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[Intervention Protocol]

Systemic treatments for eczema: a network meta-analysis

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ABSTRACT

This is a protocol for a Cochrane Review (Intervention). The objectives are as follows:

To assess the effects of different types of systemic immunosuppressive treatments for eczema.

To generate rankings of the available systemic immunosuppressive treatments for eczema, according to their efficacy and safety.

BACKGROUND

Relevant terms used in the protocol are explained in the Glossary (Table 1).

Description of the condition

Eczema (also known as atopic eczema or atopic dermatitis) is a common and chronic, relapsing inflammatory skin disorder, characterised by intense pruritus and excoriation, with erythematous, xerotic, lichenified, fissured skin, and an increased risk of skin infections (Eichenfield 2014; Hanifin 1980; McCollum 2010; Weidinger 2016).

Eczema lesions vary in appearance, and papules, vesicles, scaling, fissuring, excoriations, crusting, oedema, and lichenification may be seen. Dry skin resulting from an impaired barrier function is also a key feature of eczema (Wollenberg 2016). Acute lesions typically comprise ill-defined red scaly patches, often with oedema and vesicle formation, while lichenification and pigmentation are more typical of chronic lesions. Excoriations due to intense pruritus may be seen at any stage. Although eczema can develop on any area of skin, different distribution patterns are often observed at different stages of life. In children under two years of age, eczema typically arises on the face, the trunk, and limbs including the extensor surfaces. In older children and adults, involvement of the neck and flexural aspects of the limbs (on the inside of joints, such as behind the knees and in the elbow creases) is common, as is involvement of the hands (Akdis 2006; Bos 2010).

Commonly used criteria to diagnose eczema include the Hani-

fin and Rajka diagnostic criteria, the UK Working Party diagnostic criteria, the Japanese Dermatological Association criteria, and the American Academy of Dermatology criteria (Brenninkmeijer 2008; Vakharia 2018). The severity and extent of eczema is extremely variable, ranging from mild eczema, with localised, occasionally dry, mildly scaly patches; to moderate eczema, with slightly more redness and swelling, with little or no oozing or crusting; to a severe, generalised involvement of the whole body, resulting in acute skin failure with widespread, red, oozing, secondarily infected lesions. Both objective signs of eczema and subjective symptoms, such as itch and sleeplessness, contribute to the assessment of clinical severity (Schmitt 2014). The disease severity is routinely assessed during a patient's clinical consultation, to track the progress of the disease and judge the efficacy of therapy.

The main objective physician-assessment tools used are the SCORAD (severity SCORing of Atopic Dermatitis) index (mild eczema corresponds to SCORAD levels below 25, and severe eczema to SCORAD levels above 50 (Kunz 1997)), the EASI (Eczema Area and Severity Index) score (Ricci 2009), and the Six-Area Six-Sign Atopic Dermatitis severity score (Charman 2002). The principal patient self-assessment tools are the POEM (Patient-Oriented Eczema Measure) scale (Spuls 2017), the SA-EASI (Self-Administered Eczema Area and Severity Index) rating scale (Housman 2002), and the ADQ (Atopic Dermatitis Quickscore (Carel 2008)). The Harmonising Outcome Measures for Eczema (HOME) initiative reached a consensus agreement that EASI should be the core instrument used for clinician-reported signs and POEM should be used for patient-reported symptoms (Schmitt 2014; Spuls 2017).

Eczema affects between 5% to 20% of children and 2% to 5% of adults worldwide, posing a significant burden for the affected patients, their families, and society (Johansson 2004; Odhiambo 2009). Eczema mainly affects infants and young children, but it can persist, relapse, or first develop in adulthood (Ellis 2012). About 80% of cases develop before the age of five years (Williams 2000). While it was previously estimated that about 25% of patients with early onset eczema progress to persistent eczema in adulthood (Williams 2005), the Odense Adolescence Cohort Study (TOACS) showed that up to 50% of patients had persistent eczema in adulthood (Mortz 2015). Similarly, another study found that 50% of subjects were still affected by age 20 (Margolis 2014). The clinical presentation of eczema is similar across different populations.

The International Study of Asthma and Allergies in Childhood (ISAAC) phase 3, conducted in children aged six to seven years old and 13 to 14 years old, found a decreased prevalence of eczema in some formerly high-prevalence countries in the developed world, especially in Northwest Europe, but an increased prevalence in many formerly low-prevalence developing countries, particularly in the younger age group (Williams 2008). Latin America emerged as a region of comparatively high prevalence of eczema symptoms, and a new area of high prevalence was also seen in Southeast Asia (Odhiambo 2009). A UK-based cross-sectional survey of 1760 children with eczema, aged between one to five years, classified 84% as having mild disease, 14% with moderate disease, and 2% as having severe disease. Referral to a dermatologist was correlated with disease severity, and 43% of severe cases had been seen by a dermatologist over the preceding year (Emerson 1998).

Eczema is a complex condition, caused by a combination of genetic and environmental influences, and characterised by cutaneous inflammation, immune dysregulation with a T helper 2 cell-biased response, and epidermal barrier dysfunction. It is strongly associated with genetic factors, in particular loss-of-function mutations in filaggrin, a key protein involved in the formation of the skin barrier, making a primary skin barrier defect the likely primary trigger of eczematous skin inflammation (Flohr 2014; McAleer 2013).

Eczema often occurs in families with atopic diseases, including asthma, allergic rhinitis, hay fever (and food allergy), and atopic eczema. These diseases share a common pathogenesis, and frequently are present together, in the same individual and family. The word atopy refers to the genetic tendency to produce immunoglobulin E (IgE) antibodies in response to small amounts of common environmental proteins, such as pollen, house dust mites, and food allergens (Stone 2002; Thomsen 2015). Around 30% of people with eczema develop asthma, and 35% develop allergic rhinitis (Luoma 1983). However, it is known that atopy does not occur concurrently in all patients with atopic eczema. In view of this, there have been recent proposals to use the term 'eczema' to define patients both with and without atopy. Therefore, in agreement with the 'Revised nomenclature for allergy for global use' (Johansson 2004), and similar to other Cochrane Reviews evaluating eczema therapies (van Zuuren 2017; Yew 2018), we will use the term 'eczema' throughout the review.

Several environmental factors, such as hard water, hygiene practices, and use of antibiotics early in life have been associated with eczematous skin inflammation (Flohr 2014). Patients' skin may be prone to inflammation in the presence of environmental insults, such as soaps and detergents, washing with hard water, and exposure to house dust mites (Cork 2009).

Many studies have assessed the ways in which eczema can affect quality of life. This condition can have a profound impact on the social, emotional, and physical health of an affected individual. Symptoms and visible lesions can cause behavioural problems, dependency, irritability, sleep loss, pain, itch, physical fatigue, shame, low self-esteem, anxiety, problems with relationships, and emotional distress (Maksimović 2012). There is also an important economic impact, due to frequent visits to physicians, frequent treatments, and days lost at work, which may also lead to fewer opportunities (Brenninkmeijer 2009; Chamlin 2004). Eczema is most commonly treated with topical medications. Patients often need to alter their daily routine to incorporate regular use of emollients and other topical treatments. Topical treatments can be messy, and can cause staining of bed sheets and attire. Many make changes to

the style of their attire to hide their rashes in public. The severity of the condition bears a close relation to the degree of impact on an affected individual's quality of life. There is also a significant component of out-of-pocket direct expenses for the treatments. A systematic review estimated the annual direct and indirect costs of eczema in the United States to be USD 364 million to USD 3.8 billion (Mancini 2008).

Description of the intervention

The standard initial management of eczema includes the use of emollients and topical corticosteroids of appropriate potency to treat affected sites. Topical calcineurin inhibitors (including tacrolimus and pimecrolimus) are licensed for use in adults and children, aged two years and older, as second-line treatments for moderate to severe eczema that has not been controlled by topical corticosteroids, where there is a serious risk of important adverse effects from further topical corticosteroid use (particularly irreversible skin atrophy). Systemic immunosuppressive treatments are reserved for the treatment of more severe cases of eczema that have been inadequately controlled with topical treatments (such as topical corticosteroids and topical calcineurin inhibitors). The choice of systemic treatment for eczema in adults and children may vary (Sidbury 2014; Wollenberg 2016). For adults with severe eczema, therapeutic options are oral glucocorticosteroids (given for short courses only), cyclosporin A (ciclosporin), methotrexate, azathioprine, mycophenolate mofetil, psoralen-ultraviolet A (PUVA), and alitretinoin. For children with severe eczema, therapeutic options are cyclosporin A (ciclosporin), methotrexate, azathioprine, and mycophenolate mofetil. Based on expert opinion, the threshold for using systemic treatment in children with eczema is typically higher than for adults (Flohr 2013). The choice of systemic agent and treatment duration has not been standardised, and is made on an individual patient basis (Wollenberg 2016).

The interventions of interest in this systematic review are all systemic (oral, subcutaneous, intravenous, sublingual, or inhalation administration) immunosuppressive treatments that are used to treat severe eczema. In this review, 'immunosuppressive treatment' is used synonymously with 'anti-inflammatory treatment' and 'immune-modulatory treatment', as we consider immunosuppression or anti-inflammatory effects to be the main mechanism of action of the interventions investigated. We are aware that immunosuppression usually relates to modulation of the immune response.

We will include systemic corticosteroid, cyclosporin A (ciclosporin), methotrexate, azathioprine, mycophenolate mofetil, tacrolimus, interferon gamma, intravenous immunoglobulin (IVIG), psoralen-ultraviolet A (PUVA), alitretinoin, apremilast, infliximab, rituximab, tocilizumab, dupilumab, mepolizumab, and omalizumab in this review (Sidbury 2014; Wollenberg 2016; Zirwas 2018). These treatments cover all systemic immunomodulatory agents included in the recent European Task Force of the Academy of Dermatology/European Academy of Dermatology and Venereology (ETFAD/EADV (Wollenberg 2016)), and American Academy of Dermatology (AAD) guidelines (Sidbury 2014).

Systemic corticosteroids are used short term to manage significant flares in eczema, rather than as a long-term treatment. Anecdotally, they rapidly improve clinical symptoms of eczema, but their side-effect profile (particularly when used longer term) is unfavourable, and a flare of eczema commonly develops once the corticosteroid dose is weaned (Schmitt 2010). For this reason, and because of their largely unfavourable risk to benefit ratio, only short-term use, for a few weeks to treat severe acute exacerbations of eczema, is advised (Wollenberg 2016; Yu 2018). Different formulations of systemic corticosteroids are used to treat eczema, including prednisone, prednisolone, and triamcinolone acetonide. Prednisone and prednisolone are available as an oral tablet or oral solution; triamcinolone is available as a suspension, which is administered intramuscularly. The dosing is based on the patient's body weight, and typically, doses of 0.5 mg/kg/day to 1 mg/kg/day are administered. Adverse effects of corticosteroids are numerous, and include increased risk of infections, hypertension, glucose intolerance, weight gain, gastritis, reduced bone mineral density, adrenal suppression, ophthalmological complications, including cataracts and glaucoma, sleep disturbance, and mood lability. Systemic corticosteroids are often prescribed along with proton pump inhibitors to protect against gastric irritation, and calcium and vitamin D supplements to protect against bone density loss. Use of systemic corticosteroids in children may result in stunted growth (Daley-Yates 2004).

Cyclosporin A (ciclosporin) is an effective systemic treatment option, recommended for patients with eczema that is refractory to conventional topical treatment (AAD Guideline Strength of Recommendation: B, Level of Evidence: I, II (Sidbury 2014)), usually in doses ranging from 2 mg/kg/day to 5 mg/kg/day, taken in two divided doses (Schmitt 2007). The lowest dose to control eczema effectively, should be used. Cyclosporin may be used long term (up to 12 months) or for shorter-term courses (e.g. three to six months). Adverse effects associated with the use of cyclosporin include: increased risk of infection, nephrotoxicity, hypertension, hypertrichosis, gingival hyperplasia, tremor, and increased risk of skin malignancy and lymphoma. Drug interactions with cyclosporin are common. Caution should be exercised when individuals are on: anti-fungals (e.g. fluconazole), antibiotics (e.g. macrolides, fluoroquinolones, rifampicin), amiodarone, diuretics (e.g. furosemide), calcium channel antagonists (e.g. diltiazem), statins (e.g. atorvastatin, simvastatin), anti-epileptics (e.g. carbamazepine, phenytoin), serotonin reuptake inhibitors (e.g. fluoxetine), warfarin, or anti-HIV drugs (e.g. ritonavir).

