Clinical Commentary

Impact of a decade of research into atopic dermatitis

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Short Title: Last decade in atopic dermatitis.

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Abbreviations: AD: atopic dermatitis, AhR: Aryl hydrocarbon Receptor, CCL: C-C motif chemokine ligand, CI: confidence interval, CLDN8: claudin 8, ELOVL5: fatty acid elongase 5, FA2H: fatty acid 2-hydroxylase, FDA: Food and Drug Administration, FLG: filaggrin gene, JAK: Janus Kinase, RDBPCT: Randomized Double-Blinded, Placebo-Controlled Trial, RR: relative risk, Sbi: Second immunoglobulin-binding protein, SERPINB3: SERpin Peptidase INhibitor, clade B, member 3
Abstract

The last decade has seen an unprecedented pace of change, particularly of clinical research in atopic dermatitis (AD). This review summarizes some key discoveries. Over the last 10 years, nearly half of all studies investigated the efficacy and safety of novel therapeutic agents, particularly biologics and small molecules. Clear demonstration of benefit in clinical trials with no significant safety concerns provided strong evidence leading to subsequent Food and Drug Administration (FDA) approval and routine use of the anti-IL-4Rα antagonist dupilumab in patients 6 months and older; the selective JAK1 inhibitors upadacitinib for patients 12 years and older; abrocitinib, the IL-13 antagonist tralokinumab, and the JAK1/2 inhibitor baricitinib for adults 18 years and older. Several other drugs are in the pipeline. Other areas under the spotlight have been trials of skin moisturizers and probiotics in prevention of AD, investigating the role of filaggrin and skin barrier function, and the role of skin and gut microbiome, with Staphylococcus aureus Sbi having been found to uniquely trigger allergic skin responses in AD. Skin microbiome, epidermal metabolites/structural components, and local inflammatory biomarkers are now commonly assessed using genomic and proteomic analysis of tape strips rather than more invasive biopsy to identify factors such as CCL17 which correlate with disease severity and response to therapy. Overall, the last decade has ushered in a new and exciting era in our understanding, diagnosis and treatment of this common allergic skin disease.
Atopic dermatitis themes in the last decade with most coverage and prominence

The aim of this Clinical Commentary within the tenth Anniversary theme issue of the Journal is to review the most clinically relevant advances in atopic dermatitis (AD) over the last decade. Between January 2012 to December 2021, 14,406 peer-reviewed publications with the search term “atopic dermatitis” were listed on PubMed. This makes up 46% of all publication on AD since the first articles were listed over 70 years ago in 1948. This review covers some key advances related to our understanding and treatment of AD since 2012.

Articles focusing on treatment of AD were the most prominent focus of research making up half of all publication, with monoclonal antibody therapies (biologics) being the “flavor of the decade” accounting for 33% of all AD publications, and 65% within the treatment theme. There were 245 articles on JAK inhibitors (3%). Other themes with a relatively high publication rate were “prevention” (14%), “skin barrier” (13%) with 795 papers on “filaggrin” (6%), and “genetics” (12%) (Fig. 1).

Over 90% of all papers on “JAK inhibitors” and “microbiome” in relation to AD were published in the last decade. Other prominent topics were “skin barrier function”, “quality of life”, “genetics”, and “prevention”, where 57 – 78% of the papers on these topics were published between 2012 and 2021.

Based on this synopsis, this review focused on the following themes: (i) Preventing development of AD, (ii) Skin and gut microbiome, (iii) Filaggrin, skin barrier function and biomarkers, (iv) Treatment with biologics, small molecule therapies and specific-allergen immunotherapy. Existing gaps in knowledge requiring further research are also highlighted.

Preventing development of AD
The past decade has seen a flurry of studies investigating AD prevention strategies, with subsequent compilation and analysis within systematic reviews. Findings of recent systematic reviews are summarized below.

