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Author/s:

Rademaker, M;Agnew, K;Andrews, M;Baker, C;Foley, P;Gebauer, K;Gupta, M;Rubel, DM;Somerville, C;Sullivan, J;Wong, LC

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Managing atopic dermatitis with systemic therapies in adults and adolescents. An Australian/New Zealand narrative.

Rademaker M, Agnew K, Andrews M, Baker C, Foley P, Gebauer K, Gupta M, Rubel D, Somerville C, Sullivan J, Wong, L-C

Address for correspondence: Hon. Associate Professor Marius Rademaker, Waikato Clinical School, Auckland University Medical School, Hamilton, New Zealand

Tel: +64 78381035

Email: Rademaker@xtra.co.nz

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Rademaker	None
Agnew	None
Andrews	None
Baker	Clinical Investigator, speaker and/or advisory board: AbbVie, Janssen, Novartis, Pfizer
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Gebauer	Clinical investigator and/or Advisory Board: AbbVie, Celgene, Janseen, Eli Lilly
Gupta	None
Rubel	Clinical Investigator and/or Advisory Board: AbbVie, Amgen, Boehringer-Ingelheim, Celgene, Eli Lilly, Janssen, Novartis, Sun Pharma
Somerville	?
Sullivan	None
Wong	Advisory Board: Pfizer

Name/Degree/Affiliation

Name	Highest Degree	Affiliation/Address
Rademaker	DM FRCP	Waikato Clinical School, Auckland University Medical School, Hamilton, New Zealand
Agnew	FRACP	Dermatology Department, Greenlane Clinical Centre & Starship Children's Hospital, Auckland, New Zealand
Andrews	FACD	68 Ipswich Rd, Woolloongabba QLD, Australia
Baker	FACD	The University of Melbourne, St Vincent's Hospital, Melbourne; and Skin & Cancer Foundation Inc., Carlton,

		VIC, Australia
Foley	MD FACD	The University of Melbourne, St Vincent's Hospital, Melbourne; and Fitzroy and Probity Medical Research, Skin & Cancer Foundation Inc., Carlton, VIC, Australia
Gebauer	FACD	University of Western Australia, Perth; and Probity Medical Research, Fremantle, WA, Australia
Goh	FACD	St Vincent's Hospital, Melbourne; and Skin & Cancer Foundation Inc., Carlton, VIC, Australia
Gupta	FACD	Department of Dermatology, Liverpool Hospital, Sydney; The Skin Hospital, Darlinghurst; and University of New South Wales, Sydney, NSW, Australia
Rubel	FACD	Woden Dermatology, Phillip, ACT; and Australian National University, ACT, Australia
Somerville		
Sullivan	FACD	Kingsway Dermatology, Miranda NSW, Australia
Wong	FACD	The Children's Hospital at Westmead, Sydney, NSW, Australia

Author Manuscript

PROF. MARIUS RADEMAKER (Orcid ID : 0000-0003-3393-6748)

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Managing atopic dermatitis with systemic therapies in adults and adolescents. An Australian/New Zealand narrative.

Abstract

With the rapid development of new, targeted therapies for the treatment of moderate/severe atopic dermatitis, it is opportune to review the available conventional systemic agents. We assess the published evidence for systemic therapies for atopic dermatitis, and amalgamate this with real world experience. Discussions are centred on when systemic therapy should be considered, which drug(s), what dose, how to sequence or combine these therapies, how long they should be continued for, and what is considered success.

Introduction

There are numerous atopic dermatitis guidelines, reviews and expert opinions, yet few provide specific, practical advice, on the use of systemic therapies for patients with severe disease.⁽¹⁻⁵⁾ This is partly due to the paucity of well designed clinical trials of systemic agents for severe atopic dermatitis, as well as that most systemic agents in current use are 'off-label'. With the recent development of monoclonal antibodies and small molecules targeting specific cytokines, we may be entering a new era of therapy for severe atopic dermatitis. However, these new therapies are likely to be significantly more expensive, so it is prudent that the current systemic

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therapies have been considered and used appropriately before switching. We review the published evidence for current systemic therapies of atopic dermatitis, and amalgamate this with real world experience.

Methods

This narrative is based on an extensive literature review (search terms: alitretinoin, apremilast, azathioprine, baricitinib, ciclosporin, corticosteroids, dupilumab, interferon, IVIG, JAK inhibitors, infliximab, lebrikizumab, leflunomide, methotrexate, mepolizumab, monoclonal antibodies, montelukast, mycophenolate mofetil, nemolizumab, omalizumab, phosphodiesterase inhibitors, prebiotics, prednisone, prednisolone, probiotics, systemic antibiotics, systemic therapy, retinoids, rituximab, tacrolimus, thymic stromal lymphopoietin, tofacitinib, tralokinumab, triamcinolone, upadacitinib, ustekinumab, vitamin D, vitamin E and atopic dermatitis or its synonyms; all languages, all types of articles). We excluded phototherapy, immunotherapy and antihistamines from the review. Each therapy was given a discussion lead who synthesised the available evidence, which was presented at a daylong meeting. Group members were all experienced medical dermatologists from the main centres of Australia and New Zealand.

Discussions centred on when systemic therapy should be considered, which drug(s), dosing, sequencing, combination, duration, and what was considered success, based around 3 clinical scenarios (Supplementary material).

Results

The results are discussed as general principles followed by more detailed, specific commentary on the individual systemic agents. There was general agreement by the group as to the broader principles of when to start treatment, duration of treatment, and what determined success, with variation in which was the first choice systemic therapy and the sequencing. There was more variation within the group as to the type and frequency of monitoring for adverse effects of therapy.

Please insert Bullet points where best fits

When to start systemic therapy

The decision to start a systemic therapy for the management of atopic dermatitis is complex and should take into account severity of the patient's symptoms, the lack of response to appropriately prescribed and used topical therapies (including phototherapy), and patient co-morbidities. The three main barriers to using systemic agents are the prescriber's discomfort in using these therapies, the direct and indirect associated costs (pharmaceuticals, monitoring, medical fees, patient time, etc.) and the patient's perspective of the benefit/risk of the therapy.⁽⁶⁻⁸⁾

A number of criteria have been proposed including specific levels of clinical disease activity (e.g. SCORAD – SCORing Atopic Dermatitis, EASI – Eczema Area and Severity Index, SASSAD - Six Area, Six Sign Atopic Dermatitis), patient quality of life scores (e.g. DLQI – Dermatology Life Quality Index, EQ-5D – EuroQol 5 Dimension), the amount of potent topical corticosteroid use, the number of relapses, number of hospital admissions, etc., but as each patient's individual circumstances vary, it is difficult to develop practical recommendations.⁽⁹⁾

The group felt that systemic therapy should be offered to all patients with atopic dermatitis that was significantly affecting their quality of life. This shared decision-making should include discussion regarding:

- Specific treatment goals and expectations
- The strategy to reach these goals
- The therapeutic options and their potential adverse effects
- The added risks of any comorbidities
- Practical matters including socioeconomic considerations

Individual Systemic agents

A number of studies have surveyed systemic agent use in severe atopic dermatitis. Armstrong reviewed systemic immunomodulator therapy in 4204 American patients (67.5% female, mean age, 50.9 years) with atopic dermatitis: 51.3% received methotrexate, 17.3% mycophenolate mofetil, 16.9% ciclosporin, and

14.5% azathioprine.^(7,8) During the 1-year follow-up, 36.3% required dose escalation, while 2.8% of patients switched and 7.6% required additional therapies. The mean time to discontinuation was 88.1 days. Systemic corticosteroids were used in 72.3% of patients. Only 2.4% of patients were treated with phototherapy.