Methotrexate is recommended as a systemic agent for the treatment of refractory eczema (AAD Guideline Strength of Recommendation: B, Level of Evidence: I, II) in adults and children (El-Khalawany 2013; Schram 2011; Sidbury 2014; Weatherhead 2007). Folate supplementation is recommended during treatment

with methotrexate, as methotrexate is an anti-folate metabolite (Sidbury 2014). It can be administered in oral tablet form, or as an oral solution, auto-injected subcutaneously, which results in improved bioavailability. It is used at low doses (in contrast to its use in cancer therapy), ranging from 7.5 mg to 25 mg, usually as a single weekly dose. Potential side effects include: nausea and gastrointestinal upset (which usually can be avoided by using subcutaneous administration), oral and mucosal ulceration, bone marrow suppression, increased risk of infections, hepatotoxicity, and pulmonary fibrosis. Methotrexate is teratogenic, and must be avoided during pregnancy and breast feeding. Drug interactions occur with: folic acid antagonists (e.g. antibiotics containing trimethoprim or sulphonamides, such as co-trimoxazole), which increase the risk of toxicity, drugs which interfere with the renal excretion of methotrexate, such as non-steroid anti-inflammatory drugs (e.g. ibuprofen) and penicillins, and hepatotoxic drugs (e.g. barbiturates), which can increase the risk of hepatotoxicity.

Azathioprine is recommended as a systemic agent for the treatment of refractory eczema (AAD Guideline Strength of Recommendation: B, Level of Evidence: I, II), usually at doses ranging from 1 mg/kg/day to 3 mg/kg/day (Berth-Jones 2002; Meggitt 2006; Sidbury 2014). Its metabolism is dependent on thiopurine methyltransferase (TPMT), a key enzyme in the thiopurine pathway. There are genetic polymorphisms in TPMT, which may result in variable enzyme activity. Therefore, a baseline TPMT level should be checked before initiating azathioprine; it should be avoided in those with low or absent enzyme activity, who are at greater risk of developing azathioprine toxicity, particularly bone marrow suppression. Common side effects include nausea, vomiting, and other gastrointestinal upset. Other potential side effects include: hypersensitivity reactions, hepatotoxicity, pancreatitis, increased risk of infections and skin cancer, and bone marrow suppression. Co-administration with allopurinol increases the risk of bone marrow suppression, and ideally, should be avoided.

Mycophenolate may be considered an alternative therapy for refractory eczema (AAD Guideline Strength of Recommendation: B, Level of Evidence: II). It shows variable effectiveness, and is typically tried after other systemic immunosuppressive treatments, such as cyclosporin, methotrexate, or azathioprine have failed, or are contraindicated (Haeck 2011; Heller 2007; Sidbury 2014). Mycophenolate can be administered by oral suspension, capsules, or tablets and is given in doses ranging from 0.5 mg/day to 3 mg/day, in two divided doses. The most common side effect is gastrointestinal upset. Less common side effects include headaches, bone marrow suppression (particularly leukopaenia), and increased risk of infections. Several drugs, including rifampicin, cholestyramine, and antacids, reduce the blood levels of mycophenolate, and co-administration with acyclovir increases blood acyclovir levels.

While **topical tacrolimus** and **pimecrolimus** are licensed as second-line topical treatments for eczema, oral tacrolimus has very rarely been used off-license to manage refractory eczema that has failed to respond to other systemic immunosuppressive treatments (Schroer 2003). Pimecrolimus is currently available only in topical form.

Interferon gamma is moderately and variably effective, and may be considered as an alternative therapy for refractory eczema in adults and children who have not responded to, or have contraindications to the use of, other systemic therapies or phototherapy (AAD Guideline Strength of Recommendation: C, Level of Evidence: III (Hanifin 1993; Jang 2000; Sidbury 2014)). It is administered as a subcutaneous injection, but there is no recommended optimal dose or established regimen for the treatment of eczema. Side effects include fatigue, fever, nausea, vomiting, and myalgia.

Intravenous immunoglobulin (IVIG) has rarely been used, and only tested in small, uncontrolled studies to treat severe refractory eczema in adults and children, with variable success (Jee 2011; Paul 2002). There is no established regimen for the treatment of eczema.

Psoralen-ultraviolet A (PUVA) is a type of ultraviolet radiation treatment, which starts with a photosensitising medicine, called a psoralen, and is followed by exposure of the affected skin to UVA. For oral PUVA, oral psoralens (e.g. 8-methoxypsoralen, 5-methoxypsoralen) are taken two to three hours before exposure to UVA in a phototherapy cabinet. Phototherapy is often used as a second-line option for treating eczema, after it failed to respond to topical corticosteroids and calcineurin inhibitors, but requires regular attendance at the hospital to receive treatment, which may not be logistically feasible for all patients. Narrowband UVB phototherapy is preferred over broadband UV phototherapy, including PUVA, as the latter is associated with an increased risk of non-melanoma skin cancer, despite its effectiveness with refractory eczema (Atherton 1988; Sidbury 2014; Uetsu 2003). The dosing and scheduling of phototherapy is usually based on the patient's response to sun exposure according to Fitzpatrick skin type (Sachdeva 2009), their measured minimal erythema dose, or both. Typically, twice weekly PUVA treatments are given for eczema, and the dose of UVA radiation is gradually increased over the course of treatment. The total number of PUVA treatments will depend on individual factors. It is relatively common to experience some skin redness or itching after treatments. Overdose of PUVA may result in skin burning, and so ideally, the patient should wear the same cut of clothes or underwear during the course of treatment. Male patients are advised to cover their genitals with a close-fitting pouch or jock strap to prevent burning. Eye protection must be worn to protect against damage to the eyes, which could result in cataracts. Psoralen tablets may result in nausea. Patients with a history of cold sores triggered by sunlight, are advised to wear sunblock while receiving phototherapy, to help prevent recurrences. PUVA is not advised during pregnancy or breastfeeding, due to the potential risk of foetal damage, secondary to the use of psoralen. While limited courses of PUVA may be used, long-term continuous treatment is not advised, due to the increased risk of developing skin cancers. PUVA can be used as a monotherapy, or in combination with emollients and topical corticosteroids. Topical

calcineurin inhibitors should be avoided on days of PUVA treatment, as these are photosensitising and could increase the risk of burning. Other oral or topical photosensitising treatments should be avoided during PUVA treatment, e.g. tetracyclines.

Alitretinoin (9-*cis*-retinoic acid) is an oral retinoid, licensed in Europe and Canada, for the treatment of severe chronic hand eczema that is unresponsive to potent topical corticosteroids (Ruzicka 2008), and has also been used to successfully treat extrapalmar eczema in a small case series (Grahovac 2010). Alitretioin is generally given at a dose of 30 mg/day for periods of 24 weeks (although the dose can be reduced to 10 mg/day if side effects are problematic). The most common side effects include headache, mucocutaneous dryness, and photosensitivity. Alitretinoin can also result in hypercholesterolaemia, hypertriglyceridaemia, and rarely, hypothyroidism. It may affect night vision, so those whose jobs require good night vision, e.g. airline pilots, may not be able to take this treatment. Alitretinoin is teratogenic, and must be avoided during pregnancy and breast feeding. Alitretinoin contains soya oil; occasionally, patients with soya allergy may react to trace levels of soya proteins in soya oil. It is extremely rare for patients with peanut allergy to cross-react to alitretinoin. Very rarely, alitretinoin may result in mood changes and potentially suicidal ideation, so this treatment should be initiated cautiously in patients with previous or current depression. Due to the rare side effect of idiopathic intracranial hypertension, alitretinoin should not be combined with tetracycline antibiotics.

Apremilast is a selective inhibitor of phosphodiesterase-4 (PDE-4), and is administered orally, at a dose of 30 mg twice daily. It is licensed in Europe for the treatment of moderate to severe psoriasis and psoriatic arthritis. While apremilast showed promising results in an early pilot study and several uncontrolled case reports and case series of severe eczema, it did not meet its primary end point in a double-blind placebo-controlled trial, and therefore, has not been approved for the treatment of eczema (Samrao 2012). Of interest, a topical PDE-4 inhibitor, crisaborole, is approved in the USA for the treatment of mild to moderate eczema in children younger than two years (Paller 2016).

Infliximab is a chimeric monoclonal antibody, targeting tumour necrosis factor alpha (TNF-α), which is administered by intravenous infusion. It is not licensed for the treatment of eczema, but has been used off-label in small case reports and case series, to treat refractory cases of severe eczema, with variable success (Jacobi 2005; Ruiz-Villaverde 2012; Snast 2018).

Rituximab is a chimeric monoclonal antibody targeting CD20, a key surface marker on B-lymphocytes, and is administered by intravenous infusion. There have been inconsistent results seen in small case reports and case series when rituximab was used to treat severe, refractory cases of eczema, so this would not be a standard treatment option (McDonald 2016; Simon 2008; Sediva 2008).

Tocilizumab is a humanised monoclonal antibody targeting the interleukin-6 receptor, and is administered by subcutaneous injection or intravenous infusion. A very small case series of three patients suggested a benefit when used to treat eczema, but two developed bacterial infection (Navarini 2011). This is not a licensed treatment for eczema.

Dupilumab is a humanised monoclonal antibody targeting the alpha subunit of the interleukin-4 receptor (IL-4Rα). Through blocking this receptor, dupilumab reduces signalling through both interleukin-4 and interleukin-13 pathways. There is randomised controlled trial evidence that dupiluamb is an effective treatment for eczema (Beck 2014; Wang 2018). It has been licensed in the United States for the treatment of moderate to severe eczema, and has also recently been approved for use in Europe, at a dose of 300 mg every two weeks, administered subcutaneously, following a 600 mg loading dose. The main side effects of dupilumab are injection site reactions, conjunctivitis, and cold sores.

Mepolizumab is a humanised monoclonal antibody, administered by subcutaneous injection, which prevents interleukin 5 from binding to its receptor. It is licensed for the treatment of severe asthma with an eosinophilic phenotype in the United States and Europe. However, it did not appear to be more effective than placebo in the treatment of severe eczema in adults, and therefore, is not a licensed treatment for eczema (Oldhoff 2005).

Omalizumab is a humanised monoclonal antibody that specifically binds to free human immunoglobulin E (IgE) in the blood and interstitial fluid, and to membrane-bound forms of IgE on the surface of IgE-expressing B-lymphocytes. It is administered by subcutaneous injection, and is approved for the treatment of moderate to severe allergic asthma and chronic spontaneous urticaria. The results for using omalizumab to treat eczema are conflicting, and this is not a licensed treatment (Belloni 2007; Heil 2010; Iyengar 2013).

How the intervention might work

The different systemic immunosuppressive treatments used for eczema suppress skin and systemic inflammation to control disease signs and symptoms (Roekevisch 2014; Schmitt 2007; Simon 2014; Slater 2015). They may also help to reduce the need for regular use of topical corticosteroid therapy (Wollenberg 2016). Some have been shown to increase quality of life (Roekevisch 2014). Interruption of the inflammatory pathways implicated in eczema is the general mode of action of all systemic immunosuppressive treatments for eczema. The potential targeted interruption of the inflammatory pathways for each systemic treatment of interest for eczema include:

- Oral corticosteroids, such as prednisolone, have a broad anti-inflammatory effect. They act in a non-specific manner, and suppress several immunologic functions, such as interfering with antigen presentation to T lymphocytes, inhibiting prostaglandin and leukotriene synthesis, inhibiting neutrophil and monocyte superoxide radical generation, impairing cell migration, and causing redistribution of monocytes, lymphocytes, and neutrophils, thus blunting the inflammatory and autoimmune

responses. Therefore, they are used widely in the treatment of various inflammatory diseases, including eczema (Schmitt 2009; Schmitt 2010).

- Cyclosporin A (CyA or ciclosporin) is a calcineurin inhibitor. The immunosuppressive role of cyclosporin A can be explained by the inhibition of the transcription of T-cell cytokine genes, and this is the mechanism by which it is thought to treat various inflammatory skin conditions, including eczema. It has been shown to inhibit interleukin-2 (IL-2), IL-3, IL-3 granulocyte macrophage colony-stimulating factor, tumour necrosis factor-alpha (TNF-alpha), and interferon-gamma expression (Faulds 1993).

- Methotrexate is a folic acid antagonist, and has proved previously to be effective in chronic inflammatory diseases, such as psoriasis and rheumatoid arthritis. The mechanism(s) by which methotrexate treats eczema is unknown, although it is thought its anti-inflammatory effects may be mediated through adenosine pathways, and its immunomodulatory effects may be due to alteration of signalling and trafficking of immune cells, including T cells (Braun 2009).

- Azathioprine is a purine analogue. It inhibits de novo purine biosynthesis to produce broad immunosuppressive effects (Dutz 1998).

- Mycophenolate mofetil, or mycophenolic acid, is a purine biosynthesis inhibitor. It inhibits the synthesis of deoxyribonucleic acid (DNA) and ribonucleic acid (RNA) by interfering with de novo purine biosynthesis. Its mechanism of action in treating eczema is unknown, but it is thought to be due to inhibition of the proliferative response of both B and T lymphocytes, reducing cutaneous inflammation (Abd Rahman 2013).