Moisturizers are the mainstays of AD treatment, and have also been investigated for their ability to prevent AD. A few small randomized controlled trials published in 2014 suggested that regular use of moisturizers in early infancy might prevent AD.\(^1,2\) However, larger trials subsequently found no significant benefit.\(^3,4\) A systematic review of ten randomized controlled trials involving 3,507 participants reported no significant reduction in the development of AD with prophylactic moisturizers initiated within the first six weeks of life (RR 0.84, 95% CI 0.64-1.1).\(^5\) Similarly, a Cochrane systematic review of seven trials involving 3,075 participants reported that moisturizers did not reduce the risk of eczema at age 1-3 years (RR 1.03, 95% CI 0.81-1.31).\(^6\) However, there was significant heterogeneity between studies, and the systematic review by Zhong et al\(^5\) suggested that moisturizers may benefit children with a strong family history of atopy (8 studies: RR 0.75, 95% CI 0.62-0.91). The benefit was largely seen where moisturizers were used continuously to the point of AD assessment, and not when treatment was ceased for an interval between AD assessment, thus there is the possibility that they were masking rather than preventing the development of mild AD.

Probiotics have been studied extensively for prevention of AD based on the hypothesis that the gut microbiome contributes to the pathophysiology of allergic disease. There have been many trials with mixed results, most in children with a family history of atopy, summarized in systematic reviews and meta-analyses.\(^7,9\) The effectiveness of probiotics for preventing AD may vary depending on the strain/s used,\(^10\) and whether they are administered prenatally, postnatally or both.\(^7,8\) Prebiotics have also been investigated for the prevention of AD, with mixed results.\(^12\) At this stage neither can be recommended in clinical practice for the prevention of AD.
The role of breastfeeding in AD prevention has been extensively debated and researched. Evidence is largely limited to observational studies, with mixed results. Several systematic reviews have reported little or no association between AD and breastfeeding, however authors have noted significant heterogeneity between studies and low methodological quality of some studies.\textsuperscript{11,13,14}

**Skin and gut microbiome**

*Staphylococcus aureus* directly triggers eczema flares. Bacterial colonization has been shown to precede and may predict development of AD in infancy,\textsuperscript{15,16} and occurs at a higher density in lesional compared with non-lesional skin.\textsuperscript{17} In the Learning Early About Peanut study, *Staphylococcus aureus* colonization was not only associated with risk of AD but was also independently associated with a risk of persistent egg and peanut allergy at 5 – 6 years of age.\textsuperscript{18} Al Kindi et al\textsuperscript{19} discovered that the Second immunoglobulin-binding protein (Sbi) released from *Staphylococcus aureus* is the key bacterial trigger of the type 2 cytokines such as TSLP and IL-33 in human keratinocytes that underlie AD. Infective flares of AD can often be brought under control with topical or systemic anti-staphylococcal antibiotics. However, the widespread use of topical antimicrobials such as fusidic acid promotes antibiotic resistance in *Staphylococcus aureus* isolates from AD patients.\textsuperscript{20}

*Staphylococcus aureus* is one of many bacteria making up the skin microbiome. Probiotics and topical bacteriotherapy with skin commensals have also been considered for the treatment of AD. A 12-week RDBPCT using probiotic strains *Bifidobacterium lactis*, *Bifidobacterium longum*, and *Lactobacillus casei* given by capsule orally to children aged 4 to 17 years with moderate AD showed a 83% reduction (95% CI, −95% to −70%) in SCORAD in the treatment group compared with a 24% reduction (95% CI, −36% to −11%) in the placebo group.\textsuperscript{21} Nakatsuji et al\textsuperscript{22} recently conducted a one-week, phase 1 randomized trial of 54 adults...
with *Staphylococcus aureus* positive AD using topical *Staphylococcus hominus* A9. They found that the treatment was safe and associated with a significant reduction in *Staphylococcus aureus* as well as lesional EASI scores. Subsequently the same research group isolated coagulase negative staphylococci from non-lesional skin of 11 adults with moderate to severe AD and reapplied either the bacteria or vehicle to the forearms of the patients. They found that *Staphylococcus aureus* colonization in the treatment group was reduced by 99% and that local Eczema Area And Severity Index scores by half, suggesting that autologous bacteriotherapy may provide an alternative treatment for AD. Yu et al. found that the tryptophan metabolite indole-3-aldehyde produced by skin commensals was significantly lower in lesional than non-lesional skin. In calcipotriol-induced dermatitis mice, this metabolite attenuated dermatitis severity. This effect was aryl hydrocarbon receptor (AhR) dependent as it had no effect in AhR knockout mice or after addition of AhR inhibitors.

In summary, defining the unique virulence factor Sbi that induces type 2 immune responses by *S. aureus* may lead to the development of novel therapeutics for the treatment of AD. Although there are interesting preliminary results suggesting the potential for bacteriotherapy in the treatment of infection-induced AD, large, multi-center RDBPCT are required to determine their real potential as a novel therapy for AD.

