



ORIGINAL ARTICLE

Targeted therapy for immune mediated skin diseases. What should a dermatologist know?☆



Edinson López , Raúl Cabrera *, Cristóbal Lecaros 

Department of Dermatology, Facultad de Medicina Universidad del Desarrollo-Clinica Alemana de Santiago, Santiago, Chile

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Abstract

Background: Molecularly targeted therapies, such as monoclonal antibodies (mAbs) and Janus Kinase inhibitors (JAKis), have emerged as essential tools in the treatment of dermatological diseases. These therapies modulate the immune system through specific signaling pathways, providing effective alternatives to traditional systemic immunosuppressive agents. This review aims to provide an updated summary of targeted immune therapies for inflammatory skin diseases, considering their pathophysiology, efficacy, dosage, and safety profiles.

Methods: The review followed the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines. A systematic search was conducted on PubMed over the past 10 years, focusing on randomized clinical trials, case reports, and case series related to targeted immune therapies in dermatology. Eligibility criteria were applied, and data were extracted from each study, including citation data, study design, and results.

Results: We identified 1360 non-duplicate articles with the initial search strategy. Title and abstract review excluded 1150, while a full-text review excluded an additional 50 articles. The review included 143 studies published between 2012 and 2022, highlighting 39 drugs currently under investigation or in use for managing inflammatory skin diseases.

Study limitations: The heterogeneity of summarized information limits this review. Some recommendations originated from data from clinical trials, while others relied on retrospective analyses and small case series. Recommendations will likely be updated as new results emerge.

Conclusion: Targeted therapies have revolutionized the treatment of chronic skin diseases, offering new options for patients unresponsive to standard treatments. Paradoxical reactions are rarely observed. Further studies are needed to fully understand the mechanisms and nature of these therapies. Overall, targeted immune therapies in dermatology represent a promising development, significantly improving the quality of life for patients with chronic inflammatory skin diseases.

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☆ Study conducted at the Department of Dermatology, Facultad de Medicina Universidad del Desarrollo-Clinica Alemana de Santiago, Santiago, Chile.

* Corresponding author.

E-mail: rcabrera237@gmail.com (R. Cabrera).

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Introduction

Molecularly targeted therapies have become an important tool for treating dermatological diseases.¹

The main groups of targeted therapy for inflammatory skin diseases are Monoclonal Antibodies (mAbs) and Janus Kinase Inhibitors (JAKis), but there are also fusion proteins produced by recombinant DNA such as etanercept. Formerly referred to as biologics – since they were synthesized as products of living organisms – today these therapies are also made up of small molecules so the term targeted therapy should be preferred.² Also, the term targeted immune modulators is used in reference textbooks.³

The mechanism of action is heterogeneous among the different molecules, but all of them modulate the immune system through stimulatory or inhibitory drives, acting at specific points of the signaling pathways of inflammation.⁴ Their effectiveness and safety profile often are homologous to standard systemic immunosuppressive agents or even better. Like all new drugs, they are not free of adverse events and their cost represents an important barrier for their accessibility.⁵

The first examples of targeted immune therapies for inflammatory diseases in dermatology were the clinical trials of alefacept,⁶ efalizumab,⁷ etanercept⁸ and infliximab⁹ for psoriasis in the early 2000s. Alefacept and efalizumab have been replaced by newer molecules with a constant renewal of targeted immune therapies and therapy drugs for different inflammatory skin diseases (Fig. 1).

This narrative review aims to update, summarize, and prioritize the large quantity of information about critical inflammatory skin diseases in a handy clinical format. We suggest indications for use considering current data on the efficacy, dose, and safety profile of targeted immune therapy.

Material and methods

This review was reported based on the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines.¹⁰ We did a systematic search on Pubmed in the last 10 years (January 2012 to July 2023). (Search strategy, Supplementary Material 1). We also screened the references of all included studies to identify any additional eligible studies. Systematic reviews and Randomized Clinical Trials (RCT) in English were selected. We also included case reports and case series if they were conducted on human participants. Studies were excluded if the biological product used was in the context of alternative medicine or the quality of the report was insufficient.