- Tacrolimus, like cyclosporin A (ciclosporin), is a calcineurin inhibitor, and therefore inhibits T-cell cytokine genes, including interleukin 2, reducing inflammation. It is primarily used following solid organ transplantation, to reduce the risk of organ rejection, but is rarely used in very refractory cases of eczema. As a topical agent, tacrolimus is used commonly as a second-line intervention for eczema (Wollenberg 2016); a range of mechanisms resulting in improved eczema have been proposed (Nakahara 2018).

- Interferon gamma is a cytokine that plays a key role in the innate and adaptive immune system. It has been used rarely in cases of severe eczema unresponsive to other systemic immunosuppressive treatments. Its mechanism of action for the treatment of eczema is unclear. It is postulated to be able to correct the immunological imbalances in patients with eczema by decreasing serum IgE levels and IL-4 levels, and restoring immune balance, thereby leading to clinical improvement (Chang 2002).

- Intravenous immunoglobulins (IVIG) are blood products derived from the pooled plasma of many individuals. A variety of anti-inflammatory and immunomodulatory effects have been proposed to explain the effectiveness of IVIG in treating a wide variety of autoimmune and inflammatory conditions, including immune thrombocytopaenia, myasthenia gravis, and dermatomyositis (Ballow 2014; Gelfand 2012).

- Psoralen-ultraviolet A (PUVA) is thought to exert its therapeutic effect through multiple mechanisms, primarily through its immunomodulatory properties, including altering cytokine and cytokine receptor expression, lymphocyte apoptosis, reducing adhesion molecule expression, and affecting the function of antigen presenting cells (Johnson 1996; Laing 1995; Liszewski 2017; Singh 2010).

- Alitretinoin is a retinoid with anti-inflammatory and anti-proliferative effects, which reduce keratinocyte chemokine expression, suppress leukocyte recruitment, and inhibit dendritic cell-mediated T-cell activation (Kislat 2011).

- Apremilast is a small molecule inhibitor of phosphodiesterase-4 (PDE-4). Leukocytes from patients with eczema display elevated phosphodiesterase (PDE) activity compared to normal controls, which leads to leukocyte hyperactivity and inflammation (Hanifin 1996). Inhibition of PDE-4 results in increased intracellular cyclic adenosine monophosphate, which activates protein kinase A and other intermediate mediators, resulting in inhibition of pro-inflammatory cytokine production and reduced inflammation (Souness 2000).

- Infliximab is a chimeric monoclonal antibody that targets tumour necrosis factor alpha (TNF-alpha), and prevents TNF-alpha from binding to its receptor. Infliximab has a dual mode of action; it blocks soluble TNF-alpha, and induces lysis (breakdown of a cell) of TNF receptor bearing target cells, which is required to activate the complement complex (the key part of the autoimmune reaction). Blockade of TNF-alpha inhibits the migration of leukocytes and the release of additional TNF-alpha dependent pro-inflammatory cytokines, such as IL-1, IL-6, and IL-8. Patients with eczema reportedly have significantly elevated serum and tissue concentrations of TNF-alpha, and thus, may be responsive to treatment with TNF-ainhibitors (Ackermann 1998).

- Rituximab is an anti-CD20 monoclonal antibody that leads to the depletion of B cells, which act as antigen-presenting cells, promote T-cell activation, and produce pro-inflammatory cytokines and IgE (Grillo-Lopez 1999). The mechanism by which rituximab may help to treat eczema is not defined, but such treatment has been associated with reduced expression of interleukin 5 and interleukin 13, cytokines known to contribute to cutaneous inflammation seen in eczema (Simon 2008).

- Tocilizumab is a humanised monoclonal antibody targeting the interleukin-6 receptor, thereby, inhibiting interleukin-6 signalling. Interleukin 6 is a pro-inflammatory cytokine produced by numerous immune cells, and has been shown to be involved in T-cell activation, and induction of immunoglobulin secretion amongst other physiological reactions. T cells from the peripheral blood of patients with eczema have been shown to produce significantly higher levels of IL-6 than controls, making this cytokine a potential therapeutic target (Toshitani 1993).

- Dupilumab is a monoclonal antibody targeting the alpha subunit of the interleukin-4 receptor (IL-4 alpha). In doing so, it reduces signalling through interleukin-4 and interleukin-13 pathways, which are known to drive cutaneous inflammation in eczema (Kraft 2017).

- Mepolizumab is an anti-IL-5 monoclonal antibody that leads to reduced serum eosinophil counts. Since the inflammation of eczema is characterised by eosinophil infiltration, the depletion of eosinophils by this drug would appear to be a promising approach for eczema treatment (Leiferman 2001).

- Omalizumab is an anti-IgE monoclonal antibody. As an atopic condition, eczema is characterised by a genetic tendency to produce IgE antibodies in response to common environmental proteins, and high levels of serum IgE are commonly seen, making IgE inhibitors a potential therapeutic target in patients with eczema (Liu 2011).

Why it is important to do this review

Patients with moderate to severe eczema are often difficult to treat (Ring 2012). Current clinical practice is frequently not based on a systematic critical appraisal of the published evidence, but rather expert opinion without clear evidence for the given condition (Darsow 2010; Sidbury 2014; Wollenberg 2016). Recently, a survey among 700 dermatologists and paediatricians from eight European countries confirmed wide variation in systemic treatment approaches for children and adolescents with moderate to severe atopic eczema (Proudfoot 2013). First-line systemic agents were cyclosporin A (ciclosporin), oral corticosteroids, and azathioprine. Systemic immunosuppressive treatments are normally used in severe eczema, but their use in moderate eczema is controversial, due to safety concerns. In general, expensive systemic immunosuppressive treatments with potentially serious adverse effects should not be used for moderate cases, which usually respond well to patient education, and adequate and safe use of topical corticosteroids, including proactive control (weekend therapy) and treatment combined with topical calcineurin inhibitors (TCIs) (Sidbury 2014; Wollenberg 2016). Current clinical practice guidelines do not provide explicit guidance on systemic treatment strategies for adults and children with eczema, and their comparative effectiveness and role in treating different patient subgroups remains unclear (Ring 2012; Saeki 2016; Sidbury 2014; Wollenberg 2016). There are limited randomised studies directly comparing different systemic agents for eczema. While dupilumab has recently become the first approved biological treatment for moderate to severe eczema whose disease is not adequately controlled with topical therapies, its efficacy relative to other systemic immunosuppressive treatments for eczema has not been established (Boguniewicz 2017).
Network meta-analysis refers to a meta-analysis in which multiple treatments (i.e. three or more treatment options) are compared, using both direct comparisons of interventions within studies, and indirect comparisons across studies, based on a common comparator. Since available studies comparing different systemic immunosuppressive treatments are limited, network meta-analysis allows combination of the direct and indirect evidence, and ranking of different systemic immunosuppressive treatments (Salanti 2011; Salanti 2012). To date, there has been no network meta-analysis of this topic, although several pairwise systematic reviews on the systemic immunosuppressive treatments of eczema have been published (Roekevisch 2014; Schmitt 2007). This review is also timely, as previous reviews did not include new treatments, such as biological therapies, and they focused mainly on clinical signs, rather than addressing the core outcome domains identified by the Harmonising Outcome Measures for Eczema (HOME) initiative: clinical signs, patient symptoms, long-term control, and quality of life (Chalmers 2016; Chalmers 2018; Schmitt 2014). Moreover, the Cochrane Skin Group undertook an extensive prioritisation exercise, alongside the Global Burden of Disease and the World Health Organization, to identify a core portfolio of the most clinically important titles. The subject of systemic immunosuppressive treatments for eczema was identified as one of the top five titles for clinically important research priorities (Crowe 2012).
Our review is complemented by another Cochrane Review, 'Topical treatments for eczema: a network meta-analysis' (Yew 2018). Please note that because of this, there is considerable overlap in the background and methodology.

OBJECTIVES

To assess the effects of different types of systemic immunosuppressive treatments for eczema.

To generate rankings of the available systemic immunosuppressive treatments for eczema, according to their efficacy and safety.

METHODS

Criteria for considering studies for this review

Types of studies

We will include only randomised controlled trials (RCTs) of one or more systemic immunosuppressive treatments for eczema. We will include placebo-controlled, head-to-head trials, and multi-arm studies.

Types of participants

We will consider participants of all ages with a clinical diagnosis of eczema. They could have fulfilled diagnostic criteria, such as the Hanifin and Rajka definition (Hanifin 1980; Appendix 1), or the UK modification (Williams 1994; Appendix 2), or been diagnosed clinically by a clinical healthcare professional, using the terms 'atopic eczema', or 'atopic dermatitis'.

We will pose no restrictions on age, sex, ethnicity of the participants, or severity of eczema.

We will exclude studies that include participants with other types of eczema, such as contact dermatitis, seborrhoeic eczema (seborrhoeic dermatitis), varicose eczema, and discoid eczema.

We will only include studies in which there is a subset of relevant participants (where not all participants in the study have eczema), when we can obtain specific and separate information on participants with eczema.

Types of interventions

We will consider studies to be eligible if they investigate the efficacy or safety of at least one systemic immunosuppressive or immunomodulatory therapy for eczema, or a combination of treatments from the following: systemic corticosteroids, cyclosporin A (ciclosporin), methotrexate, azathioprine, mycophenolate mofetil, interferon gamma, intravenous immunoglobulin (IVIG), psoralen-ultraviolet A (PUVA), alitretinoin, apremilast, infliximab, rituximab, tocilizumab, dupilumab, mepolizumab, omalizumab, and others, including new immunosuppressive or immunomodulatory whose first trials are published between publication of this protocol and our final literature search.

Types of outcome measures

Outcomes of interest in this review will include the recommended core outcome domains for eczema trials following the global Harmonizing Outcome Measures for Eczema (HOME) initiative, including clinical signs (measured by using a physician-assessed instrument), symptoms (measured by using a patient-assessed instrument), health-related quality of life, and long-term control of eczema (Chalmers 2016; Chalmers 2018; Schmitt 2014; Spuls 2017).

Timing of outcomes

We will define outcomes as short term ($\leq$ 16 weeks of treatment), and long term, or maintenance (> 16 weeks of treatment (Blauvelt 2017)). For multiple times of outcome measurement, we will use the data at the end of study, and classify them as short-term outcomes if the study period is $\leq$ 16 weeks. If the study period exceeds 16 weeks, we will use the data at the end of the study and classify them as long-term outcomes. We will classify outcomes measured closest to 16 weeks as short-term outcomes.

Primary outcomes

1. Clinical severity of eczema, measured by a validated or objective measure, such as the Eczema Area and Severity Index (EASI (Ricci 2009)), Scoring Atopic Dermatitis (SCORAD (Kunz 1997)), the Six Area, Six Sign Atopic Dermatitis (SASSAD) severity score (Charman 2002), Investigators' Global Assessment (IGA), affected Body Surface Area (BSA), and other less reported measures. EASI will be the preferred instrument for this outcome measure, as there is consensus agreement by the HOME initiative that this should be a core instrument for clinician-reported signs (Schmitt 2014).
2. Participant-reported symptoms, measured by a validated measure, such as the Patient-Oriented Eczema Measure (POEM (Spuls 2017)), Self Administered Eczema Area and Severity Index (SA-EASI (Housman 2002)), Itch Severity Scale (ISS) (Majeski 2007), or other less validated measures, such as the Atopic Dermatitis Assessment Measure (ADAM (Charman 1999)), Patient-Oriented SCORAD (PO-SCORAD (Stalder 2011)), and the Leuven Itch Scale (LIS (Haest 2011)). POEM will be the preferred instrument for this outcome measure, as there is consensus agreement by the HOME initiative that this should be a core instrument for patient-reported symptoms (Spuls 2017).
3. Adverse effects: we will consider the most common serious adverse effects of each systemic treatment, such as infection with all agents, conjunctivitis with the new biologic agents, renal function impairment and hypertension with cyclosporine, and stomach upset with mycophenolate mofetil.

The instruments listed for outcomes one and two are in decreasing order of importance.

Secondary outcomes

1. Participant's self-assessment of global response of improvement (e.g. Patients' Global Assessment (PsGA) (Farina 2011)).
2. Health-related quality of life, measured by a validated measure, such as the Dermatology Life Quality Index (DLQI (Finlay 1994)), Quality of Life Index for Atopic Dermatitis (QoLIAD (Whalley 2004)), and Skindex (Chren 2012), in this order of decreasing hierarchy.
3. Long-term control of eczema, following the HOME initiative, such as repeated measurement of clinical signs (flares), symptoms, and quality of life, plus a global patient assessment of eczema (Chalmers 2014).

Search methods for identification of studies

We aim to identify all relevant RCTs, regardless of language or publication status (published, unpublished, in press, or in progress).

Electronic searches

The Cochrane Skin Information Specialist will search the following databases:

- the Cochrane Skin Group Specialised Register (current date);
- the Cochrane Central Register of Controlled Trials (CENTRAL) in the Cochrane Library (current issue);
- MEDLINE Ovid (from 1946 onwards);
- Embase Ovid (from 1974 onwards); and
- the GREAT database (Global Resource of EczemA Trials. Centre of Evidence Based Dermatology; www.greatdatabase.org.uk; current date).