**Filaggrin and skin barrier function**

The role of filaggrin, a principal structural protein in the epidermis, in AD was already well known at the start of the last decade. Loss-of-function mutations in the *FLG* gene encoding filaggrin predisposes to eczema, supporting a key role for the skin barrier. However, although genetics are clearly important, an increasing prevalence of AD over the last few decades also points to a role of environmental factors. A recent systematic review examined the evidence for interactions between *FLG* null mutations and environmental exposures in the risk of atopic
dermatitis. Environmental factors may increase the risk of AD in patients with FLG loss of function, although published studies generally have small sample sizes, and thus further large, high-quality studies are needed to draw any firm conclusion. For instance, as water hardness, and phthalates commonly used to soften plastics as well as in many consumer and personal products that potentially disrupt skin barrier function may increase the risk of AD in filaggrin deficient patients.

**Skin biomarkers of disease**

As highlighted in the previous sections, the past decade has advanced our understanding of the interplay between environmental and genetic factors causing AD. Skin biopsies are increasingly being replaced by less invasive skin tape stripping to identify genomic, metabolomic and proteomic biomarkers of AD severity and response to therapy. AD lesional skin tends to express lower levels of keratinocyte terminal differentiation markers, higher T-cell chemokines, Th2 and Th22 cytokines, and variable Th1 and Th17 cytokines. A recent study using RNA-seq profiling of tape strips in infants and toddlers with AD showed immune and skin barrier alterations in both lesional and non-lesional skin, with differential expression of Th2 (CCL17 (TARC) and IL4R) and Th22/Th17 (IL36G, CCL20, and S100A) genes. Lesional skin had downregulated genes of terminal differentiation (FLG and FLG2), lipid synthesis/metabolism (ELOVL3 and FA2H), and tight junction (CLDN8). A separate study of 25 children aged 2-14 years with AD, used tape stripping alongside skin biopsies to examine protein levels of 17 immune markers and natural moisturizing factor. Tape strips showed a general increase in innate inflammation markers (IL-1α, IL-1β, IL-8, IL-18) along with CCL17 and CCL27 (CTACK). Several of these biomarkers correlated with AD severity in both lesional and non-lesional skin. Natural Moisturizing Factor and some cytokines also differed between children with and without FLG mutations. Mass spectroscopy proteomic
analysis showed differences in 45 skin proteins in a study of 62 children with AD and found that the serpin peptidase inhibitor, clade B, member 3 (SERPINB3) had the highest positive correlation with Transepidermal Water Loss, while keratin-10 had the highest negative correlation. The challenge for future studies is to simplify complex biomarker profiles, and determine if a single, or simple set of biomarkers might be used as an objective measure of AD severity and treatment response.

**Treatment with biologics and small molecule therapies**

The last decade has seen a surge in clinical trials examining novel therapies for the treatment of moderate-to-severe AD. Many of these novel therapies are proving to be very effective in suppressing the disease, although unfortunately none are curative and AD flares typically occur on drug discontinuation unless the disease has spontaneously resolved. Most have involved systemic biologics inhibiting Th2 cell function, and small molecules, particularly JAK inhibitors that block T-cell and dendritic cell activity in the skin. Numerous systematic reviews and commentaries discussing the outcomes of these trials have been published recently. Dupilumab (an interleukin-4 receptor alpha antagonist) was the first biologic to be approved by the FDA for use in adults with moderate-to-severe AD in March 2017, adolescent patients 12 to 17 years of age in March 2019, in children over 6 years old in October 2021, and in children 6 months of age and older in June 2022. In 2021 tralokinumab (an IL-13 antagonist) and baricitinib (JAK1/2 inhibitor) were approved for treatment of adults with moderate-to-severe AD and in 2022 two selective JAK1 inhibitors, abrocitinib (for adults) and upadacitinib (for adults and children 12 years and over) were approved for use in patients with moderate-to-severe AD where systemic therapy is considered. Thus, the last five years has seen an expansion of therapeutic options for treatment of patients with severe AD that impacts most on the patient’s and family’s quality of life.
Primary publications detailing randomized, placebo-controlled clinical trials of these therapeutics in humans with clinical efficacy as the primary end point are summarized in Table I. They show substantial clinical improvement in both dermatitis scores and quality of life, particularly with dupilumab, abrocitinib and upadacitinib. Disappointingly, although the primary clinical feature of AD is pruritus, in a RDBPCT the anti-IL-31 biologic nemolizumab reduced the itch but had little or no effect on the eczematous rash.\textsuperscript{58,59} Furthermore, although \textit{in vitro} studies suggest that keratinocyte-derived TSLP and IL-33 are key cytokines that initiate the type 2 immune response in the skin, a clinical trial of tezepelumab has not shown significant benefit,\textsuperscript{47} and there are currently only proof-of-concept clinical trials of the IL-33 inhibitor etokinab.\textsuperscript{72}

