BIOLOGIC TREATMENTS
FOR ATOPIC ECZEMA
Anti-IL-4 and IL-13 biologics

Professor Mike Cork and the team from Sheffield Dermatology Research update us on new biologic treatments for atopic eczema and explain where these will fit into existing treatment options.

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Current treatment options

For children and adults who fail to respond to the first three steps of treatment (see below) for atopic eczema (atopic dermatitis), the current next options are phototherapy or immunosuppressive drugs, including cyclosporin, methotrexate, azathioprine and mycophenolate.[1]

Topical treatment, education, identifying and avoiding trigger factors

The first three steps of treatment for atopic eczema are:

Step 1 Emollients of appropriate formulation, the avoidance of all harsh soap and detergents (replacing them with emollient wash products) and intensive education.

Step 2 Identification of irritant and allergic triggers, and establishment of avoidance regimens with intensive education.

Step 3 Treatment and prevention of flares of atopic eczema with topical corticosteroids (TCS) and topical calcineurin inhibitors (TCI), along with intensive education.

The key to successful management of atopic eczema is education about every aspect of the causes and treatments of atopic eczema.[1] In addition to education, the other major area that is essential for the effective management of atopic eczema is the identification of allergic triggers.

If atopic eczema is not controlled with steps 1, 2 and 3 (as above) it is essential to work out why it is not controlled and to improve control of the atopic eczema, for several reasons:

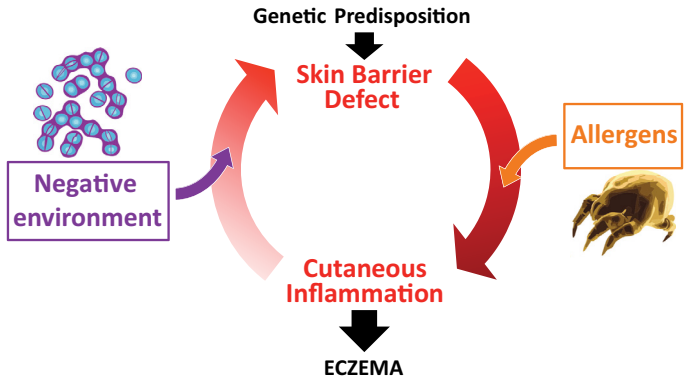
- If atopic eczema is left uncontrolled, it is likely to become progressively worse, as changes in the immune system lead to vicious cycles that increase inflammation and damage the skin barrier (**Fig. 1**).
- Uncontrolled atopic eczema can lead to the development of other related diseases, including allergies, asthma and hay fever. This is called the 'atopic march'.
- If atopic eczema is left uncontrolled for many years, the damage to the skin may lead to the body's immune system viewing the skin as foreign tissue. This can lead to the immune system attacking the skin and an autoimmune reaction developing.[2] That can lead to the atopic eczema becoming even worse.
- If atopic eczema is left uncontrolled, it can lead to depression that is not just due to the devastating effects atopic eczema can have on the person's life. There is recent evidence that inflammation in the skin in atopic eczema can also have direct effects on the brain, leading to depression.[3]

It is therefore essential to determine, in any individual, why steps 1, 2 and 3 have not led to effective control of the atopic eczema.

Phototherapy and current systemic immunosuppressants

In some cases, the atopic eczema is so severe that it will never respond to topical treatments, however much is used. In this situation, it is important to move either to phototherapy or to a current immunosuppressive drug – cyclosporin, methotrexate, azathioprine or mycophenolate – in order to attempt to control the atopic eczema. Phototherapy can be used prior to systemic therapy but, if this fails or there is rapid recurrence of uncontrolled atopic eczema, there is then a need to move to the systemic drugs.

FIGURE 1



Atopic eczema (atopic dermatitis) arises as a result of gene–environment interactions that lead to breakdown of the skin barrier. Allergens then penetrate through this defective skin barrier and this leads to inflammation. Inflammation then directly causes further damage to the skin barrier and so a vicious circle is established.