The Cochrane Skin Information Specialist has developed a draft search strategy for RCTs for MEDLINE Ovid, which we included in Appendix 3. We will use this as the basis for search strategies for the other databases listed, edited as indicated.

Trial registers

Two review authors (RS, PD) will search the following trials registers:

- the metaRegister of Controlled Trials (www.isrctn.com);
- the US National Institutes of Health Ongoing Trials Register (www.clinicaltrials.gov);
- the Australian New Zealand Clinical Trials Registry (www.anzctr.org.au);
- the World Health Organization International Clinical Trials Registry platform (www.who.int/trialsearch); and
- the EU Clinical Trials Register (www.clinicaltrialsregister.eu).

We will search the registers, using the following terms adapted from the search strategy for MEDLINE (Appendix 3):
For the population: eczema or dermatitis or atopic dermatitis.
For interventions: immunosuppressive agents, immunomodulatory agents, name of each systemic agent used for eczema, including: cyclosporin A (ciclosporin), azathioprine, methotrexate, mycophenolate mofetil or mycophenolic acid, oral glucocorticosteroids, oral prednisolone, psoralen-ultraviolet A, tacrolimus, interferon-gamma, intravenous immunoglobulin (IVIG), alitretinoin, apremilast, and biological therapies, including: infliximab, rituximab, tocilizumab, dupilumab, mepolizumab, omalizumab, or their synonyms.

Searching other resources

References from published studies

We will check the bibliographies of included studies and any identified, relevant systematic reviews, for further references to relevant trials.

Searching by contacting relevant individuals or organisations

We will contact the lead authors of all relevant study reports identified, and experts in the field, to request information on additional published and unpublished studies that may be relevant to the review.

Adverse effects

We will not perform a separate search for adverse effects of the target interventions. However, we will examine data on adverse effects from the included studies.

Data collection and analysis

Selection of studies

The Covidence software will be used to screen our search results (Covidence). At least two review authors (RS, PD, ALL, NC) will independently screen the title and abstract of all reports identified by searching the electronic databases and other search strategies, against the aforementioned criteria, to identify studies that appear relevant. Subsequently, the full text of all potentially relevant studies will be retrieved, and independently compared to the predefined inclusion criteria. We will provide reasons for the exclusion of these short-listed papers in a 'Characteristics of excluded studies' table. During the selection process, the two review authors will discuss any disagreements within the reviewing team until consensus is reached. We intend to follow the PRISMA statement and will create a flowchart for the selection of studies (Hutton 2015).

Data extraction and management

Two review authors (RS, PD) will independently extract data from all eligible studies, using a structured data collection form to ensure consistency of appraisal. We will resolve disagreements about data extraction by discussion. For each of the included studies, we will extract the following information, and transfer it into a 'Characteristics of included studies' table:

- **General information:** publication status, title, authors, source, country, language of publication, year of publication, study design, study location, study setting (single or multi-

centre), information on training methods, and alignment of assessment methods.

- **Participant characteristics:** number of people with eczema included (sample size, total, and by intervention), age (mean ± standard deviation (SD) years), sex, severity of eczema, previous treatments, atopic comorbidities, inclusion and exclusion criteria, and baseline characteristics of intervention and comparison groups.
- **Interventions:** description of intervention (treatment and comparison), mode of administration, dose, frequency, duration of active treatment and follow-up, and adjuvant treatments.
- **Outcomes:** primary and secondary outcomes, total serious adverse events, total adverse events, the most common worst side effect of each systemic treatment, such as infection with all agents, conjunctivitis with the new biologic agents, renal function impairment and hypertension with cyclosporine, and stomach upset with mycophenolate mofetil, and other defined outcomes and reported time points. In addition, we will extract data at the group level, such as effect sizes and standard error, comparing a pair of interventions (not summary effects) if possible.
- **Note:** sponsorship or funding for studies, and notable conflicts of interest of trial authors.

Assessment of risk of bias in included studies

Two review authors (RS, PD) will independently assess each study for risk of bias, using the Cochrane tool (Higgins 2011a; Higgins 2011b). This tool examines seven major sources of bias:

- Random sequence generation (selection bias)
- Allocation concealment (selection bias)
- Participants and personnel blinding (performance bias)
- Outcome assessment blinding (detection bias)
- Incomplete outcome data (attrition bias)
- Selective reporting (reporting bias)
- Other sources of bias, including design-specific risks of bias and baseline imbalance.

We will consider attrition bias at low risk of bias if the drop-out rate is < 20%. However, If a RCT had drop-outs and used an intention-to-treat (ITT) analysis, but gave no information on the handling of the missing data, we will judge the risk of bias as unclear, due to incomplete outcome information. We will judge the risk of bias in each study, against each source, as low, high or unclear risk of bias (either lack of information or uncertainty over the potential of bias). We will consider the relative importance of each item to be equal.

We will determine the overall risk of bias for each outcome (across domains) within studies as follows (Higgins 2011a; Higgins 2011b):

1. Low risk of bias, when all domains are assessed as being at low risk, or plausible bias is unlikely to seriously alter the results;
2. Unclear risk of bias, when at least one domain is classified as being at unclear risk, or plausible bias raises some doubt about the results;
3. High risk of bias, when at least one domain is judged as being at high risk, or plausible bias seriously weakens confidence in the results.

We will determine the overall risk of bias for each outcome (across domains) across studies as follows (Higgins 2011a; Higgins 2011b):

1. Most information is from studies at low risk of bias, or plausible bias is unlikely to seriously alter the results;
2. Most information is from studies at low or unclear risk of bias, or plausible bias raises some doubt about the results;
3. The proportion of information from studies at high risk of bias is sufficient to affect the interpretation of results, or plausible bias seriously weakens confidence in the results.

Measures of treatment effect

For dichotomous outcome data (i.e. rates of adverse events and withdrawals, parent's or patient's global assessment of treatment success, participant's global assessment of response of improvement, proportion of participants achieving Investigator's Global Assessment (IGA) response, proportion of participants achieving clear or almost clear eczema (POEM score 0 to 2), proportion of participant's improvement on clinical severity score by at least one category), we will use risk ratios (RR), number needed to treat for an additional beneficial outcome (NNTB), or number needed to treat for an additional harmful outcome (NNTH) for each specific comparison, with their respective 95% confidence intervals (Higgins 2011a). Clinical severity of eczema, measured by the Severity Scoring of Atopic Dermatitis (SCORAD), is classified into three categories: mild disease (SCORAD 0 to 24), moderate (SCORAD $\geq$ 25 to < 50, and severe disease (SCORAD $\geq$ 50). The Patient-Oriented Eczema Measure (POEM) score is classified into five categories: clear or almost clear (score = 0 to 2), mild (score = 3 to 7), moderate (score 8 to 16), severe (score = 17 to 24), and very severe eczema (score = 25 to 28).

For continuous outcomes, such as changes or post-treatment values of clinical severity of the disease, clinical signs and symptoms, quality of life, and flares, we will calculate mean differences (MD) with 95% confidence intervals (CI). We will use standardised mean differences (SMD) with 95% confidence intervals for continuous outcomes if the included studies use different scales for the same outcome.

Ranking probabilities

From the results of the network meta-analysis for each comparison, we will estimate the probability, for each treatment, of being at each possible rank. Using these results, we will determine a treatment hierarchy, using the surface under the cumulative ranking curve

(SUCRA) and mean ranks (Chaimani 2017; Salanti 2011). We will develop and use rankograms to reflect the uncertainty in the ranking probabilities visually and graphically (Chaimani 2017).

Unit of analysis issues

For studies with multiple intervention groups (e.g. 3-arm design), we will perform separate pairwise comparisons for each pair without splitting the control group. This means that we will include data from treatment number one compared to the control group in a pairwise meta-analysis, and include data from treatment number two and control group in the same meta-analysis. In a network meta-analysis, network meta-analysis methodology accounts for the relative effect estimates arising from multiple-arm studies, so there is no need to split the control group evenly in order to avoid a unit of analysis error (Higgins 2012).

To avoid carry-over effects in cross-over studies, we will only include data from the first part of any included study (i.e. before cross-over), assuming data for the first phase are available. If the data from the first phase of the study are not available, we will attempt to obtain the data from the study authors. We will exclude the study from the meta-analysis if we do not receive an answer from the authors within three weeks.

In cluster-randomised trials, where groups of individuals are randomised to different interventions, participants within any one cluster often tend to respond in a similar manner; therefore, the unit of analysis is a group, or cluster. To avoid a unit of analysis error, we will take into account clustering effects within participants. Therefore, we will include a study if the effect estimate, adjusted for cluster correlation, is available (Higgins 2011a).

Dealing with missing data

We will perform an intention-to-treat analysis whenever possible. In the case of missing data about key study characteristics or outcomes, we will contact the study investigators for additional information. If we do not receive an answer from the authors within three weeks, we will perform the analyses based on available information, and record that the missing data were not retrieved from the corresponding author. We will create an additional table detailing any contact with study authors.

For continuous outcomes, we will impute the standard deviation from P values, standard errors, and confidence intervals, according to guidance given in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011a). If the data are likely to be normally distributed, we will use the median for meta-analysis when the mean is not available. If it is not possible to calculate the standard deviation from available information, we will impute the standard deviation, using the largest standard deviation in other trials for that outcome. This form of imputation may decrease the weight of the study when calculating mean differences, and it may bias the effect estimate towards the line of no effect when calculating standardised mean differences (Higgins 2011a).

We will also perform sensitivity analyses to assess how the overall results were affected by including and excluding those studies with a high risk of attrition bias and incomplete outcome data.

Assessment of heterogeneity

Our review will present both pairwise and network comparisons. For pairwise meta-analysis, we will assess the treatment effects of individual trials and the heterogeneity between trial results by visually inspecting the forest plots. We will explore clinical heterogeneity by assessing clinical and methodological characteristics of the included studies (e.g. difference in study risk of bias, participants, interventions, or outcome assessments). We will only attempt to pool data in a meta-analysis if the clinical heterogeneity amongst the selected studies is negligible. If we find major discrepancies in clinical or methodological characteristics, we will determine whether to exclude some studies from the meta-analysis altogether, or to include them and perform a sensitivity analysis of the main outcome.

We will use the I^2 statistic to measure heterogeneity in the study results, and will take values greater than 50% as indicating substantial statistical heterogeneity (Higgins 2003). If we find significant statistical heterogeneity, but we consider that the studies are suitable to combine in a meta-analysis based on the clinical and methodological characteristics detailed above, we will rely on the pooled effect estimates provided by a random-effects model.

Assessment of transitivity and consistency across treatment comparisons

The validity of network meta-analysis relies on the transitivity assumption. We will assess the assumption of transitivity by comparing the distribution of the potential effect modifiers across the different pairwise comparisons. The potential effect modifiers include age, baseline severity of eczema, co-intervention, or dosage regimen. We will compare the distribution of these variables across the available direct comparisons in the network (Salanti 2012).

We will use the design-by-treatment model to evaluate inconsistency in the network as a whole. In addition, we will use loop-specific and node-splitting methods to identify which piece of evidence is responsible for the inconsistency (Cipriani 2013; Donegan 2013; Salanti 2012).

Assessment of reporting biases

Reporting biases, such as selective outcome reporting bias, can occur in systematic reviews even after a well-designed and comprehensive search strategy. We will construct, and visually assess asymmetry of comparison-adjusted funnel plots to investigate possible small-study effects for any outcome of the network (Chaimani 2013). All comparisons will be included in the plot.

Data synthesis

We will start by applying a random-effects model to the pairwise meta-analyses to calculate pooled risk ratios (RRs), mean differences (MD), or standardised mean differences (SMD) with corresponding 95% confidence intervals (95% CI) for each comparison. We will use the I^2 statistic to quantify the heterogeneity in each direct comparison; $I^2 > 50\%$ represents notable heterogeneity.

Next, we will perform the network meta-analysis, using White's frequentist framework (White 2012), where consistency and inconsistency models are formulated as multivariate random-effects meta-analysis. We will combine direct and indirect evidence from any pair of interventions to generate mixed treatment effect sizes as pooled RR, pooled MD, or pooled SMD, with corresponding 95% CI, and present them in league tables. To assess whether the direct and indirect estimates are consistent, which is the key assumption of multiple-treatments meta-analysis, we will test for inconsistency, using a design-by-treatment interaction model; if the two-sided P of the test = 0.05, this indicates significant global inconsistency (Cipriani 2013; Donegan 2013).

Our primary analysis will include RCTs that included participants with eczema, regardless of the level of severity, who used systemic immunosuppressive treatments, administered by any route. In network meta-analysis, our main comparisons will include dupilumab, infliximab, rituximab, tocilizumab, mepolizumab, and omalizumab, compared with PUVA, cyclosporin A (ciclosporin), methotrexate, azathioprine, mycophenolate, systemic corticosteroid, or placebo (plus standard topical therapies or other active agents).