Comparative studies have been conducted to investigate the relative efficacy of dupilumab and upadacitinib in the Heads-Up study,\textsuperscript{69} and between dupilumab and abrocitinib in the JADE COMPARE study.\textsuperscript{65} The results of the Heads-Up study show that 30mg of oral upadacitinib taken once a day leads to a significantly greater improvement, particularly in EASI-90, EASI-100 and pruritus NRS scores than subcutaneous dupilumab at a dose of 300mg administered every fortnight for 16 weeks. Clinical responses to abrocitinib and dupilumab in the JADE COMPARE study were similar. Additional studies directly comparing biologics and small molecule therapeutics will be important to determine their relative efficacy. None of these newer biologics led to any clinically significant serious adverse events compared with the control group.

As well as the data from clinical trials, longer term follow-up and real-world data is now available, particularly for dupilumab.\textsuperscript{73-83} In 1,028 adults who had completed week 100 of treatment, over 90% achieved a persistent $\geq$4-point change in POEM and DLQI.\textsuperscript{78} Three quarters of 94 patients treated with dupilumab achieved an EASI 75 at 26 – 30 weeks treatment. As well as an improvement in AD, patient’s asthma also improved.\textsuperscript{79} Eye symptoms are a
recognized adverse event and although most are mild and do not require discontinuation of
treatment. Specialist ophthalmology input is advised in more severe cases. There were no
significant laboratory abnormalities. In another study of 128 patients aged six years and above,
dupilumab with a mean duration of treatment of 15 months was generally well tolerated, with
the most common, typically mild side effects were head and neck dermatitis (20%),
conjunctivitis (16%), erythema, pruritus, and skin peeling (11%) and dry eyes (8%). Facial
and neck erythema is reported in up to half of the patients, and in 10% the drug needed to be
discontinued owing to this adverse event. Follow-up data is also available for the JAK1
inhibitors abrocitinib, upadacitinib and baricitinib. There is 40-week follow-up data on 1,233
patients from the JADE Abrocitinib trials (JADE REGIMEN) showing that patients whose AD
flared after coming off this JAK inhibitor had control of their disease re-established when the
drug was restarted at a dose of 100mg, but particularly 200mg once a day. Fifty-two-week
follow-up data for Updacitinib Measure Up 1 & 2 trials show sustained improvement in AD
with no significant safety concerns. Likewise, 68-week follow-on data from baricitinib
BREEZE-AD1 & AD2 trials at doses of 2mg and 4mg per day also show sustained
improvement in AD scores with no new safety concerns.

The current challenge for clinicians and their patients is to decide which of these drugs
to use for treatment of moderate-to-severe AD (Table II). There are a number of factors to
consider including (a) licensing, particularly in children where currently the only two options
are dupilumab and in older children upadacitinib, (b) long-term safety where dupilumab is
currently four years ahead of other drugs in terms of real-world data, (c) drug delivery with
biologics needing subcutaneous administration while JAK inhibitors can be given orally, and
(d) monitoring with biologics needing little if any blood monitoring, while JAK inhibitors do
require regular blood tests. Regarding long-term safety, from September 2021 the FDA
requires Box warnings about the increased risk of serious heart-related events, cancers, blood
clots and death for tofacitinib (JAK1 and 3 inhibitor). This is based on results from a randomized, open label, noninferiority, post-authorization, safety end point trial of 1,455 patients 50 years or older with active rheumatoid arthritis and one additional cardiovascular risk factor. Although the risk of cancer was statistically significant (relative risk (95% confidence interval) 1.48 (1.04 – 2.09)) compared with the TNF inhibitor group, major adverse cardiovascular events was not (1.33 (0.91 – 1.94)).