In a survey of 133 paediatric dermatologists,⁽¹⁰⁾ the preferred first-line systemic therapy was ciclosporin (45.2%), methotrexate (29.6%), and mycophenolate (13.0%). The most commonly used second-line agents were methotrexate (31.3%) and mycophenolate (30.4%); azathioprine was the most commonly cited third-line agent. The main factors that discouraged use of systemic agents were side-effect profiles (82.6%) and perceived risks of long-term toxicity (81.7%).

The group expressed two approaches to starting systemic therapy: 1) combination therapy with 6-10 weeks of a faster acting agent (in order of the group's preference: ciclosporin, systemic corticosteroids, phototherapy or admission for wet wraps) as a bridging treatment to a second, slower acting maintenance therapy (e.g. methotrexate, ciclosporin, azathioprine, mycophenolate); or 2) simply starting a slower acting therapy (in order of the groups preference: methotrexate, ciclosporin, azathioprine, mycophenolate). The rationale for a 6-10 week faster acting therapy included giving the patient 'normal' skin, often for the first time in many years, increasing the patients' confidence in subsequent systemic therapy, and ultimately a better response to the slower acting therapy.

Corticosteroids (oral, intramuscular, intravenous)

Despite the known effectiveness of systemic corticosteroids in controlling the symptoms of atopic dermatitis, most guidelines, reviews and expert commentaries discourage their use based on the known adverse effect profile and the frequent relapse/rebound on stopping.⁽¹¹⁾ The general recommendations are that they should be limited to no more than two weeks for the management of acute flares, or as a bridging treatment to another systemic agent.

Corticosteroids target gene transcription resulting in activation of anti-inflammatory genes as well as suppression of pro-inflammatory genes. Potency is

determined by affinity for the intracellular glucocorticoid receptor and duration of action. Whilst corticosteroids are immunomodulatory, above 20 mg/day prednisone equivalent may also have immunosuppressive effects. Corticosteroid insensitivity/resistance is not well recognised by dermatologists, but occurs in up to 30% of patients with chronic asthma or rheumatoid arthritis.⁽¹²⁾

Whilst there are no quality studies of oral corticosteroid use for the management of atopic dermatitis,⁽¹³⁻¹⁷⁾ they are widely prescribed, with a high satisfaction rating by patients.^(7,18) Similarly the studies of intramuscular triamcinolone,^(19,20) intravenous methylprednisone⁽²¹⁾ or sub cutaneous ACTH depot^(22,23) are all of low quality, although they do indicate short-term response. A 4-week study in 26 children with severe atopic dermatitis compared combined oral and nasal beclomethasone dipropionate (1200 µg/day) to placebo.⁽¹⁴⁾ It identified a 22% decrease in mean severity, lower parent-assessed overall disease activity and greater preference for beclomethasone. In another study beclomethasone dipropionate 600 µg 3 times daily for 4 weeks followed by 800-1800 µg daily for 6 weeks improved disease activity in 14 of 15 children with severe atopic dermatitis, but the disease relapsed in 4 children once the dose was tapered.⁽¹⁵⁾ Flunisolide 640-1200 µg/day for 2 weeks reduced clinical severity scores by 49% compared to placebo after 2 weeks in 20 children with atopic dermatitis.⁽¹⁶⁾ Intravenous methylprednisolone 20 mg/kg/d for 3 consecutive days resulted in immediate improvement of skin lesions and pruritus in 5 of 7 children.⁽²¹⁾

In a comparison of prednisolone (0.5-0.8 mg/kg/day, tapered within 2 weeks) with 6 weeks of ciclosporin (2.7-4 mg/kg/day), in adults with severe atopic dermatitis, only 1 of 27 patients treated with prednisolone achieved sustainable remission as opposed to 6 of 17 treated with ciclosporin.⁽¹⁷⁾

Oral dosing of glucocorticoids is best once daily, early in the morning, to minimise nocturnal sleep disruption. Alternate day dosing has been recommended for longer-term maintenance therapy, on the hypothesis that it reduces adverse effects.

Adverse events of systemic corticosteroids include hypertension, glucose intolerance, gastritis, weight gain, decreased bone density, adrenal suppression, and emotional lability. A systematic review of adrenal insufficiency (cortisol level ≤ 500 mol/L) after glucocorticoid included only a few patients with atopic dermatitis among 3753 participants.⁽²⁴⁾ Meta-analysis showed a significant increase in absolute risk with medium (1 month to 1 year) and long-term (>1 year) use, as well as with medium- and high-dose corticosteroids. Approximately half the patients had resolution of adrenal insufficiency upon retesting at 28 days. Tapering of corticosteroids was deemed unnecessary with courses lasting less than 1 week, but a 7-14 day or 15-30 day taper until a physiologic dose (10 mg/m²/day) was recommended for courses of 2-3 weeks or ≥ 4 weeks, respectively. Oral corticosteroids are generally considered safe for use in pregnancy and breastfeeding,^(25,26) although it has been recommended to delay breastfeeding for 3 to 4 hours after ingestion of prednisone to minimise exposure to the infant.

Some members of the group preferred systemic corticosteroids over ciclosporin as the bridging treatment to a longer term maintenance therapy, the dose used depending on the available tablet size (e.g. prednisone 20 mg tablet: 40 mg/mane for 1 week, 20 mg mane for 2 weeks, 10 mg mane for 3 weeks with a possible extension of 5 mg/mane for 4 weeks; or prednisolone 25 mg tablet: 50 mg 1 week, 25 mg 2 weeks, 12.5 mg 3 weeks; or i.m. triamcinolone 40 mg stat, repeated in one month if needed). The rationale, as well as providing patients with a symptom-free 'holiday', demonstrating to patients and families that 'normal' skin is possible, was to assess steroid responsiveness to assist in prospectively determining the value of second-line therapy. There was variation on the recommended monitoring from none (unless clinically indicated), to baseline osteoporosis investigation; there was also variation in co-prescribing, from none (unless symptomatic) to a proton pump inhibitor and osteoporosis prophylaxis.