Ranking the interventions

To rank interventions in a hierarchy in the network meta-analysis, we will estimate the rankograms, surface under the cumulative ranking (SUCRA) curves, and mean ranks (Chaimani 2017; Salanti 2011). SUCRA can also be re-expressed as a percentage, interpreted as the percentage of effectiveness or acceptability of an intervention that would be ranked first, with no uncertainty (Salanti 2012). In addition, we will produce tables showing the direct, indirect, and network meta-analysis estimates for each comparison.

Where we find results that are estimated for individual studies with low numbers of events (< 10 in total), or where the total sample size is less than 30 participants and a risk ratio is calculated, we will report the proportion of events in each group and the P value, using a Fisher's Exact test.

We will use Stata version 15 to perform standard pairwise and network meta-analysis (Stata 2017) using the self-programmed Stata routines for network meta-analysis described elsewhere (Chaimani 2013; Salanti 2018).

Subgroup analysis and investigation of heterogeneity

We plan to perform the following subgroup analyses of participant characteristics, which potentially may result in different treatment responses if there are sufficient studies to perform different subgroups for comparison. We will formally evaluate the difference in the treatment effects between subgroups using Stata to test the subgroup differences (Stata 2017).

- Age of participants: e.g. children (age ≤ 12 years, age >12 years) versus adults
- Duration: short-term treatment (≤ 16 weeks) versus long-term or maintenance treatment (> 16 weeks)
- Severity of eczema at baseline (mild or moderate versus severe)
- Dosage schedule

We will perform subgroup analysis based on severity of eczema classification specified by each study. In addition, we will perform subgroup analysis based on severity categorised by EASI > 22 or SCORAD > 50 scores.

Sensitivity analysis

To investigate the robustness of our findings, we will perform a series of sensitivity analyses using Stata as follows (Stata 2017):

- exclusion of studies with high risk of bias,
- exclusion of studies with small sample size (i.e. less than 25th percentile of total number of participants),
- exclusion of unblinded studies, and
- analysis without industry-sponsored trials.

'Summary of findings' tables and GRADE assessments

We will develop a separate 'Summary of findings' table for each primary outcome including clinical severity of eczema, participant-reported symptoms, adverse effects, estimated from direct and network meta-analysis. The GRADE approach will be used for judgment about the confidence with which an estimate of treatment effect for a particular outcome can be believed, using four levels: high, moderate, low and very low (Salanti 2014). The confidence or quality of evidence for each outcome is based on five domains: study limitations (risk of bias), inconsistency, indirectness, imprecision, and publication bias. The quality of evidence will be presented in the 'Summary of findings' tables for each primary outcome, using the Confidence in Network Meta-Analysis (CINeMA) software online version (CINeMA 2017). This software was developed from the GRADE framework (Salanti 2014). It is based on a methodological framework described in which considers six domains: within-study bias, across-studies bias, indirectness, imprecision, heterogeneity and incoherence (Salanti 2014). At least two review authors (RS, PD, ALL, NC) will independently grade the quality of evidence for each treatment effect. If there is any disagreement, the two review authors will discuss it within the reviewing team until consensus is reached.

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REFERENCES

Additional references

Abd Rahman 2013
Abd Rahman AN, Tett SE, Staatz CE. Clinical pharmacokinetics and pharmacodynamics of mycophenolate in patients with autoimmune disease. *Clinical Pharmacokinetics* 2013;**52**(5):303-31. [PUBMED: 23475567]

Ackermann 1998
Ackermann L, Harvima IT. Mast cells of psoriatic and atopic dermatitis skin are positive for TNF-alpha and their degranulation is associated with expression of ICAM-1 in the epidermis. *Archives of Dermatological Research* 1998;**290**(7):353–9. [PUBMED: 9749989]

Akdis 2006
Akdis CA, Akdis M, Bieber T, Bindslev-Jensen C, Boguniewicz M, Eigenmann P, et al. Diagnosis and treatment of atopic dermatitis in children and adults: European Academy of Allergology and Clinical Immunology/American Academy of Allergy, Asthma and Immunology/PRACTALL Consensus Report. *Allergy* 2006;**61**(8):969-87. [PUBMED: 16867052]

Atherton 1988
Atherton DJ, Carabott F, Glover MT, Hawk JL. The role of psoralen photochemotherapy (PUVA) in the treatment of severe atopic eczema in adolescents. *British Journal of Dermatology* 1988;**118**(6):791–5. [PUBMED: 3401414]

Ballow 2014
Ballow M. Mechanisms of immune regulation by IVIG. *Current Opinion in Allergy and Clinical Immunology* 2014;**14**(6):509–15. [PUBMED: 25337683]

Beck 2014
Beck LA, Thaci D, Hamilton JD, Graham NM, Bieber T, Rocklin R, et al. Dupilumab treatment in adults with moderate-to-severe atopic dermatitis. *New England Journal of Medicine* 2014;**371**(2):130–9. [PUBMED: 25006719]

Belloni 2007
Belloni B, Ziai M, Lim A, Lemercier B, Sbornik M, Weidinger S, et al. Low-dose anti-IgE therapy in patients with atopic eczema with high serum IgE levels. *Journal of Allergy and Clinical Immunology* 2007;**120**(5):1223-5. [PUBMED: 17936892]

Berth-Jones 2002
Berth-Jones J, Takwale A, Tan E, Barclay G, Agarwal S, Ahmed I, et al. Azathioprine in severe adult atopic dermatitis: a double-blind, placebo-controlled, crossover trial. *British Journal of Dermatology* 2002;**147**(2):324–30. [PUBMED: 12174106]

Blauvelt 2017
Blauvelt A, de Bruin-Weller M, Gooderham M, Cather JC, Weisman J, Pariser D, et al. Long-term management of moderate-to-severe atopic dermatitis with dupilumab and concomitant topical corticosteroids (LIBERTY AD CHRONOS): a 1-year, randomised, double-blinded, placebo-controlled, phase 3 trial. *Lancet (London, England)* 2017;**389**(10086):2287–303. [PUBMED: 28478972]

Boguniewicz 2017
Boguniewicz M, Alexis AF, Beck LA, Block J, Eichenfield LF, Fonacier L, et al. Expert perspectives on management of moderate-to-severe atopic dermatitis: a multidisciplinary consensus addressing current and emerging therapies. *Journal of Allergy and Clinical Immunology* 2017;**5**(6):1519–31. [PUBMED: 28970084]

Bos 2010
Bos JD, Brenninkmeijer EE, Schram ME, Middelkamp-Hup MA, Spuls PI, Smitt JH. Atopic eczema or atopiform dermatitis. *Experimental Dermatology* 2010;**19**(4):325-31. [PUBMED: 20100192]

Braun 2009
Braun J, Rau R. An update on methotrexate. *Current Opinion in Rheumatology* 2009;**21**(3):216–23. [PUBMED: 19373092]

Brenninkmeijer 2008
Brenninkmeijer EE, Schram ME, Leeflang MM, Bos JD, Spuls PI. Diagnostic criteria for atopic dermatitis: a systematic review. *British Journal of Dermatology* 2008;**158**(4):754–65. [PUBMED: 18241277]

Brenninkmeijer 2009
Brenninkmeijer EE, Legierse CM, Sillevis Smitt JH, Last BF, Grootenhuis MA, Bos JD. The course of life of patients with childhood atopic dermatitis. *Pediatric Dermatology* 2009;**26**(1):14-22. [PUBMED: 19250399]

Carel 2008
Carel K, Bratton DL, Miyazawa N, Gyorkos E, Kelsay K, Bender B, et al. The Atopic Dermatitis Quickscore (ADQ): validation of a new parent-administered atopic dermatitis scoring tool. *Annals of Allergy, Asthma & Immunology* 2008; **101**(5):500–7. [PUBMED: 19055204]

Chaimani 2013
Chaimani A, Higgins JPT, Mavridis D, Spyridonos P, Salanti G. Graphical tools for network meta-analysis in STATA. *PLoS One* 2013;**8**(10):e76654. [PUBMED: 24098547]

Chaimani 2017
Chaimani A, Caldwell DM, Li T, Higgins JPT, Salanti G. Additional considerations are required when preparing a protocol for a systematic review with multiple interventions. *Journal of Clinical Epidemiology* 2017;**83**: 65–74. [PUBMED: 28088593]

Chalmers 2014
Chalmers JR, Schmitt J, Apfelbacher C, Dohil M, Eichenfield LF, Simpson EL, et al. Report from the third international consensus meeting to Harmonise Core Outcome Measures for Atopic Eczema/Dermatitis clinical trials (HOME). *British Journal of Dermatology* 2014;**171**(6): 1318–25. [PUBMED: 24980543]

Chalmers 2016
Chalmers JR, Simpson E, Apfelbacher CJ, Thomas KS, von Kobyletzki L, Schmitt J, et al. Report from the fourth international consensus meeting to Harmonise Core Outcome Measures for Atopic Eczema/Dermatitis clinical trials (HOME initiative). *British Journal of Dermatology* 2016;**175**(1):69–79. DOI: 10.1111/bjd.14773; PUBMED: 27436240

Chalmers 2018
Chalmers JR, Thomas KS, Apfelbacher C, Williams HC, Prinsen CA, Spuls PI, et al. Report from the fifth international consensus meeting to Harmonise Core Outcome Measures for Atopic Eczema/Dermatitis clinical trials (HOME initiative). *British Journal of Dermatology* 2018;**178**(5):e332–41. [PUBMED: 29672835]

Chamlin 2004
Chamlin SL, Frieden IJ, Williams ML, Chren MM. Effects of atopic dermatitis on young American children and their families. *Pediatrics* 2004;**114**(3):607-11. [PUBMED: 15342828]

Chang 2002
Chang TT, Stevens SR. Atopic dermatitis: the role of recombinant interferon-gamma therapy. *American Journal of Clinical Dermatology* 2002;**3**(3):175–83. [PUBMED: 11978138]

Charman 1999
Charman D, Varigos G, Horne DJ, Oberklaid F. The development of a practical and reliable assessment measure for atopic dermatitis (ADAM). *Journal of Outcome Measurement* 1999;**3**(1):21–34. [PUBMED: 10063770]

Charman 2002
Charman CR, Venn AJ, Williams HC. Reliability testing of the Six Area, Six Sign Atopic Dermatitis severity score. *British Journal of Dermatology* 2002;**146**(6):1057–60. [PUBMED: 12072077]

Chren 2012
Chren MM. The Skindex instruments to measure the effects of skin disease on quality of life. *Dermatologic Clinics* 2012; **30**(2):231–6. [PUBMED: 22284137]

CINeMA 2017 [Computer program]
Institute of Social and Preventive Medicine, University of Bern. CINeMA: Confidence in Network Meta-Analysis [Software]. Version 2017. Bern: Institute of Social and Preventive Medicine, University of Bern, 2017.

Cipriani 2013
Cipriani A, Higgins JP, Geddes JR, Salanti G. Conceptual and technical challenges in network meta-analysis. *Annals of Internal Medicine* 2013;**159**(2):130–7. [PUBMED: 23856683]

Cork 2009
Cork MJ, Danby SG, Vasilopoulos Y, Hadgraft J, Lane ME, Moustafa M, et al. Epidermal barrier dysfunction in atopic dermatitis. *Journal of Investigative Dermatology* 2009;**129** (8):1892–908. [PUBMED: 19494826]

Covidence [Computer program]
Veritas Health Innovation. Covidence. Version accessed prior to 24 September 2018. Melbourne, Australia: Veritas Health Innovation, 2017.

Crowe 2012
Crowe S. Generating research questions from treatment research priorities in eczema. www.jla.nihr.ac.uk/priority-setting-partnerships/eczema/downloads/Eczema-PSP-final-workshop-report.pdf (accessed prior to 27 September 2018).