New and updated warnings are also required for two other arthritis biologics of the same drug class baricitinib and upadacitinib, which are used in the treatment of AD. The FDA recommend that clinicians take these box warnings into account when counselling patients about relative benefits and risks of these medication, although their relevance to most AD patients, who will be younger and less likely to have additional cardiovascular risk factors is unclear.

Pharmaceutical companies are working to make administration of subcutaneous biologics as easy as possible with the replacement of needle and syringes with pre-filled pens. Other important factors to consider are the relative efficacy of available therapies, with upadacitinib currently leading the field, and cost, although pharmaceutical companies are likely to position their drugs to maximize clinical use and financial return. Regarding cost, it will be important to maximize patient compliance of these high-cost drugs and reduce wastage from unnecessary use, or excessive home delivery.

As well as RDBPCT trials of systemic JAK inhibitors, there have also been a few RDBPCT investigating topical therapies in patients with less severe AD. Ruxolitinib cream, a selective JAK1 and 2 inhibitor was applied topically twice a day in two RDBPCT trials with a total of 1,249 AD patients ≥12 years old and IGA scores of 2/3. Significantly more patients applying the drug achieved the primary end point of an IGA of 0/1 compared with those just using the vehicle during the 8-week period. Two RDBPCT applying the topical pan-JAK inhibitor delgocitinib twice daily have also been published; one 16-week trial in
adults with chronic hand eczema inadequately controlled with topical corticosteroids or where steroids were contraindicated, and one 4-week trial in children aged 2 – 15 years old followed by 52-week open-label follow-up period. Both showed a significant improvement in IGA scores compared with the vehicle. Topical JAK inhibitors were without clinically serious adverse effects. Future trials comparing these novel topical biologics with routinely available topical immune suppressants are required to evaluate their relative efficacy and potential place in treatment of mild to moderate AD.

**Role of allergen-specific immunotherapy**

There have been few RDBPCT examining the use of allergen-specific immunotherapy for the treatment of AD. A Chinese multicenter RDBPCT of 239 adults with AD (baseline SCORAD 10 - 40) where 179 patients were given *D. farinae* sublingual immunotherapy (SLIT) did not show a significant improvement in SCORAD in the per protocol treatment set reviewed at the end of the study at 36-weeks. In a Brazilian RDBPCT of 91 children with AD (baseline SCORAD ≥15), where 35 patients were administered *D. pteronyssinus* SLIT for 18 months, the primary outcome of a ≥15-point decrease in SCORAD was not significantly different to 31 controls (relative risk 1.3, 95% CI 0.9 – 1.8), although secondary outcome measures of reduction of SCORAD from baseline and Investigator Global Assessment scores of 0/1 were significantly better in the treatment group. Larger multi-center RDBPCT with preferably with longer 3-year follow-up are required to draw any definite conclusions as to the usefulness of this therapy.

**Resume and existing gaps in knowledge requiring further research**

Despite the proliferation of published research in atopic dermatitis, multiple gaps in knowledge remain. There have recently been efforts to reach consensus on the most important research
questions yet to be answered in AD. In one recent publication, eight priority research questions were determined through an electronic Delphi consensus process with 68 clinician members of the International Eczema Council from 22 countries involved in AD patient care and research.\textsuperscript{93} The priority research questions related to prediction of disease course (identifying those who will develop chronic disease, comorbidities and/or adverse outcomes); identification of clinically meaningful disease subtypes; evaluation of safe, effective and disease-modifying therapies; comparative effectiveness and safety of topical and systemic treatments; biomarker assessment for prediction of severity; disease course; treatment response; and comorbidities; and mechanisms and treatment of disease flares. The authors noted that answering these research questions will require multidisciplinary research including epidemiology, clinical trials and molecular medicine.

One area that has been identified as hampering progress in AD research is the wide range of definitions and outcomes that have been measured in individual studies, limiting the ability to combine and compare data from different studies. The ability to combine data from individual trials in systematic reviews and meta-analyses is critically important for informing patient care and treatment decisions. To address this issue, the “Harmonising Outcome Measures for Eczema” group used a series of research methods including Delphi and nominal group techniques informed by systematic reviews of properties of candidate instruments to define a set of core outcome measures that they have recommended for including in all clinical trials of atopic dermatitis.\textsuperscript{94} The use of harmonized outcome measures in future clinical trials has the potential to increase knowledge and improve patient care.
References


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Simpson EL, Papp KA, Blauvelt A, Chu CY, Hong HC, Katoh N, et al. Efficacy and Safety of Upadacitinib in Patients With Moderate to Severe Atopic Dermatitis: Analysis of Follow-up Data From the Measure Up 1 and Measure Up 2 Randomized Clinical Trials. JAMA Dermatol. 2022;158:404-413.