Several members also used long term (>1 year), low dose prednisone/ prednisolone (5-10 mg/day) for the management of late onset atopic dermatitis in the elderly (>75 years) patient with significant itch affecting their quality of life.⁽¹³⁾

Methotrexate

Low-dose methotrexate (< 0.4 mg/kg per week) is anti-inflammatory, rather than immunosuppressive, with a long history of use in dermatology.⁽²⁷⁾ Although generally of poor to moderate quality, multiple small studies of methotrexate show a 40-70% improvement in atopic dermatitis disease activity scores.⁽²⁸⁻³³⁾ It is as effective as ciclosporin and azathioprine⁽³¹⁾ in the short term, has prolonged drug survival and post-drug survival compared to ciclosporin,⁽³³⁾ and is generally well tolerated.

An open-label dose-ranging study in 12 adults with moderate to severe atopic dermatitis initiated treatment at 10 mg/week, which was increased by 2.5 mg/week until a response or until toxicity occurred.⁽²⁹⁾ The mean improvement in the primary outcome of SASSAD score was 52%, accompanied by significant improvements in BSA, DLQI, itch and loss of sleep scores. One patient withdrew because of side effects. The majority of patients had persistent improvement 12 weeks after ceasing methotrexate.

Two randomised controlled trials have investigated methotrexate in atopic dermatitis. The first assigned 42 patients to methotrexate 10-22.5 mg/week or azathioprine 1.5-2.5 mg/kg/day for 12 weeks;⁽³⁰⁾ at week 12, patients in the methotrexate group had a mean relative reduction in SCORAD of 42% compared to 39% in the azathioprine group (P=0.52). Proportions of patients achieving at least mild disease and reductions on impact of quality of life and were similar. No statistically significant differences were found in the number and severity of adverse events but abnormalities in blood count were more common in the azathioprine group. Long-term follow-up after 2 years suggested sustained benefits from 12 weeks' treatment with either drug.⁽³¹⁾ In an intention-to-treat analysis there was a 63% relative reduction in SCORAD from baseline in the methotrexate group and 53% reduction in the azathioprine group, with no significant difference between them.

A randomised, multicentre trial, evaluated the efficacy and safety of methotrexate (15 mg/week) versus ciclosporin (2.5 mg/kg/day) for 8 weeks in 97 patients with moderate-to-severe atopic dermatitis.⁽³²⁾ When SCORAD 50, the primary endpoint, was not achieved at week 8, methotrexate was increased to 25 mg/week and ciclosporin to 5 mg/kg/day for a further 16 weeks. Methotrexate was inferior to ciclosporin at week 8, but similar by week 20. Methotrexate demonstrated a better safety profile than ciclosporin.

Drug survival (time on the drug) and post-drug survival (time after ceasing the medication to commencing another one), was used to compare 25 children and adults treated with ciclosporin (mean maximum dose 3.6 mg/kg/day) to 31 treated with methotrexate (mean maximum dose 16 mg/week).⁽³³⁾ Mean drug survival was 8 months for ciclosporin and 23 months for methotrexate, and median post-drug survival was 2 months and 12 months respectively. Both differences were statistically significant. Controlled disease was the most common reason for discontinuing methotrexate, while primary failure was the most common reason for ceasing ciclosporin. In a larger drug survival report of 89 patients, 60% of patients remained on methotrexate (reasons for stopping: ineffective -15%, adverse effects -25%).⁽³⁴⁾

The adverse effects of methotrexate, recommended monitoring, advice on vaccines and pregnancy concerns have previously been reviewed by the group.⁽²⁷⁾ For pre-treatment, consider testing full blood count (FBC), liver and renal function, non-fasting lipids, hepatitis serology, HbA1c and glucose. Optional investigations in at-risk groups include an HIV test, an interferon-gamma release assay (e.g. QuantiFERON-TB Gold) and a chest X-ray. In patients without complications, repeat the FBC at 2-4 weeks, then every 3-6 months and the liver/renal function test at 3 months and then every 6 months. Methotrexate is a teratogen.

The group favoured methotrexate (15-25 mg/week) as both a first (with or without bridging therapy) and second line therapy. They were also happy to consider combination with prednis(ol)one,⁽³⁵⁾ ciclosporin, azathioprine and mycophenolate,

but at a slightly reduced dose (10-15 mg/week). Methotrexate is generally well tolerated; this can be improved by subcutaneous administration.⁽³⁵⁾

Ciclosporin

Ciclosporin is one of the few systemic treatments indicated for the treatment of atopic dermatitis. It has a narrow therapeutic index, complicated by variable inter-patient and intra-patient bioavailability. A review of systemic treatments for atopic dermatitis identified 14 trials, which consistently found that ciclosporin improved clinical signs of atopic dermatitis in children and adults.⁽²⁸⁾ In practice, twice daily ciclosporin (3-5 mg/kg/day for 8-12 weeks) is used most commonly for control of acute flares, and as intermittent short courses (8-12 weeks) for continued disease control.^(36,37) A significant reduction in disease activity can be expected in 2-6 weeks, and response should be formally assessed at 6-8 weeks. Ciclosporin should be discontinued after 12 weeks if insufficient response. Unfortunately relapse/rebound on stopping ciclosporin occurs frequently.⁽³⁷⁾ Continuous maintenance for one to two years is sometimes used, but there is concern regards long term adverse effects.

Close monitoring (monthly blood pressure, full blood count, renal and liver function tests) is recommended because of potential adverse effects including infection, nephrotoxicity, hypertension, tremor, hypertrichosis, headache, gingival hyperplasia, and increased risk of skin cancer and lymphoma.⁽³⁸⁾ Dosing is based on ideal body weight. Ciclosporin is a pregnancy category C drug, with studies showing a slightly higher incidence of low birth weight and prematurity but no increased risk of foetal anomalies.⁽³⁹⁾ Live vaccines should be avoided. There are a number of potentially significant drug-drug interactions.

The group were divided in their use of ciclosporin: most were happy to use ciclosporin as an alternative to systemic corticosteroids (e.g. as bridging therapy), but were less comfortable in using ciclosporin as a longer term 1st or 2nd line treatment, mostly due to concerns around rebound and toxicity. Some members were comfortable adding ciclosporin to methotrexate, azathioprine or

mycophenolate for recalcitrant dermatitis, but not with phototherapy, due to increased risk of cutaneous malignancy.⁽⁴⁰⁾

Azathioprine

The use of azathioprine in dermatology is off-label but it is widely prescribed as a steroid-sparing agent. Azathioprine is rapidly absorbed and metabolised but the active metabolite 6-thioguanine accumulates slowly, so maximal efficacy may not be achieved for 3-6 months. Polymorphisms in the enzyme thiopurine methyltransferase (TPMT) influence the efficacy and toxicity of azathioprine;^(2,30,38) 11% of Caucasians have low levels, which increases the risk of neutropenia. The xanthine oxidase inhibitor allopurinol can advantageously switch thiopurine metabolism towards 6-thioguanine in a subgroup of patients with an inadequate response to azathioprine, but should be used with caution to avoid the risk of azathioprine toxicity.