Daley-Yates 2004
Daley-Yates PT, Richards DH. Relationship between systemic corticosteroid exposure and growth velocity: development and validation of a pharmacokinetic/pharmacodynamic model. *Clinical Therapeutics* 2004;**26** (11):1905–19. [PUBMED: 15639702]

Darsow 2010
Darsow U, Wollenberg A, Simon D, Taieb A, Werfel T, Oranje A, et al. ETFAD/EADV eczema task force 2009 position paper on diagnosis and treatment of atopic dermatitis. *Journal of the European Academy of Dermatology & Venereology* 2010;**24**(3):317-28. [PUBMED: 19732254]

Donegan 2013
Donegan S, Williamson P, D'Alessandro U, Tudur Smith C. Assessing key assumptions of network meta-analysis: a review of methods. *Research Synthesis Methods* 2013;**4**(4): 291–323. [PUBMED: 26053945]

Dutz 1998
Dutz JP, Ho VC. Immunosuppressive agents in dermatology. An update. *Dermatologic Clinics* 1998;**16**(2):235–51. [PUBMED: 9589197]

Eichenfield 2014
Eichenfield LF, Tom WL, Berger TG, Krol A, Paller AS, Schwarzenberger K, et al. Guidelines of care for the

management of atopic dermatitis: section 2. Management and treatment of atopic dermatitis with topical therapies. *Journal of the American Academy of Dermatology* 2014;**71**(1): 116–32. [PUBMED: 24813302]

El-Khalawany 2013
El-Khalawany MA, Hassan H, Shaaban D, Ghonaim N, Eassa B. Methotrexate versus cyclosporine in the treatment of severe atopic dermatitis in children: a multicenter experience from Egypt. *European Journal of Pediatrics* 2013; **172**(3):351–6. [PUBMED: 23229188]

Ellis 2012
Ellis CN, Mancini AJ, Paller AS, Simpson EL, Eichenfield LF. Understanding and managing atopic dermatitis in adult patients. *Seminars in Cutaneous Medicine & Surgery* 2012; **31**(3 Suppl):S18-22. [PUBMED: 23021781]

Emerson 1998
Emerson RM, Williams HC, Allen BR. Severity distribution of atopic dermatitis in the community and its relationship to secondary referral. *British Journal of Dermatology* 1998; **139**(1):73–6. [PUBMED: 9764151]

Farina 2011
Farina S, Gisondi P, Zanoni M, Pace M, Rizzoli L, Baldo E, et al. Balneotherapy for atopic dermatitis in children at Comano spa in Trentino, Italy. *Journal of Dermatological Treatment* 2011;**22**(6):366–71. [PUBMED: 21254853]

Faulds 1993
Faulds D, Goa KL, Benfield P. Cyclosporin. A review of its pharmacodynamic and pharmacokinetic properties, and therapeutic use in immunoregulatory disorders. *Drugs* 1993;**45**(6):953–1040. [PUBMED: 7691501]

Finlay 1994
Finlay AY, Khan GK. Dermatology Life Quality Index (DLQI) - a simple practical measure for routine clinical use. *Clinical and Experimental Dermatology* 1994;**19**:210–6. [PUBMED: 8033378]

Flohr 2013
Flohr C, Irvine AD. Systemic therapies for severe atopic dermatitis in children and adults. *Journal of Allergy and Clinical Immunology* 2013;**132**(3):774. [PUBMED: 23993356]

Flohr 2014
Flohr C, Mann J. New insights into the epidemiology of childhood atopic dermatitis. *Allergy* 2014;**69**(1):3-16. [PUBMED: 24417229]

Gelfand 2012
Gelfand EW. Intravenous immune globulin in autoimmune and inflammatory diseases. *New England Journal of Medicine* 2012;**367**(21):2015–25. [PUBMED: 23171098]

Grahovac 2010
Grahovac M, Molin S, Prinz JC, Ruzicka T, Wollenberg A. Treatment of atopic eczema with oral alitretinoin. *British Journal of Dermatology* 2010;**162**(1):217-8. [PUBMED: 19886882]

Grillo-Lopez 1999
Grillo-Lopez AJ, White CA, Varns C, Shen D, Wei A, McClure A, et al. Overview of the clinical development of rituximab: first monoclonal antibody approved for the treatment of lymphoma. *Seminars in Oncology* 1999;**26**(5 Suppl 14):66–73. [PUBMED: 10561020]

Haeck 2011
Haeck IM, Knol MJ, Ten Berge O, van Velsen SG, de Bruin-Weller MS, Bruijnzeel-Koomen CA. Enteric-coated mycophenolate sodium versus cyclosporin A as long-term treatment in adult patients with severe atopic dermatitis: a randomized controlled trial. *Journal of the American Academy of Dermatology* 2011;**64**(6):1074–84. [PUBMED: 21458107]

Haest 2011
Haest C, Casaer MP, Daems A, De Vos B, Vermeersch E, Morren MA, et al. Measurement of itching: validation of the Leuven Itch Scale. *Burns* 2011;**37**(6):939–50. [PUBMED: 21596477]

Hanifin 1980
Hanifin JM, Rajka G. Diagnostic features of atopic dermatitis. *Acta Dermato-venereologica* 1980;**60**(Suppl 92): 44–7. DOI: 10.2340/00015555924447

Hanifin 1993
Hanifin JM, Schneider LC, Leung DY, Ellis CN, Jaffe HS, Izu AE, et al. Recombinant interferon gamma therapy for atopic dermatitis. *Journal of the American Academy of Dermatology* 1993;**28**(2 Pt 1):189–97. [PUBMED: 8432915]

Hanifin 1996
Hanifin JM, Chan SC, Cheng JB, Tofte SJ, Henderson WR Jr, Kirby DS, et al. Type 4 phosphodiesterase inhibitors have clinical and in vitro anti-inflammatory effects in atopic dermatitis. *Journal of Investigative Dermatology* 1996;**107** (1):51–6. [PUBMED: 8752839]

Heil 2010
Heil PM, Maurer D, Klein B, Hultsch T, Stingl G. Omalizumab therapy in atopic dermatitis: depletion of IgE does not improve the clinical course - a randomized, placebo-controlled and double blind pilot study. *Journal der Deutschen Dermatologischen Gesellschaft [Journal of the German Society of Dermatology]* 2010;**8**(12):990–8. [PUBMED: 20678148]

Heller 2007
Heller M, Shin HT, Orlow SJ, Schaffer JV. Mycophenolate mofetil for severe childhood atopic dermatitis: experience in 14 patients. *British Journal of Dermatology* 2007;**157**(1): 127–32. [PUBMED: 17489974]

Higgins 2003
Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. *BMJ* 2003;**327** (7414):557–60. [PUBMED: 12958120]

Higgins 2011a
Higgins JPT, Green S, editor(s). Cochrane Handbook for Systematic Reviews of Interventions, Version 5.1.0 (updated March 2011). The Cochrane Collaboration, 2011. Available from handbook.cochrane.org.

Higgins 2011b
Higgins JP, Altman DG, Gotzsche PC, Juni P, Moher D, Oxman AD, et al. Cochrane Bias Methods Group, Cochrane Statistical Methods Group. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. *BMJ (Clinical research ed.)* 2011;**343**:d5928. [PUBMED: 22008217]

Higgins 2012
Higgins JPT, Jackson D, Barrett JK, Lu G, Ades AE, White IR. Consistency and inconsistency in network meta-analysis: concepts and models for multi-arm studies. *Research Synthesis Methods* 2012;**3**(2):98–110.

Housman 2002
Housman TS, Patel MJ, Camacho F, Feldman SR, Fleischer AB Jr, Balkrishnan R. Use of the Self-Administered Eczema Area and Severity Index by parent caregivers: results of a validation study. *British Journal of Dermatology* 2002;**147**(6):1192–8. [PUBMED: 12452870]

Hutton 2015
Hutton B, Salanti G, Caldwell DM, Chaimani A, Schmid CH, Cameron C, et al. The PRISMA extension statement for reporting of systematic reviews incorporating network meta-analyses of health care interventions: checklist and explanations. *Annals of Internal Medicine* 2015;**162**(11):777–84. [PUBMED: 26030634]

Iyengar 2013
Iyengar SR, Hoyte EG, Loza A, Bonaccorso S, Chiang D, Umetsu DT, et al. Immunologic effects of omalizumab in children with severe refractory atopic dermatitis: a randomized, placebo-controlled clinical trial. *International Archives of Allergy and Immunology* 2013;**162**(1):89–93. [PUBMED: 23816920]

Jacobi 2005
Jacobi A, Antoni C, Manger B, Schuler G, Hertl M. Infliximab in the treatment of moderate to severe atopic dermatitis. *Journal of the American Academy of Dermatology* 2005;**52**(3 Pt 1):522–6. [PUBMED: 15761436]

Jang 2000
Jang IG, Yang JK, Lee HJ, Yi JY, Kim HO, Kim CW, et al. Clinical improvement and immunohistochemical findings in severe atopic dermatitis treated with interferon gamma. *Journal of the American Academy of Dermatology* 2000;**42**(6):1033–40. [PUBMED: 10827410]

Jee 2011
Jee SJ, Kim JH, Baek HS, Lee HB, Oh JW. Long-term efficacy of intravenous immunoglobulin therapy for moderate to severe childhood atopic dermatitis. *Allergy, Asthma & Immunology Research* 2011;**3**(2):89-95.

Johansson 2004
Johansson SG, Bieber T, Dahl R, Friedmann PS, Lanier BQ, Lockey RF, et al. Revised nomenclature for allergy for global use: report of the Nomenclature Review Committee of the World Allergy Organization, October 2003. *Journal of Allergy and Clinical Immunology* 2004;**113**(5):832-6. [PUBMED: 15131563]

Johnson 1996
Johnson R, Staiano-Coico L, Austin L, Cardinale I, Nabeya-Tsukifuji R, Krueger JG. PUVA treatment selectively induces a cell cycle block and subsequent apoptosis in human T-lymphocytes. *Photochemistry and Photobiology* 1996;**63**(5):566–71. [PUBMED: 8628746]

Kislat 2011
Kislat A, Meller S, Mota R, Gerber PA, Buhren BA, Bünemannet E, et al. Alitretinoin - molecular and cellular mechanisms of action. *Journal of Translational Medicine* 2011;**9**(Suppl 2):16.

Kraft 2017
Kraft M, Worm M. Dupilumab in the treatment of moderate-to-severe atopic dermatitis. *Expert Review of Clinical Immunology* 2017;**13**(4):301–10. [PUBMED: 28165826]

Kunz 1997
Kunz B, Oranje AP, Labreze L, Stalder JF, Ring J, Taieb A. Clinical validation and guidelines for the SCORAD index: consensus report of the European Task Force on Atopic Dermatitis. *Dermatology (Basel, Switzerland)* 1997;**195**(1):10–9. [PUBMED: 9267730]

Laing 1995
Laing TJ, Richardson BC, Toth MB, Smith EM, Marks RM. Ultraviolet light and 8-methoxypsoralen inhibit expression of endothelial adhesion molecules. *The Journal of Rheumatology* 1995;**22**(11):2126–31. [PUBMED: 8596155]

Lefebvre 2011
Lefebvre C, Manheimer E, Glanville J. Chapter 6: Searching for studies. In: Higgins JP, Green S, editor(s). Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 (updated March 2011). The Cochrane Collaboration, 2011. Available from handbook.cochrane.org.

Leiferman 2001
Leiferman KM. A role for eosinophils in atopic dermatitis. *Journal of the American Academy of Dermatology* 2001;**45**(1 Suppl):S21–4. [PUBMED: 11423867]

Liszewski 2017
Liszewski W, Naym DG, Biskup E, Gniadecki R. Psoralen with ultraviolet A-induced apoptosis of cutaneous lymphoma cell lines is augmented by type I interferons via the JAK1-STAT1 pathway. *Photodermatology, Photoimmunology & Photomedicine* 2017;**33**(3):164–71. [PUBMED: 28196286]

Liu 2011
Liu FT, Goodarzi H, Chen HY. IgE, mast cells, and eosinophils in atopic dermatitis. *Clinical Reviews in Allergy & Immunology* 2011;**41**(3):298–310. [PUBMED: 21249468]

Luoma 1983
Luoma R, Koivikko A, Viander M. Development of asthma, allergic rhinitis and atopic dermatitis by the age of five years. A prospective study of 543 newborns. *Allergy* 1983;**38**(5):339-46. [PUBMED: 6614406]

Majeski 2007
Majeski CJ, Johnson JA, Davison SN, Lauzon CJ. Itch Severity Scale: a self-report instrument for the measurement of pruritus severity. *British Journal of Dermatology* 2007;**156**(4):667–73. [PUBMED: 17263803]

Maksimović 2012
Maksimović N, Janković S, Marinković J, Sekulović LK, Zivković Z, Spirić VT. Health-related quality of life in patients with atopic dermatitis. *Journal of Dermatology* 2012;**39**(1):42-7. [PUBMED: 22044078]

Mancini 2008
Mancini AJ, Kaulback K, Chamlin SL. The socioeconomic impact of atopic dermatitis in the United States: a systematic review. *Pediatric Dermatology* 2008;**25**(1):1–6. [PUBMED: 18304144]

Margolis 2014
Margolis JS, Abuabara K, Bilker W, Hoffstad O, Margolis DJ. Persistence of mild to moderate atopic dermatitis. *JAMA Dermatology* 2014;**150**(6):593–600. [PUBMED: 24696036]

McAleer 2013
McAleer MA, Irvine AD. The multifunctional role of filaggrin in allergic skin disease. *Journal of Allergy and Clinical Immunology* 2013;**131**(2):280-91. [PUBMED: 23374260]

McCollum 2010
McCollum AD, Paik A, Eichenfield LF. The safety and efficacy of tacrolimus ointment in pediatric patients with atopic dermatitis. *Pediatric Dermatology* 2010;**27**(5):425-36. [PUBMED: 20678096]

McDonald 2016
McDonald BS, Jones J, Rustin M. Rituximab as a treatment for severe atopic eczema: failure to improve in three consecutive patients. *Clinical and Experimental Dermatology* 2016;**41**(1):45–7. [PUBMED: 26033316]

Meggitt 2006
Meggitt SJ, Gray JC, Reynolds NJ. Azathioprine dosed by thiopurine methyltransferase activity for moderate-to-severe atopic eczema: a double-blind, randomised controlled trial. *Lancet* 2006;**367**(9513):839–46. [PUBMED: 16530578]

Mortz 2015
Mortz CG, Andersen KE, Dellgren C, Barington T, Blinslev-Jensen C. Atopic dermatitis from adolescence to adulthood in the TOACS cohort: prevalence, persistence and comorbidities. *Allergy* 2015;**70**(7):836-45. [PUBMED: 25832131]

Nakahara 2018
Nakahara T, Morimoto H, Murakami N, Furue M. Mechanistic insights into topical tacrolimus for the treatment of atopic dermatitis. *Pediatric Allergy and Immunology* 2018;**29**(3):233–8. [PUBMED: 29205511]

Navarini 2011
Navarini AA, French LE, Hofbauer GF. Interrupting IL-6-receptor signaling improves atopic dermatitis but associates with bacterial superinfection. Journal of Allergy and Clinical Immunology 2011; Vol. 128, issue 5:1128–30. [PUBMED: 21962991]

Odhiambo 2009
Odhiambo J, Williams H, Clayton T, Robertson CF, Asher MI, ISAAC Phase Three Study Group. Global variations in prevalence of eczema symptoms in children from ISAAC Phase Three. *Journal of Allergy and Clinical Immunology* 2009;**124**(6):1251–8. [PUBMED: 20004783]

Oldhoff 2005
Oldhoff JM, Darsow U, Werfel T, Katzer K, Wulf A, Laifaoui J, et al. Anti-IL-5 recombinant humanized monoclonal antibody (mepolizumab) for the treatment of atopic dermatitis. *Allergy* 2005;**60**:693-6.