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Before progressing to phototherapy or a current immunosuppressive drug, it is essential to check that there is no other explanation for the atopic eczema being uncontrolled. The following are examples of questions that should be asked, but this is not an exhaustive list:

- Have all topical therapies (with extensive education) been used to the highest dose possible that is safe?
  - For TCS: the quantity and potency should be taken into consideration, plus age, body site and extent of the disease. Recording how long a tube of each TCS lasts (in days and weeks) is a useful method of monitoring TCS use. From this it can be seen if the use of TCS is insufficient – or too much, which could lead to adverse effects.
- Have all irritants and allergens been identified and avoided to the extent practicable?
- Has infection been controlled?
  - This may be both bacterial (i.e. *Staphylococcus aureus*) and/or viral (i.e. herpes simplex).
- Has the vitamin D level been checked?
  - This is because vitamin D is needed to produce antimicrobial peptides, which defend the skin against bacteria such as *Staph. aureus* and viruses (in particular, the cold sore virus herpes simplex). If there is a deficiency of vitamin D, this results in fewer antimicrobial peptides and more infections with *Staph. aureus* and herpes simplex. These infections can be serious and they produce chemicals that make the atopic eczema worse.[4] Correcting vitamin D deficiency can lead to improvement of the atopic eczema.[5]
- Is the atopic eczema diagnosis correct?
  - Sometimes other diseases can be mixed with or confused with atopic eczema: one example is dermatitis herpetiformis – an intolerance of gluten in the diet (this is extremely rare).

Having excluded all the above reasons for the atopic eczema not being adequately controlled, it is then appropriate to consider phototherapy and then current systemic therapies (cyclosporin, methotrexate, azathioprine and mycophenolate). These drugs suppress many different chemical messengers that control inflammation, whereas the new biologic drugs suppress just one or two chemical messengers.[6] As a result, current systemic therapies can slightly reduce the body's response to infection, and monitoring by blood tests for levels of things such as white cells, plus kidney and liver function is also required as these drugs can affect such levels and functions. In some children and adults with atopic eczema, one or more of these immunosuppressive drugs may have to be discontinued due to adverse effects. In some patients, one or more (and sometimes all) of these immunosuppressive drugs do not control the atopic eczema. In this very severe atopic eczema, the effects on the person's life can be devastating,[7] with up to 100% of their skin affected severely by the atopic eczema. This is the group of people for whom there has been an unmet need for new therapies.

Atopic eczema arises as a result of complex interactions between genetic and environmental factors, which we covered in an earlier *Exchange* article, using our Skin Wars cartoons.[8] You will find a copy of that article on the National Eczema Society website at **www.eczema.org/articles**. The principles of this interaction are illustrated in **Fig. 1**, which shows how allergens can penetrate through a defective skin barrier and then trigger inflammation, leading to the development of eczema in the skin. With eczema, the skin barrier is even more defective and so allows more allergens to penetrate, producing more inflammation – and so, a vicious cycle is created.

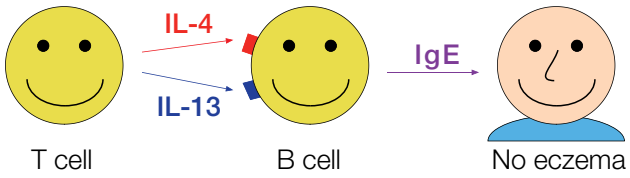
How inflammation develops in atopic eczema

Fig. 2 depicts a child or adult who does not have atopic eczema. T-cells and B-cells are involved in controlling infections and can cause inflammation in the skin. Normally the T-cells produce low levels of a chemical messenger called interleukin-4 (IL-4). This chemical messenger goes to the B-cells and binds to a receptor on the B-cell (this is like a key fitting into a lock). The low level of IL-4 tells the B-cell to produce low levels of many other messengers, including IgE. The low levels of IgE (and other messengers) mean that atopic eczema does not develop.