The efficacy of azathioprine in moderate to severe atopic dermatitis despite optimal topical therapy has been assessed in a placebo-controlled trial in 54 patients dosed by TPMT activity.⁽⁴¹⁾ After 12 weeks there was a 37% improvement in the SASSAD compared to only 20% in the placebo group (17% difference; 95% confidence interval (CI) 4.3-29). A similar study in 37 patients reported a SASSAD reduction of 26% in azathioprine-treated patients compared to a 3% reduction in those randomised to placebo ($p < 0.01$).⁽⁴²⁾ Note however, 12 weeks is relatively short for a trial of azathioprine.

Gastrointestinal side effects are the most common dose-limiting feature and can be addressed by reducing the dose, dividing the dose or taking the medication with food. The risk of myelosuppression and hypersensitivity require initial monitoring. Azathioprine hypersensitivity syndrome can develop 1 to 4 weeks after commencing therapy, and is more common than TPMT related neutropenia. Routine blood and liver function tests at baseline and every 2 weeks for 2 months, and then monthly for 4 months has been recommended.⁽³⁸⁾ Whilst azathioprine has a

pregnancy risk classification of D, it is generally considered safe.⁽³⁹⁾ Live vaccines should be avoided.

The group's clinical experience suggests that an excellent response to azathioprine (1-3 mg/kg/day) can be expected in about one-third of patients after 6 months, with a partial response in another one-third of patients. Because of this delay in response, bridging treatment is usually necessary, and it relegates azathioprine to 2nd or 3rd line treatment choice. As the mode of action is similar to that of mycophenolate, there may be little value in combining these two drugs. Once good control has been established, the dose can slowly be reduced; long-term maintenance may only require daily doses of 25-50 mg.

Mycophenolate mofetil

Mycophenolate modulates the proliferative responses of T- and B-lymphocytes leading to lower levels of immunoglobulins and a decrease in delayed hypersensitivity responses. A number of small studies and case series have reported inconsistent efficacy of off-label use in atopic dermatitis.^(28,38) In the largest reported study, 55 patients with severe atopic dermatitis were randomised to ciclosporin 3 mg/kg or 1440 mg/day enteric-coated mycophenolate.⁽⁴³⁾ Disease activity assessed by SCORAD after 30 weeks of maintenance therapy was comparable in both study arms and the side effects of both drugs were mild and transient. Disease activity significantly increased in the ciclosporin arm compared to the mycophenolate arm after withdrawal of the study medications.

The typical starting dose of mycophenolate mofetil is 500 mg/day, increasing weekly to 1-2 gm/day. Monitoring is by full blood count, renal and liver function tests after 1 month and then every 3-4 months in otherwise healthy individuals. Dose-dependent gastrointestinal side effects include nausea, diarrhoea, soft stools, anorexia, abdominal cramps, vomiting and peptic ulcer disease. Urinary, infectious and neurological adverse events have been reported but are rarely severe. A number of potential drug interactions need to be considered. Although initially classified as Pregnancy Risk category C, mycophenolate is potentially teratogenic, so

is contraindicated in pregnancy.⁽³⁹⁾ Relative contraindications include lactation, peptic ulcer disease, hepatic disease and renal disease. Live vaccines should be avoided.

There was heterogeneity in the group regarding the positioning of mycophenolate with some members using mycophenolate as a 1st line systemic therapy, and others only as an add-on to (or following) ciclosporin or methotrexate.

Systemic antibiotics (anti-*Staphylococcus aureus*)

The skin microbiome is emerging as a key element in inflammatory skin conditions including atopic dermatitis. There is a complex symbiotic relationship between microbial communities and tissue, mediated by the innate and the adaptive immune systems.⁽⁴⁴⁾ Differences in the skin microbiome between patients with atopic dermatitis and the general population have been identified.⁽⁴⁵⁾ They include an increase in *Staphylococcus aureus*, which is proportional to disease severity, thought to be due to defects in innate immune responses, compromised barrier integrity, and changes in sphingolipids, adhesins and Th2/IL-4 activity. *S. aureus* colonisation in atopic dermatitis has been associated with increased toxin production and the presence of super antigens. Other changes include a reduced presence of *S. epidermidis*, coagulase-negative staphylococci and cutibacteria. Exacerbation of disease is commonly associated with *S. aureus* infection, which generates exoproteins that enable invasion and dissemination within the skin and also activates the immune system.⁽⁴⁶⁾

Systemic and topical antimicrobial therapy reduces *S. aureus* numbers but the change generally does not translate well to clinical benefit. Patients treated with antibiotics quickly become recolonised with the same toxin-secreting organisms, and long-term treatment is not recommended because of the concerns for antibiotic resistance. Colonisation with methicillin-resistance *S. aureus* (MRSA) is a concern. Its prevalence is estimated at 11-34% in patients with atopic dermatitis who carry the organism compared to 1-3% of the general population.⁽⁴⁷⁾ MRSA increases the risk of developing active infection and of super antigen production.

If antibiotics are to be used for atopic dermatitis, they should be accompanied by active treatment with topical corticosteroids and emollients. In the absence of an exudate or crust, the efficacy of antibiotics is uncertain and the elimination of staphylococci carriage is unlikely. Whilst there is no evidenced based role for prophylactic oral antibiotics in atopic dermatitis, they are commonly used.

The group generally avoided the use of systemic antibiotics in adults, other than for short term (1-2 weeks) control of *S. aureus* infected dermatitis. Longer term courses (≥ 3 months) were occasionally recommended for patient with co-morbidities such as recurrent *S. aureus* boils.