Paller 2016
Paller AS, Tom WL, Lebwohl MG, Blumenthal RL, Boguniewicz M, Call RS, et al. Efficacy and safety of crisaborole ointment, a novel, nonsteroidal phosphodiesterase 4 (PDE4) inhibitor for the topical treatment of atopic dermatitis (AD) in children and adults. *Journal of the American Academy of Dermatology* 2016;**75**(3):494–503. [PUBMED: 27417017]

Paul 2002
Paul C, Lahfa M, Bachelez H, Chevret S, Dubertret L. A randomized controlled evaluator-blinded trial of intravenous immunoglobulin in adults with severe atopic dermatitis. *British Journal of Dermatology* 2002;**147**(3):518-22. [PUBMED: 12207594]

Proudfoot 2013
Proudfoot LE, Powell AM, Ayis S, Barbarot S, Baselga Torres E, Deleuran M, et al. The European treatment of severe atopic eczema in children taskforce (TREAT) survey. *British Journal of Dermatology* 2013;**169**(4):901-9. [PUBMED: 23855450]

Ricci 2009
Ricci G, Dondi A, Patrizi A. Useful tools for the management of atopic dermatitis. *American Journal of Clinical Dermatology* 2009;**10**(5):287–300. [PUBMED: 19658441]

Ring 2012
Ring J, Alomar A, Bieber T, Deleuran M, Fink-Wagner A, Gelmetti C, et al. Guidelines for treatment of atopic eczema (atopic dermatitis) Part II. *Journal of the European Academy of Dermatology and Venereology: JEADV* 2012;**26**(9):1176-93. [PUBMED: 22813359]

Roekevisch 2014
Roekevisch E, Spuls PI, Kuester D, Limpens J, Schmitt J. Efficacy and safety of systemic treatments for moderate-to-severe atopic dermatitis: a systematic review. *Journal of Allergy and Clinical Immunology* 2014;**133**(2):429-38. [PUBMED: 24269258]

Ruiz-Villaverde 2012
Ruiz-Villaverde R, Galan-Gutierrez M. Exacerbation of atopic dermatitis in a patient treated with infliximab. Actas Dermo-sifiliograficas 2012; Vol. 103, issue 8:743–6. [PUBMED: 22683017]

Ruzicka 2008
Ruzicka T, Lynde CW, Jemec GB, Diepgen T, Berth-Jones J, Coenraads PJ, et al. Efficacy and safety of oral alitretinoin (9-cis retinoic acid) in patients with severe chronic hand eczema refractory to topical corticosteroids: results of a randomized, doubleblind, placebo-controlled, multicentre trial. *British Journal of Dermatology* 2008;**158**(4):808-17. [PUBMED: 18294310]

Sachdeva 2009
Sachdeva S. Fitzpatrick skin typing: applications in dermatology. *Indian Journal of Dermatology, Venereology and Leprology* 2009;**75**(1):93–6. [PUBMED: 19172048]

Saeki 2016
Saeki H, Nakahara T, Tanaka A, Kabashima K, Sugaya M, Murota H, et al. Clinical practice guidelines for the management of atopic dermatitis 2016. *Journal of Dermatology* 2016;**43**(10):1117–45. [PUBMED: 27076388]

Salanti 2011
Salanti G, Ades AE, Ioannidis JP. Graphical methods and numerical summaries for presenting results from multiple treatment meta-analysis: an overview and tutorial. *Journal of Clinical Epidemiology* 2011;**64**(2):163-71. [PUBMED: 20688472]

Salanti 2012
Salanti G. Indirect and mixed-treatment comparison, network, or multiple-treatments meta-analysis: many names, many benefits, many concerns for the next generation evidence synthesis tool. *Research Synthesis Methods* 2012;**3**(2):80–97. [PUBMED: 26062083]

Salanti 2014
Salanti G, Del Giovane C, Chaimani A, Caldwell DM, Higgins JP. Evaluating the quality of evidence from a network meta-analysis. *PloS One* 2014;**9**(7):e99682. [PUBMED: 24992266]

Salanti 2018
Salanti G, Mavridis D, Nikolakopoulou A, Chaimani A, Efthimiou O. Multiple-Treatments Meta-Analysis: using Stata for standard pairwise and network meta-analysis. www.mtm.uoi.gr/index.php/stata-routines-for-network-meta-analysis (accessed 15 January 2018).

Samrao 2012
Samrao A, Berry TM, Goreshi R, Simpson EL. A pilot study of an oral phosphodiesterase inhibitor (apremilast) for atopic dermatitis in adults. *Archives of Dermatology* 2012; **148**(8):890-7. [PUBMED: 22508772]

Schmitt 2007
Schmitt J, Schakel K, Schmitt N, Meurer M. Systemic treatment of severe atopic eczema: a systematic review. *Acta Dermato-venereologica* 2007;**87**(2):100-11.

Schmitt 2009
Schmitt J, Schmitt NM, Kirch W, Meurer M. Outpatient care and medical treatment of children and adults with atopic eczema. *Journal der Deutschen Dermatologischen Gesellschaft: [Journal of the German Society of Dermatology]* 2009;**7**(4):345-51.

Schmitt 2010
Schmitt J, Schakel K, Folster-Holst R, Bauer A, Oertel R, Augustin M, et al. Prednisolone vs. ciclosporin for severe adult eczema. An investigator-initiated double-blind placebo-controlled multicentre trial. *British Journal of Dermatology* 2010;**162**(3):661–8. [PUBMED: 19863501]

Schmitt 2014
Schmitt J, Spuls PI, Thomas KS, Simpson E, Furue M, Deckert S, et al. The Harmonising Outcome Measures for Eczema (HOME) statement to assess clinical signs of atopic eczema in trials. *Journal of Allergy and Clinical Immunology* 2014;**134**(4):800–7. [PUBMED: 25282560]

Schram 2011
Schram ME, Roekevisch E, Leeflang MM, Bos JD, Schmitt J, Spuls PI. A randomized trial of methotrexate versus azathioprine for severe atopic eczema. *Journal of Allergy and Clinical Immunology* 2011;**128**(2):353–9. [PUBMED: 21514637]

Schroer 2003
Schroer B, Lockey R. Oral tacrolimus for severe recalcitrant atopic eczema. *Journal of Allergy and Clinical Immunology* 2003;**111**(6):1409–10. [PUBMED: 12789248]

Sediva 2008
Sediva A, Kayserova J, Vernerova E, Polouckova A, Capkova S, Spisek R, et al. Anti-CD20 (rituximab) treatment for atopic eczema. *Journal of Allergy and Clinical Immunology* 2008;**121**(6):1515-6; author reply 1516-7. [PUBMED: 18410962]

Sidbury 2014
Sidbury R, Davis DM, Cohen DE, Cordoro KM, Berger TG, Bergman JN, et al. Guidelines of care for the management of atopic dermatitis: section 3. Management and treatment with phototherapy and systemic agents. *Journal of the American Academy of Dermatology* 2014;**71**(2): 327–49. [PUBMED: 24813298]

Simon 2008
Simon D, Heosli S, Kostylina G, Yawalkar N, Simon HU. Anti-CD20 (rituximab) treatment improves atopic eczema. *Journal of Allergy and Clinical Immunology* 2008;**121**(1): 122-8. [PUBMED: 18206507]

Simon 2014
Simon D, Bieber T. Systemic therapy for atopic dermatitis. *Allergy* 2014;**69**(1):46-55. [PUBMED: 24354911]

Singh 2010
Singh TP, Schon MP, Wallbrecht K, Michaelis K, Rinner B, Mayer G, et al. 8-methoxypsoralen plus ultraviolet A therapy acts via inhibition of the IL-23/Th17 axis and induction of Foxp3+ regulatory T cells involving CTLA4 signaling in a psoriasis-like skin disorder. *Journal of immunology (Baltimore, Md.: 1950)* 2010;**184**(12): 7257–67. [PUBMED: 20488788]

Slater 2015
Slater NA, Morrell DS. Systemic therapy of childhood atopic dermatitis. *Clinics in Dermatology* 2015;**33**(3):289-99. [PUBMED: 25889129]

Snast 2018
Snast I, Reiter O, Hodak E, Friedland R, Mimouni D, Leshem YA. Are biologics efficacious in atopic dermatitis? A systematic review and meta-analysis. *American Journal of Clinical Dermatology* 2018;**19**(2):145–65. [PUBMED: 29098604]

Souness 2000
Souness JE, Aldous D, Sargent C. Immunosuppressive and anti-inflammatory effects of cyclic AMP phosphodiesterase (PDE) type 4 inhibitors. *Immunopharmacology* 2000;**47**(2-3):127–62. [PUBMED: 10878287]

Spuls 2017
Spuls PI, Gerbens LAA, Simpson E, Apfelbacher CJ, Chalmers JR, Thomas KS, et al. Patient-Oriented Eczema Measure (POEM), a core instrument to measure symptoms in clinical trials: a Harmonising Outcome Measures for Eczema (HOME) statement. *The British Journal of Dermatology* 2017;**176**(4):979–84. [PUBMED: 27858989]

Stalder 2011
Stalder JF, Barbarot S, Wollenberg A, Holm EA, De Raeve L, Seidenari S, et al. Patient-Oriented SCORAD (PO-SCORAD): a new self-assessment scale in atopic dermatitis validated in Europe. *Allergy* 2011;**66**(8):1114–21. [PUBMED: 21414011]

Stata 2017 [Computer program]
StataCorp LLC. Stata Statistical Software. Version 15. College Station, TX: StataCorp LLC, 2017.