Table I Randomized, double-blinded, placebo-controlled clinical trials in humans investigating efficacy of systemic biologics and small molecules in patients with moderate to severe AD

<table>
<thead>
<tr>
<th>Drug(s)</th>
<th>Action</th>
<th>Cohort</th>
<th>Control group</th>
<th>Primary end point</th>
<th>Significant adverse events</th>
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<tbody>
<tr>
<td>Omalizumab 150 – 375mg Q2-4</td>
<td>IgE</td>
<td>8 patients 4 – 22y</td>
<td>TCS only</td>
<td>No significant improvement in SCORAD</td>
<td>Not significantly different between groups</td>
<td>Iyengar et al, 201345</td>
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<td>Omalizumab 150mg</td>
<td>IgE</td>
<td>62 children 4 – 19y</td>
<td>TCS only</td>
<td>SCORAD at 24w 43%* vs 49% (adjusted for IgE and age)</td>
<td>Not significantly different between groups</td>
<td>Chan et al, 202046</td>
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<td>Tezepelumab 280mg Q2</td>
<td>TSLP</td>
<td>113 adults</td>
<td>TCS only</td>
<td>EASI-50 not significantly different at 12w</td>
<td>Not significantly different between groups</td>
<td>Simpson et al, 201947</td>
</tr>
<tr>
<td>Lebrikizumab 125mg Q4, 250mg Q4 or Q2</td>
<td>IL-13</td>
<td>280 adults</td>
<td>TCS only</td>
<td>% least squares mean change of EASI 37-38%* vs 56% at 16w</td>
<td>Not significantly different between groups</td>
<td>Guttman-Yassky et al, 202048</td>
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<td>Tralokinumab 300mg Q2</td>
<td>IL-13</td>
<td>Adults</td>
<td>TCS only</td>
<td>IGA 0-1 16%* vs 7%, EASI-75 25%* vs 13% at 16w</td>
<td>Not significantly different between groups</td>
<td>Wollenberg et al, 202149</td>
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<td>Tralokinumab 300mg Q2</td>
<td>IL-13</td>
<td>277 adults</td>
<td>TCS only</td>
<td>EASI-75 64%* vs 50% at 16w</td>
<td>Not significantly different to control</td>
<td>Gutermuth, et al, 202250</td>
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<tr>
<td>Dupilumab 100mg Q4, 200mg Q2,</td>
<td>IL-4/13</td>
<td>380 adults</td>
<td>TCS only</td>
<td>Significant improvement in pruritus NRS, POEM, SCORAD, DLQI at 16w</td>
<td>Not significantly different between groups</td>
<td>Simpson et al, 201651</td>
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<tr>
<td>Dose</td>
<td>Frequency</td>
<td>Population</td>
<td>Treatment</td>
<td>Endpoint</td>
<td>Outcome</td>
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<tr>
<td>Dupilumab</td>
<td>300mg Q1, 300mg Q2</td>
<td>IL-4/13 380 adults</td>
<td>TCS only</td>
<td>EASI SE vs baseline -74%<em>, -68%</em>, -65%<em>, -64%</em>, -45%, vs -18% at 16w</td>
<td>Not significantly different between groups</td>
<td>Thaci et al, 2016</td>
</tr>
<tr>
<td>Dupilumab</td>
<td>300mg Q1, 300mg Q2</td>
<td>IL-4/13 740 adults</td>
<td>TCS only</td>
<td>IGA 1-2 39%<em>, 39% vs 12%, EASI-75 64%</em>, 69%*, vs 23% at 16w</td>
<td>Not significantly different between groups</td>
<td>Blauvelt et al, 2017</td>
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<td>Dupilumab</td>
<td>300mg Q1, 300mg Q2</td>
<td>IL-4/13 325 adults</td>
<td>TCS only</td>
<td>EASI-75 59-63%* vs 30% at 16w</td>
<td>Not significantly different between groups</td>
<td>Bruin-Weller et al, 2018</td>
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<td>Dupilumab</td>
<td>200mg/300mg Q2, 300mg Q4</td>
<td>IL-4/13 251 adolescents (12 – 18y)</td>
<td>TCS only</td>
<td>EASI-75 42%<em>, 38%</em> vs 8% or IGA 1-2 24%<em>, 18%</em>, vs 25* at 16w</td>
<td>Not significantly different between groups</td>
<td>Simpson et al, 2020</td>
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<tr>
<td>Dupilumab</td>
<td>300mg Q1, Q2, Q4, Q8</td>
<td>IL-4/13 422 adults</td>
<td>NOT BLINDED</td>
<td>%EASI from SOLO baseline at 36w: placebo, Q4 &amp; Q8 significantly poorer control than Q1-Q2</td>
<td>Not significantly different between groups</td>
<td>Worm et al, 2020</td>
</tr>
<tr>
<td>Secukinumab</td>
<td>300mg Q1</td>
<td>IL-17A 41 adults</td>
<td>TCS only</td>
<td>Secondary endpoints: no clinical improvement in AD</td>
<td>Not significantly different between groups</td>
<td>Ungar et al, 2021</td>
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<td>Nemolizumab</td>
