

# ECZEMA TREATMENT OPTIONS

## SYSTEMIC TREATMENTS FOR SEVERE ECZEMA IN ADULTS AND CHILDREN

**Professor Andrew Wright**, Consultant Dermatologist, St Luke's Hospital, Bradford, gives an overview of available treatments.

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**Systemic treatments are drugs taken as tablets or injections that travel through the bloodstream, dampening down the immune system to reach and treat eczema all over the body.**

Generally, systemic drugs are prescribed and supervised by your consultant dermatologist and – during your course of treatment – you will be closely monitored by dermatology healthcare professionals and your GP or practice nurse. It is important that you understand what systemic treatments are, how they work, under what circumstances they may be used, what possible side effects may occur and how you will be monitored throughout your course of treatment.

There are several types of systemic treatment currently available. In a previous Exchange article 'Systemic treatments for eczema' (December 2010), I outlined the use of the drugs alitretinoin, azathioprine, ciclosporin and corticosteroids. Here, I will revisit these four options and additionally discuss methotrexate, mycophenolate mofetil and systemic drugs used to treat children.

### When are systemic treatments recommended?

Systemic treatments are recommended for adults and children with severe eczema who are troubled with repeated, widespread flare-ups of the disease, or who have eczema that is hard to control with topical treatments alone.

Generally, this applies to adults and children with difficult atopic eczema, but other types of eczema that become widespread may also be treated systemically.

For example, if you have severe eczema on your hands over an extended period of time and it is not responding to topical corticosteroids, you may have contact dermatitis (caused by an allergic reaction) or chronic hand eczema (also known as chronic hand or contact dermatitis). In such cases you may be prescribed the oral treatment alitretinoin (used especially for hand eczema). If as an adult you are suffering from an acute, extensive flare of atopic eczema or florid contact dermatitis, you may be given a short course of oral corticosteroids.



## How do systemic treatments work?

The systemic drugs that are currently available are immunosuppressants (azathioprine, ciclosporin, methotrexate or mycophenolate mofetil), retinoids (alitretinoin) and corticosteroids.

Immunosuppressants work by lowering the body's normal immune response. This is helpful because in severe eczema the body's immune system has become over-active and this causes constant flares or persistent eczema.

Retinoid drugs are derived from vitamin A and regulate cell growth, helping to reduce eczema flares and dampen down the immune system.

Corticosteroids are produced naturally by the body but when they are used in a different form as medical treatments they help to control inflammation and calm down the fiery red skin caused by eczema flares.

## Immunosuppressants

It is important to understand that immunosuppressant drugs used to treat severe eczema were originally developed to prevent skin graft rejection in transplant patients. Nowadays immunosuppressant drugs are used to treat many conditions, including skin diseases, as a means of reducing oral steroid use. Azathioprine and methotrexate have been available for 40 years, and mycophenolate mofetil for 20 years. These three drugs are not licensed for use in atopic eczema and are prescribed 'off-licence' only by dermatologists. Ciclosporin, however, is licensed for severe atopic eczema when systemic therapy is required.

### Azathioprine

Azathioprine is generally used for cases of severe, persistent atopic eczema that are unresponsive to topical treatment, or that require frequent courses of oral steroids. Azathioprine interferes with the proliferation of certain types of white blood cells

(lymphocytes) that are involved in generating the inflammation associated with eczema.

Azathioprine is available as 25-mg and 50-mg tablets, which are taken once or twice a day with or after food. Azathioprine takes a little longer to take effect than ciclosporin (see below), and you won't usually see benefits until after 4–5 weeks. Therefore, it is less suitable for acute flares. Further improvements are then likely to occur over the next few months.

### What are the potential side effects?

Some people experience nausea, diarrhoea and loss of appetite. Azathioprine can also make you more prone to infections. If you are taking this drug and come into contact with chickenpox or shingles, it is very important you see a doctor for preventative treatment.

Hair loss can occur but this is usually mild and your hair will grow back after you stop taking azathioprine. Occasionally a drug hypersensitivity syndrome may develop – this feels like 'flu', with aches, pains and fever. If you experience these symptoms you should immediately stop taking azathioprine and inform your prescribing doctor. There is also a theoretical concern that long-term treatment may predispose people to certain types of malignancy. However, there is no evidence that this is the case with short-to-medium-term use. Azathioprine can cause photosensitivity, so you should be careful to avoid the sun and sunbed exposure and protect yourself with sunscreens and protective clothing.

The main risk of treatment with azathioprine is bone-marrow suppression. This can result in severe anaemia and the risk of infection. A blood test is now available to determine which patients are most at risk of developing this side effect. Approximately one in 200 people have low levels of an enzyme called thiopurine

methyltransferase (TPMT). They are unable to break down azathioprine in the normal way and are at high risk of dangerous bone-marrow suppression and should therefore not receive this drug. You should seek medical advice if you become unwell or develop any signs of infection during your course of treatment. It is also important to report any unusual bruising or bleeding, which may be a sign that the bone marrow is being affected.