Leflunomide

Leflunomide is an immune-modulator approved for the treatment of rheumatoid arthritis and psoriatic arthritis.⁽⁴⁸⁾ It has been proposed as a novel treatment for atopic dermatitis,⁽⁴⁹⁾ but there is very little evidence on its efficacy in the disease and it is rarely considered in clinical practice. It is contraindicated in pregnancy.⁽³⁹⁾

Montelukast

A systematic review of off-label use of montelukast in atopic dermatitis included 11 studies in children and adults.⁽⁵⁰⁾ The studies were small in size (the largest included 61 patients) and assessed as being of low quality. Treatment duration ranged from 4 to 20 weeks, at doses of 10 mg/day in adults. Montelukast improved symptoms such as pruritus in four studies; in two studies it improved symptoms similar to the standard regimen of topical corticosteroid and oral antihistamine; and in five studies it had no effects on symptoms. Montelukast was associated with a similar safety profile to placebo, was well tolerated with minimal adverse effects. Montelukast is classified as pregnancy risk category B1; studies in asthma have indicated an increased risk in of preterm birth and maternal complications, but no increased risk of congenital anomalies.⁽⁵¹⁾

Oral tacrolimus

Tacrolimus, a calcineurin inhibitor with a higher potency than ciclosporin, has a narrow therapeutic index. There is considerable data on topical tacrolimus in atopic dermatitis, but relative little for oral tacrolimus. In an open-label study in 12 patients, 3 weeks of oral monotherapy (0.08 mg/kg/day in divided dose), followed by 3 weeks in combination with topical tacrolimus and then 8 weeks of topical therapy, was associated with improvements in EASI, Physician Global Assessment score and pruritus scores.⁽⁵²⁾ In another open label study, 9 adults (5 female, mean age 42.5 years) were switched from ciclosporin to an extended release formulation of tacrolimus (starting dose 0.15–0.2 mg/ kg/day) for six months.⁽⁵³⁾ After two weeks, the mean SASSAD decreased from 31.4 to 15.2 ($p < 0.05$) and mean BSA from 62% to 43% ($p < 0.05$), which persisted in 7 of the 9 patients. Side effects included nausea, vomiting and diarrhoea, and elevated serum creatinine in one patient. Other reports of its use in atopic dermatitis are limited to small case series.^(54,55)

Intravenous immunoglobulin (IVIG) and intramuscular immunoglobulin

Intravenous immunoglobulin, a plasma product pooled from up to 20,000 donors, has been assessed in a randomised placebo-controlled study in 40 children with moderate to severe atopic dermatitis; significant improvement was noted after 3 doses of IVIG (2 gm/kg/month).⁽⁵⁶⁾ In another study of 10 children refractory to systemic immunosuppression, monthly treatment for 2 years was associated with significant symptomatic improvement, fewer infection-related exacerbations, a decrease in IgE, and being able to stop immunosuppressants in five cases.⁽⁵⁷⁾ Small open-label and randomised prospective studies in adults have had mixed outcomes but suggested benefit when used as adjunctive therapy.⁽⁵⁸⁾

Treatment of atopic dermatitis with intramuscular immunoglobulin has been described in a pilot study of 17 adults.⁽⁵⁹⁾ A regimen of 50 mg of autologous immunoglobulin twice weekly for 4 weeks was associated with a significant decrease in SCORAD and followed by remission for at least 8 weeks, with no evident side effects.

Adverse effects of IVIG are usually minor and self-limiting, and result from aggregate formation of gamma globulin complexes with subsequent complement activation. Premedication with systemic corticosteroids, antihistamines and NSAIDs, and slowing the rate of infusion, can minimise adverse effects.

The expense and paucity of supply limits the use of immunoglobulin therapy.

Interferon-gamma

A double-blind placebo controlled trial of interferon- γ randomised 83 adults and children with severe atopic dermatitis to 50 $\mu\text{g}/\text{m}^2$ daily for 12 weeks, or placebo.⁽⁶⁰⁾ Those randomised to active treatment had a statistically significant improvement in symptoms. There was a reduction in eosinophil counts, which was considered a biomarker of treatment response. The response in children was better than in adults. Efficacy has been confirmed in subsequent studies including a placebo-controlled trial of thrice-weekly dosing in 51 patients.⁽⁶¹⁾ Czarnowicki⁽⁶²⁾ reported that patients with severe atopic dermatitis had a deficiency of T cell-derived interferon in skin-homing T cells and defective responses to bacterial infection.

Side effects including influenza-like symptoms (headache, malaise, fever, myalgia), transient elevation of liver enzymes and neutropenia limits its usability.

Alitretinoin

Alitretinoin (9-cis-retinoic acid), a first-generation retinoid, is licenced in some countries as an oral treatment for severe chronic hand dermatitis and is particularly effective in the hyperkeratotic subtype. A number of randomised placebo-controlled studies have established its efficacy, including a multicentre trial in 1,032 patients.⁽⁶³⁾ Patients were assigned to alitretinoin 10 mg or 30 mg, or placebo, for 24 weeks with 48% achieving clearance. The median time to relapse, while not using any systemic therapy, was 6 months. Improvement has also been seen in patients' atopic dermatitis,^(64,65) but specific atopic dermatitis trials are needed.

Vitamin D

Vitamin D stimulates the expression of antimicrobial peptides, decreases pro-inflammatory cytokine expression, increases regulatory cytokine expression leading to reduced T cell activation, and facilitates the production of profilaggrin and the lipid lamellae essential for skin barrier function.

A recent systematic review concluded that there is a significant inverse correlation between vitamin D levels and severity of atopic dermatitis.⁽⁶⁶⁾ Fourteen of 21 studies reported a significant reduction in disease severity with supplementation, although its efficacy remains controversial. A 2016 systematic review analysed the effects of vitamin D supplementation in patients with atopic dermatitis; they found four randomised controlled trials comparing vitamin D with a placebo; vitamin D supplementation showed a higher mean difference in severity symptoms (mean difference of -5.81).⁽⁶⁷⁾ Perversely, vitamin D supplementation in the first year of life may increase the risk of later atopic disease.⁽⁶⁸⁾

Large prospective studies using differing doses and durations of vitamin D supplementation are needed.

Vitamin E

Vitamin E supplementation has been shown to decrease serum IgE in atopic patients. A randomised double-blind trial in 70 patients with mild to moderate atopic dermatitis compared 4 months' treatment with vitamin E (400 IU/day) or placebo.⁽⁶⁹⁾ Improvement in symptoms were observed after 3 months. However, a 2012 Cochrane systematic review found no convincing evidence of the benefit of dietary supplements in atopic dermatitis.⁽⁷⁰⁾

New therapies

With an increased understanding of the cytokine pathways of atopic dermatitis, new specific targeted therapies have been developed, including monoclonal antibodies and small molecules.^(71,72) 'Small molecule' drugs have a low molecular weight, are able to enter cells, and can directly influence second messenger pathways. The data are still immature for many of these newer agents, but many show promise. Because

of their significantly greater costs, they are likely to be used after failure of conventional systemic agents, unless data emerges that they are curative.

At this moment in time, the group felt it appropriate that patients should have tried and failed, or be contraindicated, to conventional systemic therapies (at least two of phototherapy, ciclosporin, methotrexate, azathioprine, or mycophenolate), over a period of at least six months, before considering one of the newer agents.