<td>IL-31</td>
<td>264 adults</td>
<td>Placebo, TCS as rescue only</td>
<td>Pruritus VAS -44%<em>, -60%</em>, 63%* vs 21% at 12w</td>
<td>Not significantly different between groups</td>
<td>Ruzicka et al, 2017</td>
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<tr>
<td>Treatment</td>
<td>Comparator</td>
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<td>Comparator Details</td>
<td>Primary Efficacy Outcome</td>
<td>Comparator Details</td>
<td>Significance</td>
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<tr>
<td>Nemolizumab 60mg Q4</td>
<td>IL-31</td>
<td>215 adults</td>
<td>TCS only</td>
<td>Pruritis VAS 43%* vs 21% at 16w</td>
<td>Not significantly different between groups</td>
<td>Kabashima et al, 2020⁵⁹</td>
</tr>
<tr>
<td>Baricitinib 2mg, 4mg / day</td>
<td>JAK1/2</td>
<td>329 adults</td>
<td>TCS only</td>
<td>IGA 0-1 2mg 24%, 4mg 31%* vs 15% at 16w</td>
<td>Not significantly different to control</td>
<td>Reich et al, 2020⁶⁰</td>
</tr>
<tr>
<td>Baricitinib 1mg, 2mg / day</td>
<td>JAK1/2</td>
<td>440 adults</td>
<td>TCS only</td>
<td>EASI-75 13% 1mg, 30%* 2mg, 8% placebo at 16w</td>
<td>Not significantly different to control</td>
<td>Simpson et al, 2021⁶¹</td>
</tr>
<tr>
<td>Abrocitinib 10mg, 30mg, 100mg, 200mg / day</td>
<td>JAK1</td>
<td>267 adults 18-75y</td>
<td>TCS only</td>
<td>IGA 1-2 11%, 9%, 30%, 44%* vs 6% at 12w</td>
<td>Not significantly different between groups</td>
<td>Gooderham et al, 2019⁶²</td>
</tr>
<tr>
<td>Abrocitinib 100mg, 200mg / day</td>
<td>JAK1</td>
<td>391 ≥12y</td>
<td>TCS only</td>
<td>IGA 1-2 28-38%* vs 9%, EASI-75 44-61%* vs 10% at 12w</td>
<td>Not significantly different to control</td>
<td>Silverberg et al, 2020⁶³</td>
</tr>
<tr>
<td>Abrocitinib 100mg, 200mg / day</td>
<td>JAK1</td>
<td>387</td>
<td>TCS only</td>
<td>IGA 1-2 24%, 44%* vs 8%, EASI-75 40%<em>, 63%</em> vs 12% at 12w</td>
<td>Not significantly different to control</td>
<td>Simpson et al, 2020⁶⁴</td>
</tr>
<tr>
<td>Abrocitinib 100mg, 200mg / day</td>
<td>JAK1</td>
<td>285 adolescents 12-17y</td>
<td>TCS only</td>
<td>IGA ≥2 42-46%* vs 24%, EASI-75 68-72%* vs 42% at 12w</td>
<td>Not significantly different to control</td>
<td>Eichenfield et al, 2021⁶⁵</td>
</tr>
<tr>
<td>Abrocitinib 100mg, 200mg</td>
<td>JAK1 vs IL-4/13</td>
<td>838 adults</td>
<td>NOT BLINDED Comparison of the two drugs and TCS only</td>
<td>IGA 0-1 Abro 100 36%, Abro 200mg 48%, Dupi 36%, Control 14%, EASI-75 Abro 100 59%, Abro 200mg 70%, Dupi</td>
<td>Not significantly different between groups</td>
<td>Bieber et al, 2021⁶⁶</td>
</tr>
<tr>
<td>Treatment</td>
<td>Target</td>
<td>Participants</td>
<td>Intervention</td>
<td>Efficacy Measures</td>
<td>Significance</td>
<td>Reference</td>
</tr>
<tr>
<td>------------------------------------------------</td>
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<td>-----------------------------------------------------------------------------------</td>
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</tr>
<tr>
<td>Upadacitinib 15mg, 30mg / day</td>
<td>JAK1</td>
<td>901 adults</td>
<td>TCS only</td>
<td>IGA 0-1 40%<em>, 59%</em> vs 11%, EASI-75 65%<em>, 77%</em> vs 26% at 16w</td>
<td>Not significantly different between groups</td>
<td>Reich et al, 2021(^67)</td>
</tr>
<tr>
<td>Upadacitinib 7.5mg, 15mg, 30mg / day</td>
<td>JAK1</td>
<td>167 adults</td>
<td>TCS only</td>
<td>%EASI 39%<em>, 62%</em>, 74%* vs 23% at 16w</td>
<td>Not significantly different between groups</td>
<td>Guttman-Yassky et al, 2020(^68)</td>
</tr>
<tr>
<td>Upadacitinib 30mg vs dupilumab 300mg / day</td>
<td>JAK1 vs IL-4/13</td>
<td>692 adults</td>
<td>Comparison of the two drugs</td>
<td>EASI-75 71%* vs 61% at 16w</td>
<td>Not significantly different between drug groups</td>
<td>Blauvelt et al, 2021(^69)</td>
</tr>
<tr>
<td>SHR0302 4mg, 8mg / day</td>
<td>JAK1</td>
<td>105 Chinese 18-75y</td>
<td>TCS only</td>
<td>IGA ≥2 26-54%* vs 6% at 12w</td>
<td>Not significantly different to control</td>
<td>Zhao et al, 2021(^70)</td>
</tr>
<tr>
<td>Apremilast 30mg or 40mg bd</td>
<td>PDE4</td>
<td>146 adults</td>
<td>TCS only</td>
<td>% EASI 30mg 26%, 40mg 31%* vs 11% at 12w</td>
<td>40mg dose associated with high cellulitis</td>
<td>Simpson et al, 2019(^71)</td>
</tr>
</tbody>
</table>