In a child or adult with atopic eczema, the defective skin barrier allows allergens such as house-dust mites to penetrate and trigger inflammation **(Fig. 1)**. This can also be seen in **Fig. 3**, where allergens such as house-dust mites make the T-cell produce more of the chemical messengers IL-4 and IL-13. Bacteria such as *Staph. aureus* are present in large numbers on the skin of people with atopic eczema and may also make the T-cell produce more IL-4 and IL-13 **(Fig. 3)**.

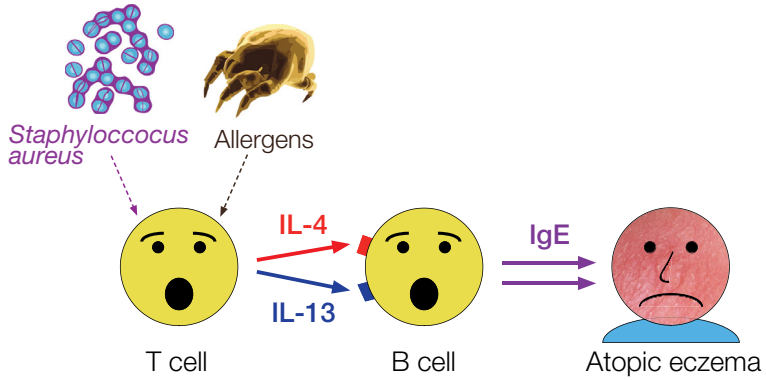
The high levels of IL-4 and IL-13 pass to the B-cell and bind to the receptors on its surface. This results in the B-cell producing many messengers, including IgE, which then cause inflammation and atopic eczema. This pathway – T-cell >> IL-4 + IL-13 >> B-cell => producing IgE and other chemical messengers – is the central pathway that generates inflammation in atopic eczema.

FIGURE 2



In the blood of someone who does not have atopic eczema, T-cells produce low levels of a chemical messenger called IL-4. IL-4 binds to a receptor on a B-cell and tells it to produce low levels of IgE and other chemical messengers. As a result of these low levels of IL-4 and IgE, atopic eczema does not develop.

FIGURE 3



In the blood of someone with atopic eczema, T-cells produce high levels of the chemical messenger IL-4, which tells the B cells to produce high levels of the antibody IgE and other chemical messengers. This leads to the development of atopic eczema.

How current systemic immunosuppressants work

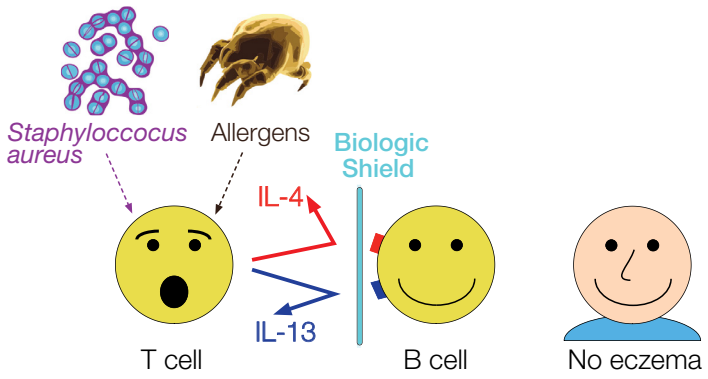
The current systemic drugs (cyclosporin, methotrexate, azathioprine and mycophenolate) suppress the actions of immune cells such as B and T, generally. They also have effects on many other parts of the body, such as liver, kidney and bone marrow, and this is why they have several groups of potential adverse effects. However, these existing immunosuppressive drugs have far fewer adverse effects than do oral corticosteroids such as prednisolone. (However, prednisolone can be used in short courses to gain control of a severe flare. In this situation, the prednisolone has fewer adverse effects.) It is also important to remember that the use of the current immunosuppressive drugs has far fewer adverse effects than leaving the atopic eczema uncontrolled.