Monoclonal antibodies

IL-4/13 antagonists

Dupilumab, a human monoclonal antibody against interleukin (IL)-4 receptor alpha, inhibits signalling of both IL-4 and IL-13, which are type 2 cytokines that drive atopic dermatitis.⁽⁷³⁾ Two identical phase 3 trials, SOLO 1 and SOLO 2, randomised a total of 1,379 adults with moderate to severe atopic dermatitis inadequately controlled by topical treatment to 16 weeks' treatment with dupilumab 300 mg weekly, dupilumab 300 mg every other week, or placebo.⁽⁷³⁾ The primary outcome was the proportion of patients who had both a score of 0 or 1 (clear or almost clear) on the Investigator's Global Assessment (IGA) and a reduction of 2 points or more in that score from baseline at week 16.

In SOLO 1 the primary outcome was achieved in 37% of those who received dupilumab weekly, 38% of patients who received dupilumab every other week, and 10% of those who received placebo ($P < 0.001$). The results were similar in SOLO 2 (36%, 36% and 8%, respectively). Injection-site reactions and conjunctivitis were more frequent in the dupilumab groups.

A subsequent study randomised 740 patients to the regimens used in the SOLO studies but for 1 year.⁽⁷⁴⁾ All three groups were also treated with topical corticosteroids or calcineurin inhibitors. The study showed that dupilumab, when added to standard topical corticosteroid treatment, improved atopic dermatitis signs and symptoms with acceptable safety, with 39% achieving IGA 0/1 compared

to 12% on placebo and topical corticosteroids. Dupilumab is now indicated for the treatment of atopic dermatitis.

IL-13 antagonists

IL-13 is a pleiotropic type 2 cytokine implicated in the pathogenesis of atopic dermatitis; tralokinumab and lebrikizumab are anti IL-13 monoclonal antibodies. In a phase 2b study, 204 adults with moderate to severe atopic dermatitis were randomised to receive 45, 150, or 300 mg of subcutaneous tralokinumab or placebo every 2 weeks for 12 weeks with concomitant topical corticosteroids.⁽⁷⁵⁾ At week 12, tralokinumab 300 mg significantly improved EASI compared to placebo and a greater percentage of participants achieved an IGA response, defined as a 0/1 score or reduction of at least 2 grades from baseline (26.7% vs 11.8%). Participants also demonstrated improvements in SCORAD, DLQI, and pruritus scores versus placebo.

The phase 2 TREBLE study investigated the efficacy and safety of lebrikizumab as an add-on to topical corticosteroid treatment in 209 adults with moderate to severe atopic dermatitis.⁽⁷⁶⁾ It compared lebrikizumab 125 mg single dose, 250 mg single dose or 125 mg every 4 weeks for 12 weeks, or placebo every 4 weeks for 12 weeks. At week 12, significantly more patients achieved EASI-50 with lebrikizumab 125 mg every 4 weeks than placebo (82.4% vs. 62.3%, $P=0.026$). Adverse events were similar between groups.

IL-31 antagonists

There is increasing evidence that IL-31 has a key role in the pathogenesis of atopic dermatitis and pruritus. Nemolizumab, a humanised antibody against IL-31 receptor A, was investigated in a phase 2, 12-week trial in 264 patients with moderate-to-severe atopic dermatitis inadequately controlled by topical treatments.⁽⁷⁷⁾ They were randomised to subcutaneous nemolizumab 0.1 mg, 0.5 mg, or 2.0 mg/kg or placebo every 4 weeks. At week 12, among the patients who received nemolizumab every 4 weeks, the scores on the pruritus visual-analogue scale were reduced by 43.7% in the 0.1 mg group, 59.8% in the 0.5 mg group, and 63.1% in the 2.0 mg group compared to 20.9% in the placebo group ($P<0.01$ for all comparisons).

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Reductions in the EASI were 23.0%, 42.3%, 40.9%, respectively in the nemolizumab groups, and 26.6% in the placebo group.

Other biologics

Omalizumab is a monoclonal antibody that blocks IgE function, indicated for the treatment of chronic urticaria. To date, studies in atopic dermatitis are disappointing with an open-label study in 21 patients, four case series totalling 64 patients, and two small randomised controlled trials in a total of 28 patients not providing convincing evidence of efficacy.^(78,79)

Mepolizumab, a monoclonal antibody to IL-5 that reduces peripheral blood eosinophils, failed to show a significant clinical benefit in a randomised controlled trial of 40 patients with atopic dermatitis.⁽⁸⁰⁾ Although treatment led to a reduction in peripheral blood eosinophils, a subsequent analysis showed there was no effect on numbers of tissue eosinophils in skin biopsies.

The monoclonal anti-CD20 antibody rituximab depletes B cells, which are thought to have a central role in the pathogenesis of atopic dermatitis. A study in 6 patients administered two doses of rituximab 1000 mg, 2 weeks apart.⁽⁸¹⁾ All patients showed an improvement of their skin symptoms within 4 to 8 weeks with EASI falling from 29.4 at baseline to 8.4 at week 8 ($P < 0.001$).

An open label study treated 9 patients with the TNF- α antagonist infliximab at weeks 0, 2, 6, 14, 22, 30, and 38.⁽⁸²⁾ There was a significant improvement in various clinical parameters during the induction phase, but this was not sustained during maintenance.

Ustekinumab, indicated for the treatment of psoriasis, targets the shared p40 subunit of IL-12 and IL-23. A phase 2 study randomised 33 patients to either ustekinumab or placebo at weeks 0, 4, and 16 with a crossover to the other agent at weeks 16, 20, and 32.⁽⁸³⁾ The ustekinumab group achieved higher SCORAD50 responses at weeks 12, 16 (the primary endpoint) and 20 compared to placebo, but the difference between groups was not significant.

Thymic stromal lymphopoietin (TSLP) is a cytokine produced by epithelial cells, induced by pro-inflammatory stimuli, which drives Th2 responses; tezepelumab binds to, and blocks, thymic stromal lymphopoietin (TSLP). In a phase 2a study in 113 patients, a numerically greater percentage of tezepelumab-treated patients achieved EASI50 compared to placebo (64.7% vs. 48.2%, $P=0.091$).⁽⁸⁴⁾ Greater than expected response rates in placebo-treated patients were possibly attributable to the concomitant use of topical corticosteroids permitted in the study.

The group considered that, at this moment in time, the data for the efficacy of various monoclonal antibodies remains immature, other than that of dupilumab. Because of expense, it is likely that dupilumab use will be after other established systemic agents (e.g. phototherapy, systemic corticosteroids, ciclosporin, methotrexate, mycophenolate or azathioprine).