## Ciclosporin

The reasons for prescribing ciclosporin are similar to those for prescribing azathioprine. Ciclosporin will start to work rapidly (within 1–2 weeks). Further improvements can occur up to 12–16 weeks after the start of treatment. Many patients find this drug to be very effective, including a marked improvement in the itching and appearance of their skin.

Ciclosporin comes in four strengths and you take it in capsule or liquid form, twice daily. Although it is currently licensed only for short-term treatment (8 weeks) for patients with severe atopic eczema for whom conventional therapy is ineffective or inappropriate, dermatologists may prescribe longer maintenance courses for adults.

### What are the potential side effects?

The main side effects of ciclosporin are hypertension (high blood pressure) and reduced efficiency of the kidneys (renal toxicity). Side effects are more likely to occur with higher doses.

There is a potential increase in the likelihood of developing certain types of cancer with long-term treatment due to the effect of ciclosporin on the immune system. For this reason, if you are female and taking ciclosporin, you are especially advised to keep your cervical smear

tests up to date and regularly check your breasts for lumps. Discuss this with your GP if you have any concerns.

Since ciclosporin suppresses the immune system, the risk of bacterial, fungal and viral infection is greater when you are on this medication.

Other, less serious but troublesome side effects include increased hair growth. This is a relatively common problem and can be distressing, particularly for women. You may also experience swelling and enlargement of the gums, although this usually only happens with higher doses. Nausea, diarrhoea, tiredness, tremor (shaky hands) and altered sensation (pins and needles) can also occur.

## Methotrexate

Methotrexate was originally introduced as an anti-cancer drug (used especially to treat leukaemia and similar cancers). It was soon discovered to be effective in the treatment of psoriasis and psoriatic arthropathy, and more recently it has been shown to be helpful in controlling severe eczema.

The drug is usually taken in a single weekly dose. Folic acid is commonly used to supplement treatment on the non-methotrexate days as it helps to reduce side effects.

Only a hospital specialist dermatologist experienced in monitoring methotrexate therapy should initiate treatment. This use of the drug is off-licence and you should remain under the care and supervision of a dermatology service.

### What are the potential side effects?

Methotrexate can cause quite marked nausea. Although it suppresses the immune system, generally there are fewer problems with the

risk of infection than with azathioprine or ciclosporin. However, infection and anaemia can occur as the result of methotrexate causing bone-marrow suppression. It can also cause liver inflammation leading to fibrosis and lung fibrosis.

## Mycophenolate mofetil

Mycophenolate mofetil was developed as an immunosuppressive drug for transplant patients. It acts by decreasing the activity of white cells in the body, thus suppressing the immune system. It has been used for quite a wide variety of skin problems, including psoriasis, eczema and other inflammatory skin disorders.

The use of mycophenolate mofetil in eczema is off-licence and treatment should be introduced and monitored under the supervision of a dermatology service.

### What are the potential side effects?

Most patients tolerate mycophenolate mofetil well. Although the risk of infection is less than with azathioprine or cyclosporine, you will still need to go for regular blood tests to check for infection and anaemia. Like azathioprine, mycophenolate may cause some photosensitivity. Patients should therefore take extra precautions when exposed to UV light and sunlight.

## Retinoids

Alitretinoin is a retinoid drug, developed specifically and licensed for adults with hand eczema. It is recommended by NICE for severe hand eczema that has gone on for a long time, that has not responded adequately to potent topical corticosteroids or light treatment, or that keeps coming back.

It is taken as a capsule once a day with a meal for 12–24 weeks depending on how your condition responds. If the treatment is successful but the symptoms return, you may be given a further course.

### What are the potential side effects?

It is known that retinoid drugs such as alitretinoin are very likely to cause severe birth defects if taken during pregnancy. This means that women must avoid becoming pregnant during treatment and for 5 weeks after stopping treatment – for example, by using two effective methods of contraception.

The most common side effect is headaches. Other side effects included flushing, dry skin and lips, lip inflammation, raised blood fats such as cholesterol, and decreased levels of thyroid hormone. The effects of UV light (sunbeds and sunlight) are enhanced when on alitretinoin, so sunbeds should be avoided and sun protection used.

## Corticosteroids

Corticosteroids are very helpful for controlling acute, severe flares of atopic eczema and lead to a marked and rapid reduction in the redness, weeping and irritation associated with the disease. Short courses of oral steroids may also be very useful for florid cases of acute allergic contact dermatitis (for example, hair-dye reactions), or for cases of severe vesicular (blistering) hand eczema.

Corticosteroids are taken in tablet or liquid form as a single dose in the morning. A high dose is used initially as a short course lasting up to 2 weeks and then the dose is slowly reduced over several weeks.

Sometimes rebound flares of eczema can occur when you stop treatment, and side effects limit

long-term use. It follows that corticosteroids are not suitable for long-term maintenance therapy.

### What are the potential side effects?

Corticosteroids have numerous side effects, particularly if they are taken for a long period of time. For this reason, they are not recommended for long-term treatment of atopic eczema. If used, doctors will aim to keep the dose as low as possible.