Stone 2002
Stone KD. Atopic diseases of childhood. *Current Opinion in Pediatrics* 2002;**14**(5):634–46. [PUBMED: 12352260]

Thomsen 2015
Thomsen SF. Epidemiology and natural history of atopic diseases. *European Clinical Respiratory Journal* 2015;**2**(1): 24642. [PUBMED: 26557262]

Toshitani 1993
Toshitani A, Ansel JC, Chan SC, Li SH, Hanifin JM. Increased interleukin 6 production by T cells derived from patients with atopic dermatitis. *Journal of Investigative Dermatology* 1993;**100**(3):299–304. [PUBMED: 8440909]

Uetsu 2003
Uetsu N, Horio T. Treatment of persistent severe atopic dermatitis in 113 Japanese patients with oral psoralen photo-chemotherapy. *Journal of Dermatology* 2003;**30**(6): 450–7. [PUBMED: 12810992]

Vakharia 2018
Vakharia PP, Chopra R, Silverberg JI. Systematic review of diagnostic criteria used in atopic dermatitis randomized controlled trials. *American Journal of Clinical Dermatology* 2018;**19**(1):15–22. [PUBMED: 28624959]

van Zuuren 2017
van Zuuren EJ, Fedorowicz Z, Christensen R, Lavrijsen A, Arents BWM. Emollients and moisturisers for eczema. *Cochrane Database of Systematic Reviews* 2017, Issue 2. DOI: 10.1002/14651858.CD012119.pub2

Wang 2018
Wang FP, Tang XJ, Wei CQ, Xu LR, Mao H, Luo FM. Dupilumab treatment in moderate-to-severe atopic dermatitis: a systematic review and meta-analysis. *Journal of Dermatological Science* 2018;**90**(2):190–8. [PUBMED: 29472119]

Weatherhead 2007
Weatherhead SC, Wahie S, Reynolds NJ, Meggitt SJ. An open-label, dose-ranging study of methotrexate for moderate-to-severe adult atopic eczema. *British Journal of Dermatology* 2007;**156**(2):346–51. [PUBMED: 17223876]

Weidinger 2016
Weidinger S, Novak N. Atopic dermatitis. *Lancet* 2016;**387** (10023):1109-22. [PUBMED: 26377142]

Whalley 2004
Whalley D, McKenna SP, Dewar AL, Erdman RA, Kohlmann T, Niero M, et al. A new instrument for assessing quality of life in atopic dermatitis: international development of the Quality of Life Index for Atopic Dermatitis (QoLIAD). *British Journal of Dermatology* 2004; **150**(2):274–83. [PUBMED: 14996098]

White 2012
White IR, Barrett JK, Jackson D, Higgins JP. Consistency and inconsistency in network meta-analysis: model estimation using multivariate meta-regression. *Research synthesis methods* 2012;**3**(2):111–25. [PUBMED: 26062085]

Williams 1994
Williams HC, Burney PG, Hay RJ, Archer CB, Shipley MJ, Hunter JJ, et al. The U.K. Working Party's diagnostic criteria for atopic dermatitis. I. Derivation of a minimum set of discriminators for atopic dermatitis. *British Journal of Dermatology* 1994;**131**(3):383–96. [PUBMED: 7918015]

Williams 2000
Williams HC, Wuthrich B. The natural history of atopic dermatitis. In: Williams HC editor(s). *Atopic Dermatitis*. Cambridge: Cambridge University Press, 2000:41–59. [10.1017/ CBO9780511545771.005]

Williams 2005
Williams HC. Clinical practice. Atopic dermatitis. *New England Journal of Medicine* 2005;**352**(22):2314–24. [PUBMED: 15930422]

Williams 2008
Williams H, Stewart A, von Mutius E, Cookson W, Anderson HR, International Study of Asthma and Allergies in Childhood (ISAAC) phase one and three study groups. Is eczema really on the increase worldwide?. *Journal of Allergy and Clinical Immunology* 2008;**121**(4):947–54. [PUBMED: 18155278]

Wollenberg 2016
Wollenberg A, Oranje A, Deleuran M, Simon D, Szalai Z, Kunz B, et al. ETFAD/EADV eczema task force 2015 position paper on diagnosis and treatment of atopic dermatitis in adult and paediatric patients. *Journal of the*

European Academy of Dermatology and Venereology: JEADV 2016;**30**(5):729–47. [PUBMED: 27004560]

Yew 2018

Yew YW, Ho MSL, Kok WL, Chan ESY, Shi L, Zheng Q, et al. Topical treatments for eczema: a network meta-analysis. Cochrane Database of Systematic Reviews (in press).

Yu 2018

Yu SH, Drucker AM, Lebwohl M, Silverberg JI. A systematic review of the safety and efficacy of systemic corticosteroids in atopic dermatitis. *Journal of the American Academy of Dermatology* 2018;**78**(4):733–40. [PUBMED: 29032119]

Zirwas 2018

Zirwas MJ. New and emerging therapies for atopic dermatitis. *Journal of the American Academy of Dermatology* 2018;**78**(3 Suppl 1):S25–84.

* *Indicates the major publication for the study*

ADDITIONAL TABLES

Table 1. Glossary of terms

Term	Definition
Atrophy	Thinning of overlying skin due to long-term or excessive usage of steroids
Cyclic adenosine monophosphate (cAMP)	A chemical compound used in intracellular signal communications in various biological processes and pathways, including the pathway dealing with inflammation
Cytokine	A chemical secreted by certain cells of the immune system; it has an effect on other cells
Erythematous	Redness of the skin
Excoriations	Linear breaks in the skin surface due to scratching
First-line	Treatment regimen accepted by the medical establishment for initial treatment
Fissured	Cracking of the superficial layer of the skin
Fitzpatrick skin type	Skin type classification, which was developed by Thomas B. Fitzpatrick, based on a person's skin color and responses to sun exposure in terms of degree of burning and tanning. Six different skin types were classified from very fair (skin type I) to very dark (skin type VI) depending upon whether the patient burns at the first average sun exposure or tans at the first average sun exposure
Glucocorticosteroid	A type of corticosteroid hormone with anti-inflammatory and immunosuppressive effects
Immunomodulatory	Regulating the immune system, either via auto-regulatory processes (homeostasis) or therapeutically

Table 1. Glossary of terms (*Continued*)

Immunosuppressive	Reducing the activation or efficacy of the immune system
Lesions (skin)	A region of the skin that has suffered damage through injury or disease of the skin
Lichenification	Thickening of the skin
Lichenified	Thickening of the first layer of the skin, with the skin lines being more obvious
Oedema	Swelling
Palmoplantar	Palms and soles
Papules	Small bump-like swellings of the skin, forming part of the rash
Pruritus	Severe itching
Second-line	Treatment regimen that follows if there is failure of response to standard or first line therapy
T cell	Also known as the T lymphocyte; a type of lymphocyte or white blood cell that carries T cells; a T-cell receptor on the cell surface
Xerotic	Dryness of the skin

APPENDICES

Appendix 1. Hanifin and Rajka Diagnostic Criteria

Three or more basic features:

1. Pruritus
2. Typical morphology and distribution:
    i) Flexural lichenification or linearity in adults
    ii) Facial and extensor involvement in infants and children
3. Chronic or chronically-relapsing dermatitis
4. Personal or family history of atopy (asthma, allergic rhinitis, atopic dermatitis)

Plus 3 or more minor features:

(*Continued*)

• Xerosis • Ichthyosis, palmar hyperlinearity, keratosis pilaris • Nipple eczema • Cheilitis • Recurrent conjunctivitis • Dennie-Morgan infraorbital fold • Keratoconus • Anterior subcapsular cataracts • Orbital darkening • Facial pallor, facial erythema • Pityriasis alba • Anterior neck folds • White dermatographism, delayed blanc	• Immediate (type 1) skin test reactivity • Elevated serum IgE • Early age of onset • Tendency toward cutaneous infections (especially *S. aureus* & HSV), impaired cell-mediated immunity • Tendency toward non-specific hand or foot dermatitis • Itch when sweating • Intolerance to wool or lipid solvents • Perifollicular accentuation • Food intolerance • Course influenced by environmental or emotional factors (or both)

Appendix 2. UK Working Party Diagnostic Criteria

Mandatory:
An itchy skin condition (parental report of scratching or rubbing in a child)

Plus 3 or more of the following:

- History of involvement of the skin creases, such as folds of elbow, behind the knees, fronts of ankles, or around the neck (including cheeks in children under 10)
- A personal history of asthma or hay fever (or history of AD in a first-degree relative in children under 4)
- History of general dry skin in the last year
- Visible flexural eczema (or eczema involving the cheeks, forehead, and outer limbs in children under 4)
- Onset under the age of 2 (not used if child is under 4)

Appendix 3. Draft search strategy for MEDLINE Ovid

1. exp Eczema/ or eczema.ti,ab.
2. exp Dermatitis, Atopic/
3. exp Dermatitis/ or dermatitis.ti,ab.
4. or/1-3
5. Cyclosporine/
6. (c?closporin* or CyA or Cy-A or CsA or Cs-A or csaneoral or neoral or sandimmun*).tw.
7. exp Aminopterin/
8. (aminopterin or MTX or methotrexate).tw.
9. Azathioprine/
10. (az?thioprine or im?uran).tw.
11. Leukotriene Antagonists/
12. Quinolines/
13. (antileukotriene* or anti-leukotriene* or (leukotriene adj3 (antagonist* or block* or inhibitor*))).tw.
14. (leukast* or zafirlukast* or zileuton* or quinoline*).tw.
15. Peptide Fragments/

16. exp Thymus Hormones/
17. exp Recombinant Proteins/
18. Interferon-gamma/
19. (rIFN* or bioferon or biogen or immuneron or imukin or kw-2202 or polyferon or ru-42369 or ru42369 or s-6810 or sch-36850 or sun-4800).tw.
20. ((r or recombinant) adj3 (interferon* or IFN or IFNg or IFNgamma)).tw.
21. ((Interferon* or IFN or IFNg or IFNgamma) adj3 (therap* or treat* or administ* or given or deliver* or systemic* or oral*)).tw.
22. (etanercept or enbrel or tnfr fc fusion protein).tw.
23. alefacept.tw.
24. (((tnf or tumor necrosis factor) adj2 receptor) or (tnf adj2 (fusion adj protein*))).tw.
25. Tumor Necrosis Factor-alpha/
26. (anti-TNF* or anti tumo?r necrosis factor).tw.
27. Antibodies, Monoclonal/
28. ((humanized adj8 (monoclonal* or antibod* or MoAb* or mAb or mAbs or fab*1)) or rhuMAb*).tw.
29. (chim?eric adj3 (monoclonal* or antibod* or MoAb* or mAb or mAbs)).tw.
30. ((against or anti) adj IgE adj2 (monoclonal* or antibod* or MoAb* or mAb or mAbs)).tw.
31. ((anti or against or block* or MoAb* or mAb or mAbs or antibod* or monoclonal*) adj3 (IL5 or IL-5 or interleukin-5 or LFA1 or LFA-1 or CD11a)).tw.
32. (omalizumab or (olizumab or hu-901 or hu901 or tnx-901 or tnx901 or xolair)).tw.
33. (infliximab or avakine or remicade).tw.
34. (efalizumab or raptiva or xanelim or hu1124 or hu-1124).tw.
35. (adalimumab or humira or D2E7 or trudexa).tw.
36. (rituximab or idec c2b8 or mabthera or rituxan or rituxin).tw.
37. (keliximab or sb 210396 or sb210396).tw.
38. (mepolizumab or bosatria or sb 240563 or sb240563).tw.
39. Mycophenolic Acid/
40. (mycophen?lat* or mycophenol* or mycofen?lat* or mycofenol* or mofetil* or MMF or erl-080* or erl080* or melbex or myfortic or nsc-129185 or nsc129185).tw.
41. Immunoglobulins, Intravenous/
42. (((intravenous or IV) adj (immune globulin* or IG or immun?globulin* or antibod*)) or IVIG or HdIVIg).tw.
43. exp Prednisolone/ or Beclomethasone/ or exp Fluocinolone Acetonide/ or Adrenal Cortex Hormones/
44. (prednison* or methylprednis* or dehydrocortisone or dexamethason* or beclomethasone or flunisolide).tw.
45. exp pimecrolimus/ or (asm981 or asm 981 or elidel).tw.
46. exp tacrolimus/ or (fk506 or fk 506).tw.
47. ((systemic or oral* or sublingual* or "per os" or inhal* or nasal* or parenteral*) adj3 (steroid* or glucosteroid* or corticosteroid* or glucocorticosteroid*)).tw.
48. ((biological*1 or biologic*1) adj (treatment* or therap* or medicine* or drug* or agent* or product*)).tw.
49. (biologic* response modifier* or BRM*).tw.
50. targeted therap*.tw.
51. dupilumab.tw.
52. Puva.tw. or Puva therapy/ or Psoralen ultraviolet A Therapy.tw.
53. alitretinoin.tw.
54. apremilast.tw.
55. tocilizumab.tw.
56. (systemic adj immunosuppressive treatment$).tw.
57. immuno-modulatory treatment$.tw.
58. anti inflammatory treatment$.tw.
59. Immunosuppressive Agents/
60. Anti-Inflammatory Agents/
61. or/5-60
62. randomized controlled trial.pt.
63. controlled clinical trial.pt.
64. randomized.ab.

65. placebo.ab.
66. clinical trials as topic.sh.
67. randomly.ab.
68. trial.ti.
69. 62 or 63 or 64 or 65 or 66 or 67 or 68
70. exp animals/ not humans.sh.
71. 69 not 70
72. 4 and 61 and 71
[Lines 62-71: Cochrane Highly sensitive search strategy for identifying randomized trials in MEDLINE: sensitivity and precision-maximizing version (2008 revision) (Lefebvre 2011)]

CONTRIBUTIONS OF AUTHORS

NC was the contact person with the editorial base.

RS, PD, ALL, RD, NML, SC, and NC coordinated the contributions from the co-authors and wrote the final draft of the protocol.

RS, PD, ALL, NML, and NC worked on the methods sections.

RS, ALL, RD, NML, and NC drafted the clinical sections of the background and responded to the clinical comments of the referees.

RS, PD, NML, and NC responded to the methodology and statistics comments of the referees.

RS, PD, ALL, RD, NML, and NC contributed to writing the protocol.

SC was the consumer co-author and checked the protocol for readability and clarity. He also ensured that the outcomes are relevant to consumers.

NC is the guarantor of the final review.

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