TCS: topical corticosteroid, EASI: Eczema Area and Severity Index, IGA: Investigator Global Assessment, JAK: Janus Kinase, VAS: visual analogue scale *significantly different

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\(^{67}\) Reich et al, 2021
\(^{68}\) Guttman-Yassky et al, 2020
\(^{69}\) Blauvelt et al, 2021
\(^{70}\) Zhao et al, 2021
\(^{71}\) Simpson et al, 2019
Table II Considerations clinicians face when deciding which drugs to prescribe for patients with moderate-severe atopic dermatitis requiring systemic therapy

<table>
<thead>
<tr>
<th><strong>Clinical</strong></th>
<th><strong>Economic</strong></th>
<th><strong>Logistic</strong></th>
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<tbody>
<tr>
<td>Efficacy in clinical trials</td>
<td>Cost</td>
<td>Licensed</td>
</tr>
<tr>
<td>Efficacy based on real life data</td>
<td>Avoiding excessive home delivery</td>
<td>Approved: national and local</td>
</tr>
<tr>
<td>Improvement in other atopic diseases e.g. asthma</td>
<td>Patient compliance</td>
<td></td>
</tr>
<tr>
<td>Safety and side-effects in clinical trials</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Safety and side-effects from real life data</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mode of delivery: oral vs parenteral</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Requirement for drug monitoring</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Figure legends

Figure 1 Comparison of percentage of atopic dermatitis theme areas published in 2012 – 2021 and pre-2012.