Weight gain is the most common initial side effect. In children it is important to keep an eye on growth. Osteoporosis (thinning of the bones) is a significant problem in adults. Extra care is needed for patients who are already known to have diabetes or high blood pressure as these conditions may be exacerbated by steroid treatment. Other side effects may include indigestion, changes in mood, reduced healing of cuts, bruising and skin thinning, muscle weakness and joint pain.

Corticosteroids can suppress the immune system. This means that the risk of bacterial, fungal and viral infection is greater when you are on this type of medication. If you are taking oral steroids, you should seek your doctor's advice before being vaccinated or if you are exposed to measles, chickenpox or shingles.

If steroid tablets are given as a short course (i.e. 2 weeks), there is usually no problem with stopping them. However, if you take them for longer, you should not suddenly stop taking them. This is because systemic steroids switch off the natural production of steroid hormones by the adrenal glands.

If treatment is to be discontinued, the dose should be gradually reduced to allow the glands to start working normally again.

**Table 1: Systemic treatment monitoring for adults**

	<b>BLOOD TESTS</b> (ON ASSESSMENT, THEN WEEKLY, THEN EVERY 2-3 MONTHS)	<b>URINE TESTS</b> (ON ASSESSMENT, THEN WEEKLY, THEN EVERY 3 MONTHS)	<b>BLOOD PRESSURE</b> (ON ASSESSMENT, THEN WEEKLY, THEN EVERY 4 WEEKS)	<b>PREGNANCY TESTING</b> (ON ASSESSMENT, THEN EVERY 4 WEEKS)
<b>Alitretinoin (Tocfino)</b>	<i>Blood lipids. Cholesterol. Fasting triglycerides.</i>	X	X	<i>Pregnancy must be prevented during treatment and for 5 weeks after treatment. Pregnancy test prior to treatment and every 4 weeks.</i>
<b>Azathioprine (Imuran)</b>	<i>Bone-marrow suppression. TPMT levels. Liver function. Liver function tests. Blood count. Urea and electrolytes. Haemoglobin.</i>	X	X	X
<b>Ciclosporin (Deximune, Neoral)</b>	<i>Kidney function. Creatinine levels.</i>	<i>Creatinine levels. Blood tests. 24-hour urine collection.</i>	✓	X
<b>Methotrexate (Maxtrex)</b>	<i>Liver function. Liver function tests (if blood tests show abnormal liver function, occasionally liver scans may be advised). Blood count. Urea and electrolytes. Haemoglobin.</i>	X	X	X
<b>Mycophenolate mofetil (Arzip, Cellcept)</b>	<i>Blood count. Urea and electrolytes. Haemoglobin.</i>	X	X	X
<b>Corticosteroids (Prednisolone)</b>	X	X	✓	X

Note: Carry a steroid treatment card or wear a MedicAlert bracelet.

## Special considerations for children being treated with systemic treatments

Occasionally, atopic eczema in children is severe enough to need systemic treatment. Ciclosporin and azathioprine are the most common systemic drugs prescribed for children, although usually they are only used for relatively short periods of time to bring the eczema under control. They are prescribed for children under the supervision of a consultant dermatologist.

Actually, the only systemic drug that is licensed for children aged 2–18 years is ciclosporin, although azathioprine is often prescribed off-licence as a short-term treatment for children. Children may also be prescribed ciclosporin off-licence from the age of one month and up to the age of 2 years under the supervision of a consultant dermatologist. Occasionally, methotrexate and mycophenolate mofetil may be used for older children.

Alitretinoin is not prescribed or used for children under 18 years.

The most commonly used short-term systemic treatment would be a gradually decreasing course of oral corticosteroids. Longer-term steroids are generally avoided in the case of children because of the effects on general growth and bone formation. Close monitoring of treatment is essential and children on systemic treatment for eczema would usually be under the care of a hospital-based skin specialist experienced in the use and monitoring of systemic treatments.

## Further advice and information

All of the systemic treatments discussed in this article will be started and supervised by a dermatology consultant, but may be monitored by dermatology nurse specialists and/or your GP and practice nurse. It is important to remember that no one systemic treatment is a 'cure' for eczema but in severe cases they can lead to a gradual improvement of the condition. As your eczema improves, often so does your self-confidence and quality of life.

**Please note that this article has purely provided an overview of systemic treatments and has not listed all the side effects.**

More information on all the systemic treatments discussed, can be found by visiting the websites below.

- The Electronic Medicines Compendium (eMC) is continually updated and contains information about all prescription medicines. The website is **[www.medicines.org.uk](http://www.medicines.org.uk)** and, by searching the name of the drug, you will find the individual specific product characteristics (SpC) and patient information leaflets (PIL).
- The recent NICE guidance on alitretinoin (2008) and the treatment of atopic eczema in children under 12 years (2007), as well as quality standards for children with atopic eczema (2013) can be accessed at **[www.nice.org.uk](http://www.nice.org.uk)**
- The British Association of Dermatologists and the New Zealand Dermatology Society also publish good sources of patient information on systemic treatments in eczema on their websites, **[www.bad.org.uk](http://www.bad.org.uk)** and **[www.dermnetnz.org](http://www.dermnetnz.org)**