Data extraction

The titles and abstracts of all records were independently screened for eligibility by two authors (E.L. and C.L.). The full texts of papers deemed potentially eligible were critically appraised and assessed for eligibility. Any disagreement on the inclusion or exclusion of a paper between

the two investigators was reviewed by a third investigator (R.C.) to reach a consensus. Data extracted from each study included citation data (title of the study, authors, publication year), study design (study aim, period, setting), and results (demography of the population, outcome measures).

Results

Literature search

We identified 1360 non-duplicate articles with the initial search strategy. Title and abstract review excluded 1150, while a full-text review excluded an additional 50 articles. One hundred and forty-three studies were included in this review, as outlined in the PRISMA flow diagram (Fig. 2).

Psoriasis

Psoriasis is a chronic, immune-mediated skin disease that affects approximately 1% of the population worldwide.^{11–13} Despite compelling evidence supporting the use of targeted immune therapies, the selection of a specific drug can be challenging.¹⁴ The final decision for treatment should include the patient's preference and eventually consultation with physicians of other specialties to balance risks and benefits.

Eligibility criteria

Patients should be considered for targeted immune therapy in a variety of circumstances: if severe psoriasis,^{15–17} defined as involvement of greater than 10% of the total Body Surface Area (BSA), a PASI or a DLQI scores greater than 10 or compromised of specific locations (hands, feet, scalp, face, or genital area), when psoriasis causes intractable pruritus or has serious emotional consequences with a disease duration greater than 6-months,¹⁵ or is unresponsive to conventional therapy, or cannot receive standard systemic therapy due to patient's general condition, comorbidities, or has a severe disease such as erythrodermic, pustular psoriasis or psoriatic arthritis.^{15–17}

Therapy

There are multiple targeted immune therapy for psoriasis. Targeted therapies like anti-TNF- α , anti-IL17, anti-IL23, and anti-IL12/23 can reach PASI-90 in more patients than previous systemic treatment (i.e., cyclosporin and methotrexate).¹⁸ Anti-IL17 (i.e., ixekizumab, secukinumab, and brodalumab) and anti-IL23 (risankizumab, tildrakizumab and guselkumab) treatments showed a higher proportion of patients reaching PASI 90 compared to all the systemic interventions evaluated in the last network meta-analysis.¹⁸

TNF- α inhibitors were the first biologics drugs approved for the treatment of psoriasis.^{12,19} Meta-analysis shows that among this class infliximab has the highest efficacy, followed by certolizumab, adalimumab, and etanercept.^{18,19} The FDA approved sequentially etanercept (2004), infliximab (2005),