Small molecules

Apremilast

Phosphodiesterase-4 is a key regulator of inflammatory cytokine production in atopic dermatitis through its effects on the degradation of cAMP. The oral phosphodiesterase-4 inhibitor apremilast, indicated for psoriasis/psoriatic arthritis, is anti-inflammatory with minimal immunosuppressive effects. In a phase 2 study in 10 patients with 'recalcitrant' atopic dermatitis, only 2 patients achieved the primary endpoint of a ≥ 2 point improvement in IGA at week 12.⁽⁸⁵⁾ In a phase 2 study in 191 adults with moderate to severe atopic dermatitis, apremilast did not achieve the primary endpoint of improvement in EASI compared to placebo (NCT02087943). It has a narrow therapeutic window for gastrointestinal adverse events including nausea, diarrhoea and dyspepsia; depression/suicide has been reported.

JAK inhibitors

The Janus kinase (JAK) associated pathways are utilised by a number of cytokines as they bind to their specific receptors and activate downstream signal transduction.

Cytokines dependent on JAK include IL-2 (which enhances effector and regulatory responses), IL-9 (atopic disease and inflammatory bowel disease), IL-5 (allergies, asthma and eosinophilic disease) and IL-6 (the prototypic proinflammatory cytokine implicated in many autoimmune disorders).^(86,87)

Baricitinib, a first-generation JAK inhibitor is selective for JAK1 and JAK2 over JAK3. A phase 2 study randomised 124 patients with moderate to severe atopic dermatitis to placebo, 2mg or 4mg/day baricitinib for 16 weeks.⁽⁸⁸⁾ Use of topical corticosteroids was permitted during the study. Significantly more baricitinib 4 mg patients achieved EASI50 compared to placebo at 16 weeks (61% vs. 37%, $P=0.027$), with benefit evident as early as week 4. Baricitinib also improved pruritus and sleep loss. Phase 3 trials are in progress.

Upadacitinib, a second-generation selective JAK1 inhibitor, has been investigated in rheumatoid arthritis, Crohn disease, ulcerative colitis and atopic dermatitis. Sixteen-week results are available from a phase 2b study in 165 adults with moderate to severe atopic dermatitis not adequately controlled by topical treatments, or for whom topical treatments were not medically advisable.⁽⁸⁹⁾ The EASI score at week 16 was reduced by 74% in patients randomised to upadacitinib 30 mg/day, ($P<0.001$ vs. placebo), 62% with upadacitinib 15 mg ($P<0.001$), 39% with upadacitinib 7.5 mg ($P<0.05$) and 23% with placebo. The most common adverse events were upper respiratory tract infection, paradoxical worsening of atopic dermatitis, and worsening of acne. Phase 3 trials are in progress.

A pilot study of tofacitinib in 6 patients with moderate to severe disease who had failed standard treatment reported a reduction in affected body surface area, erythema, oedema/papulation, lichenification and excoriation.⁽⁹⁰⁾ The SCORAD decreased from 36.5 to 12.2 ($P<0.05$) during 8 to 29 weeks of treatment. There were no adverse events. Despite these promising results no further studies of tofacitinib appear to have been planned.

When to stop

There are four main reasons for stopping a systemic agent: lack of response, adverse effects, achieving remission or the patients withdraw their consent. There is no clear definition of a lack of response as it is a complex interplay between pharmacological responses, the natural history of the disease and the patients' expectations.⁽⁹¹⁾

Whilst reduction in clinical scores is important, improvement in patient related outcome measures (e.g. DLQI) should be the main consideration. The minimal clinically important difference (MCID) in DLQI is a reduction by 4 points, but the goal is to achieve a score of 0 or 1. However, there can be a significant delay between achieving a complete clinical response and achieving a DLQI of 0/1, particularly as itch may persist for many months after 'clearing' the skin. The timing of making a 'lack of response' decision needs to take into account the pharmacodynamics of the various agents (e.g. systemic corticosteroids 2-4 weeks, ciclosporin 4-8 weeks, dupilumab 12 weeks, methotrexate or azathioprine 12-16 weeks).

Stopping because of significant adverse effects is often determined by the clinician's risk assessment and/or patient's tolerability, and will vary with co-morbidities, age, and the specific drug being used. Dose adjustment, short term withholding of the systemic agent and co-prescribing (e.g. omeprazole, antihypertensive, anti-emetic, etc.) may be sufficient.

Whilst determining remission is relatively straightforward, the timing of stopping the systemic agent is more difficult. There is little evidence base to direct how long treatment should be continued. None of the current systemic agents are curative, so relapse is not uncommon. There was heterogeneity in the group with some recommending tapering/stopping as soon as clinical improvement occurred, but with no hard definition of what constituted clinical improvement, and others in the group recommending to continue treatment (\pm taper) for a number of months after complete clinical response, acknowledging that this could be many years.

Members of the group recommended the first line systemic agent be re-evaluated after 3 months, to check adherence/compliance, patient satisfaction, and adverse

effects; if at this stage the response was considered inadequate, to increase the dose, switch to a second agent or add in a second systemic agent (with dose adjustment of the first drug)(see Table 1). A lack of response should encourage a review of the clinical diagnosis and exclusion of significant trigger factors (e.g. infection, contact dermatitis, etc.). Depending on the patient's co-morbidities, the group were generally comfortable in switching between the four main systemic agents (ciclosporin, methotrexate, azathioprine and mycophenolate). Most were also comfortable in adding any two together (other than azathioprine with mycophenolate as they have a similar mode of action), but usually with a dose adjustment.

Several members noted that, if the patient had failed to show good initial clinical response to systemic steroids (prednisone/prednisolone 40-50 mg/day), then it was less likely that they would response to steroid sparing agents (methotrexate, azathioprine or mycophenolate).

The group also recommended consideration be given to short term hospital or day unit admission for wet wraps, either as a bridging treatment to systemic therapy, or as rescue treatment at any time.

Summary

Immune-modulatory agents are appropriate for patients with atopic dermatitis refractory to topical regimens and phototherapy, or when quality of life is significantly affected. There is a paucity of data indicating the relative efficacy of each systemic agent but ciclosporin, methotrexate, azathioprine and mycophenolate are all widely used. Whilst there is some evidence for other systemic agents, including interferon-gamma, montelukast, tacrolimus, and leflunomide, it is generally of poor quality and demonstrates only moderate improvement at best. The evidence of benefit for IVIG and systemic retinoids (alitretinoin) is also limited, but the potential improvements appear greater. Whilst guidelines recommend that systemic corticosteroids and systemic antibiotics should be avoided, they retain an important role in the management of a small number of patients.

There is little published data to recommend the sequencing of systemic therapies, their use in combinations, optimal dosing, and when to stop treatment for remission.