Some systemic drugs – methotrexate in particular – would, on average, have fewer adverse effects than the others. All of these systemic drugs can be used for many years, with few adverse effects. A choice of drug is important, as the best drug for one person may not be the best for another.

The new biologic treatments for atopic eczema

A biologic antibody is a highly targeted treatment administered as a subcutaneous injection (i.e. just under the skin) that only blocks one individual pathway, such as the IL-4 or IL-13. In **Fig. 4**, the effect of a biologic therapy that just blocks the actions of IL-4 and IL-13 is illustrated. Using the analogy that a chemical messenger, such as IL-4, binds to a receptor – like a key fitting into a lock – a biologic therapy is like fixing a coin over the keyhole so that the key (IL-4) cannot get into the lock. This is a very specific block of the inflammation pathway and, as a result, it could be predicted that a monoclonal antibody blocking IL-4 and IL-13 would have fewer potential adverse effects than a conventional immunosuppressive drug (cyclosporin, methotrexate, azathioprine and mycophenolate).

FIGURE 4



The new biologic therapies such as Dupilumab are able to block the receptor for IL-4 on the B-cell. This is like stopping a key going into a lock by putting a penny over the keyhole. As a result, the B-cell does not produce high levels of IgE and other chemical messengers, and the eczema is switched off.

There are three new biologic drugs, currently in development, that are targeted at blocking the actions of IL-4 and IL-13:

Dupilumab	Pitrakinra	Lebrikizumab
blocks IL-4 and IL-13	**blocks IL-4 and IL-13**[9]	**blocks IL-13**[10]

Dupilumab trials

The biologic that is most advanced in terms of clinical trial programmes is Dupilumab, which has now completed both phase 2 and phase 3 trials in adults.[11,12]

Two of the phase 3 trials for Dupilumab were published in the *New England Journal of Medicine* in 2016. These trials were called 'SOLO 1' and 'SOLO 2'. They enrolled 671 and 708 adults with moderate-to-severe atopic eczema, respectively, and both demonstrated excellent efficacy. The Dupilumab was compared with a placebo and the severity of the atopic eczema was assessed by multiple methods. The primary efficacy endpoint was a change in the Investigator's Global Assessment (IGA) to both – 'a score of 0 or 1' (clear or almost clear) and a reduction of 2 points or more at week 16. This was reached in 38% of the Dupilumab group compared with only 8% in the placebo group. This endpoint is a difficult one to achieve. The reduction in the Eczema Area Severity Index (EASI score) was 72% in the group receiving Dupilumab and 36% in the placebo group.

For many participants receiving Dupilumab in the trials, the improvements were life-changing, eventually clearing their atopic eczema completely. Some of these adults had not responded to any of the current systemic immunosuppressants. Although there were few adverse effects seen in these Dupilumab trials, as with all new drugs where long-term use is envisaged, it is important to establish whether there are any long-term adverse effects.

Dupilumab has now completed one phase 2 trial in children with severe atopic eczema and the results are currently being analysed.

We now look forward to the results from the clinical trials of the other anti-IL-4/IL-13 biologics.[13]

This is the most exciting time in the treatment of atopic eczema, with several new classes of treatments in, and about to enter, clinical trials. These will be reviewed in future articles in *Exchange*.

Dupilumab will not be available in the UK (outside of clinical trials) for adults with severe atopic eczema/atopic dermatitis, until 2018.

For children, it will be a couple of years after that.

Next Dupilumab clinical trials in the UK:

Children: 6-months to 6-years Dupilumab, randomised controlled trial.

The only way to gain a place on this trial is to be referred by a Dermatologist or Paediatric Allergist to one of the trial centres.

Other trials will follow.

Declaration of interests

Michael J Cork is Chief Investigator for Dupilumab trials in the UK of both children and adults – funded by Regeneron and Sanofi. He is also a member of the advisory boards regarding the design and analysis of the clinical trials.

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