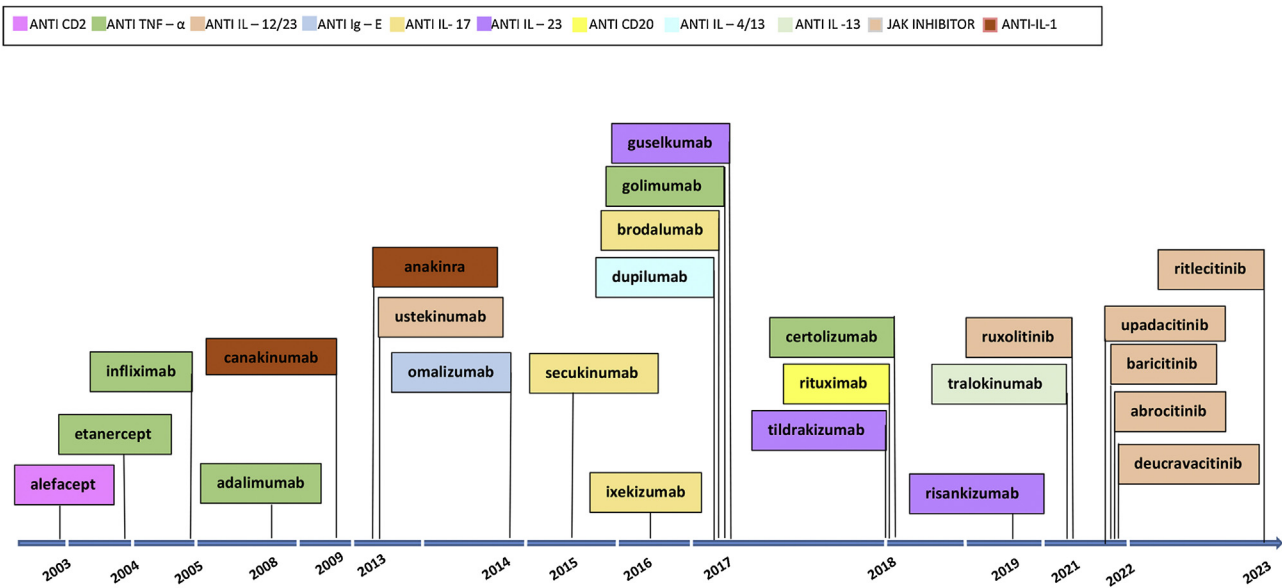


Fig. 1 Approved treatments of targeted immune therapies by the FDA for inflammatory skin diseases.

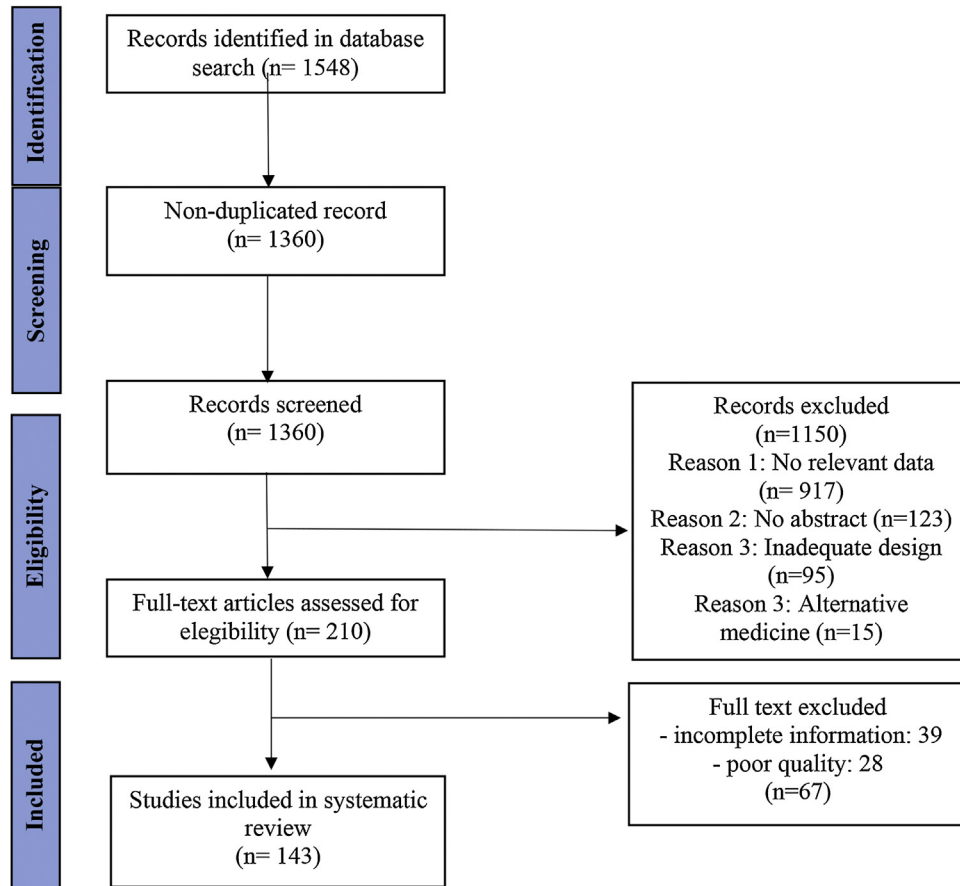


Fig. 2 PRISMA Flowchart.

adalimumab (2008), golimumab (2017), and certolizumab (2018).

IL-17 inhibitors reach a total clearance of disease (i.e. PASI-100) in about half of the patients^{11,12} and have the fastest onset of action. The drugs approved by FDA to treat

psoriasis are secukinumab (2015), ixekizumab (2016), and brodalumab (2017).

IL-23 inhibitors risankizumab and guselkumab have recently demonstrated a better efficacy and safety profile compared to anti-IL-17 and a convenient dosing regimen.^{20,21}

The drugs approved by FDA are guselkumab (2017), tildrakizumab (2018) and risankizumab (2019). Ustekinumab (2013) is a mAbs that inhibits IL-12 and IL-23.