The data on the newer specific targeted therapies, including monoclonal antibodies and small molecules, is very encouraging, but cost may limit their availability. For this reason, it is reasonable for patients to have tried and failed, or be contraindicated to at least two conventional systemic therapies (phototherapy, ciclosporin, methotrexate, azathioprine, or mycophenolate), over a period of at least six months.

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Table 1. Systemic therapy for adult atopic dermatitis (dosages are indicative only and are affected by renal function, lean body mass, co-morbidities and other drugs)

Agent	1 st line	2 nd line	3 rd line	As an add on	Monitoring
Prednisone/ Prednisolone	<p>Bridging to methotrexate, azathioprine or mycophenolate:</p> <ul style="list-style-type: none"> ➤ 6-10 weeks ➤ 40-50 mg/day for 1 week, 20-25 mg/day for 2 weeks, 10-12.5 mg/day for 3 weeks, (± 5 mg/day for 4 weeks) <p>Rescue therapy:</p> <ul style="list-style-type: none"> ➤ 3-6 days ➤ 40-50 mg for 2 days, 20-25 mg/day for 2 days, 10-12.5 mg/day for 2 days 	<p>For acute flares/rescue therapy:</p> <ul style="list-style-type: none"> ➤ 3-6 days ➤ 40-50 mg for 2 days, 20-25 mg/day for 2 days, 10-12.5 mg/day for 2 days 	<p>For late onset atopic dermatitis in the elderly:</p> <ul style="list-style-type: none"> ➤ >1 year ➤ 5-10 mg/day 	<p>Can be combined with all other agents:</p> <ul style="list-style-type: none"> ➤ <20 mg/day 	<p><12 weeks – nil unless clinically indicated</p> <p>>12 weeks – HbA1c, blood pressure, osteoporosis screening</p>
Ciclosporin	<p>Bridging to methotrexate, azathioprine or mycophenolate:</p> <ul style="list-style-type: none"> ➤ 1-3 months 	<ul style="list-style-type: none"> ➤ 1-3 months ➤ 3-5 mg/kg/day <p>May be used intermittently for long</p>	-	<p>Add to methotrexate or azathioprine:</p> <ul style="list-style-type: none"> ➤ 1-3 mg 	<p>Initially monthly blood pressure, fbc/renal/liver, then 2-4 monthly</p>

	<ul style="list-style-type: none"> ➤ 3-5 mg/kg/day <p>May be used intermittently for long term control (>1 yr):</p> <ul style="list-style-type: none"> ➤ 3 months ➤ 3-5 mg/kg/day 	term control (>1 yr)		mg/kg/day	
Methotrexate	<ul style="list-style-type: none"> ➤ 6-12 months ➤ 15 mg/week (range 10-25 mg/week) <p>May be used for long term control (>1 yr)</p>	<ul style="list-style-type: none"> ➤ 6-12 months ➤ 15 mg/week (range 10-25 mg/week) <p>May be used for long term control (>1 yr)</p>	-	Add to ciclosporin, azathioprine or biologics:	Initially monthly fbc/renal/liver, then 4-6 monthly
Azathioprine	<ul style="list-style-type: none"> ➤ 6-12 months ➤ 1-3 mg/kg/day, tapering when disease control achieved <p>May be used for long term control (>1 yr)</p>	<ul style="list-style-type: none"> ➤ 6-12 months ➤ 1-3 mg/kg/day, tapering when disease control achieved <p>May be used for long term control (>1 yr)</p>	<ul style="list-style-type: none"> ➤ 6-12 months ➤ 1-3 mg/kg/day, tapering when disease control achieved <p>May be used for long term control (>1 yr)</p>	Add to methotrexate or ciclosporin:	Initial TPMT 1 st 12 weeks: 2-4 weekly fbc/renal/liver >12 weeks: 3-6 monthly fbc/renal/liver
Mycophenolate mofetil	<ul style="list-style-type: none"> ➤ 6-12 months ➤ 1-3gm/day (start with 500 mg/day, increase 	<ul style="list-style-type: none"> ➤ 6-12 months ➤ 1-3gm/day (start with 500 mg/day, 	<ul style="list-style-type: none"> ➤ 6-12 months ➤ 1-3gm/day (start with 500 	Add to methotrexate or ciclosporin:	Initially monthly fbc/renal/liver, then 3-6 monthly

	weekly) May be used for long term control (>1 yr)	increase weekly) May be used for long term control (>1 yr)	mg/day, increase weekly) May be used for long term control (>1 yr)	➤ 1gm/day	
Anti-Staphylococcus antibiotics	Acute infection: Flucloxacillin 500 g tid for 3-7 days	Long term atopic dermatitis control: Flucloxacillin 500 g bd with food for 2-3 months	-	-	Skin swabs for sensitivities
Alitretinoin	-	Cost may restrict to 3 rd line	With significant hand dermatitis: ➤ 6-12 months ➤ 10-30 mg/day	Add to methotrexate or azathioprine: ➤ 10 mg/day	
Dupilumab	-	Cost may restrict to 3 rd line	After failure of standard systemic therapies: ➤ 6-24 months ➤ 300 mg sc every 2 weeks	-	
IVIg	-	-	Various dosages: ➤ 3-6 months ➤ 2 gm/kg/month	-	Nil, unless clinically indicated

Interferon-gamma	-	-	<ul style="list-style-type: none"> ➤ 3-6 months ➤ 50 µg/m² 3 times/week 	-	Initially monthly fbc/renal/liver
Tacrolimus	-	-	<ul style="list-style-type: none"> ➤ 3-6 months ➤ dosage dependent on formulation (narrow therapeutic window) 	Add to methotrexate or azathioprine: dosage dependent on formulation	Initially monthly blood pressure, fbc/renal/liver, then 2-4 monthly
Montelukast	-	-	3-6 month 10 mg/day	Add to methotrexate or ciclosporin	Nil, unless clinically indicated
Vitamin D	-	-	-	Add to all other agents: <ul style="list-style-type: none"> ➤ 600-700 IU/day 	6 monthly calcium
Leflunomide	-	-	-	Little evidence of benefit: <ul style="list-style-type: none"> ➤ 10-20 mg/day 	Initially monthly fbc/renal/liver, then 3-4 monthly
Omalizumab	-	-	-	Little evidence of benefit. May be of benefit	

				if also has significant chronic urticaria	
Other biologics: IL-5 IL12/23 IL-13 IL-31 Anti-TNFs Anti-CD20 Anti-TSLP	-	Cost may restrict to 3 rd line	Data still too immature to determine place in management	-	
JAK inhibitors: tofacitinib, baricitinib and upadacitinib	-	Cost may restrict to 3 rd line	Data still too immature to determine place in management	-	
Apremilast	-	Cost may restrict to 3 rd line	<ul style="list-style-type: none"> ➤ 3-12 month ➤ Titrate up to 30 mg twice daily 	-	