17]

Dupilumab, a fully human anti-interleukin-4 receptor (anti-IL-4) alpha monoclonal antibody that inhibits both IL-4 and IL-13 signalling, has been extensively studied in clinical trials with promising results and is now TGA approved for use in Australia.[18] Dupilumab is already approved for use and available in the US and Europe for the treatment of moderate-to-severe AD in adults, and was recently approved for use in Japan.

Dupilumab trials

With the forthcoming release of dupilumab for the treatment of moderate-to-severe AD in adults, we may be entering an exciting new era in the treatment of AD. Promising trials included three randomised, double-blinded, placebo-controlled phase III trials: SOLO 1 and SOLO 2, followed by LIBERTY AD CHRONOS. The SOLO 1 and SOLO 2 trials were both 16-week monotherapy trials where patients either received dupilumab or placebo weekly, or dupilumab every other week (alternating with placebo). The LIBERTY AD CHRONOS trial was subsequently conducted as a 52-week trial where patients either received dupilumab weekly or every other week, or placebo weekly. The trials involved the use of concomitant topical corticosteroids and regular moisturiser. In all three trials, dupilumab was found to be superior to placebo.[18-20] Furthermore, dupilumab has been shown to improve quality of life in adult patients.[19,21]

Dupilumab therapy and precautions

The recommended dose of dupilumab is 300 mg subcutaneously every fortnight, following an initial dose of 600 mg.[19] It is not designed for episodic use. The following adverse reactions were observed in clinical trials (in order of most frequent): injection site reaction, conjunctivitis, blepharitis, oral herpes, keratitis, eye pruritis, other herpes simplex infection and dry eyes.[19] The safety and efficacy of

FIGURES 1 TO 3 © ASSOCIATE PROFESSOR SHUMACK

dupilumab has not been established in asthma, despite trials investigating this, therefore patients with comorbid asthma should not discontinue their regular asthma treatments without consultation. Similarly, patients with parasitic infections were excluded from trials, hence the effect of dupilumab on the immune system is unknown. In terms of drug interactions, live vaccines should be avoided, and interactions with CYP450 substrates must be considered. The use of dupilumab in pregnant and breastfeeding women has not been studied.

Other targeted biologic therapies

In addition to the success of dupilumab trials, targeted biologic therapies aimed at blocking other parts of the immune process in AD are being investigated. These include the anti-IL inhibitors, janus kinase (JAK) enzyme inhibitors and phosphodiesterase (PDE4) inhibitors.

Tralokinumab, an anti-IL-13 antibody, is being investigated in a phase III monotherapy clinical trial in patients with moderate-to-severe AD. Lebrikizumab, an anti-IL-13 antibody, is being investigated in a phase II clinical trial. Nemolizumab, an IL-31 antibody, is being investigated in another phase II clinical trial, which has shown improvement in itch. ABT-494, a JAK enzyme inhibitor, is being studied in a phase IIb clinical trial. The outcomes of other clinical trials have been variable.[20]

Conclusion

Biologics could revolutionise the treatment of moderate-to-severe AD in adults and benefit maintenance therapy regimens, leading to improved quality of life. Results have been promising in previous research and in countries where it is approved and available for use. It is hopeful that this trend will continue in Australia now that dupilumab has been granted TGA approval. Its use is aimed to be an adjunct to current standard therapies including emollients and topical corticosteroids, not as a sole replacement. Information dissemination will assist the role of the GP with awareness and an appreciation of dupilumab introduction in a select population of patients. Although the specific PBS criteria are yet to be determined, it will likely require specialist approval. It will be important for the wider medical community to be aware of potential associated adverse events. The future may look towards paediatric and adolescent extension of biologic research and treatment options. MT

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