JAKis (deucravacitinib, peficitinib, baricitinib, solcitinib, itacitinib, abrocitinib, brepocitinib, ruxolitinib and tofacitinib) have also been used for the treatment of psoriatic patients.^{22,23} Although we still lack complete data on their final clinical impact on psoriasis treatment, recent trials are showing a better response than certain conventional therapies (e.g., methotrexate, cyclosporine) but inferior to targeted immune therapy (e.g., risankizumab).¹⁸ Deucravacitinib^{24,25} a selective allosteric Tyrosine Kinase 2 (TYK2) inhibitor is the only JAKi approved by the FDA (2022), achieving a 70% PASI-75 at week 24.

In recent years (2004 to 2020), 51 clinical guidelines addressing the management of psoriasis have been published, and 41 of these mention the use of biologics.²⁶ During 2021–2022 several dermatological societies have updated their clinical guidelines considering the approval of new molecules by drug regulatory agencies.^{27–33} Guidelines recognize anti-IL-23 and anti-IL-17 drugs as part of the first-line treatment profile for psoriasis management. A major concern results from their high cost and accessibility. The final decision for the selection of a drug for the treatment of a psoriatic patient depends on several clinical and epidemiological factors (Table 1).

The safety profile of targeted immune therapy for psoriasis

The safety profile of targeted immune therapy for psoriasis is well described, the most common adverse events being upper respiratory tract infections and injection site reactions for all drug classes.^{34,35} General considerations should be taken concerning reactivation of tuberculosis, hepatitis B and C. The usage of JAKis should also consider previous infections by viruses of the Herpes family.^{36,37}

Current evidence shows that targeted immune therapy does not increase the risk of major adverse cardiovascular events such as myocardial infarction, cerebrovascular accident cardiovascular death, or the incidence of malignancies.^{35,37–39}

A common cutaneous adverse reaction is the phenotypic switch from psoriasis to atopic eczema that occurs in up to 1%–12.1% of patients taking anti-TNF- α or anti-IL-17/IL-23 drugs.⁴⁰ Topical treatment was successful in some cases, but in others, the biologic treatment needs to be discontinued.

A paradoxical reaction – psoriatic worsening and/or new psoriatic lesions – has been reported with the use of certain drugs (e.g., anti-TNF- α drugs and ustekinumab). These reactions usually do not require cessation of therapy and are self-limited.³⁷ Other relevant adverse reactions with anti-TNF- α class are urinary tract infection, back pain, arthralgia, pruritus and erysipelas, invasive fungal infections, lymphoma, heart failure, cytopenia, induction or exacerbation of demyelinating disease and lupus-like syndrome (e.g., infliximab).⁴⁰

Anti-IL-17 and anti-IL-12/23 drugs have less data about their safety profile. An adverse reaction of interest in IL-17 and IL-12/23 inhibitors is mucocutaneous candidiasis (1.7% in patients treated with secukinumab, 3.3% ixekizumab, 4.0% brodalumab, 2.3% ustekinumab).⁴¹ Episodes of exacer-

beration of inflammatory bowel disease have also been observed using these drugs. Patients with a history of Crohn's disease or ulcerative colitis should be treated with another targeted immune therapy.³⁷

For JAKis the most common adverse effects were herpes simplex reactivation, mouth ulcers, pneumonia, COVID-19, malignancies including lymphoma, rhabdomyolysis, increased creatine phosphokinase, increased triglycerides, and increased transaminases.²³

With the available data the, rates of any adverse effect were the lowest for tildrakizumab, certolizumab, and etanercept.³⁴ For serious AE the lowest were for certolizumab, risankizumab, and etanercept. In the long-term treatment, risankizumab had the most favorable benefit-risk profile.³⁴

Special populations

Pregnancy: the only FDA-approved mAbs for use in pregnant patients is certolizumab pegol. It is a PEGylated Fab mAb directed against TNF- α that does not cross the placental membrane.^{12,19}

Pediatric: The mAbs authorized by the FDA for children over 4 years of age are etanercept and adalimumab, secukinumab from 6 years, and ustekinumab from 12 years old.^{18,19,42}

Atopic dermatitis

Atopic dermatitis (AD) is a chronic relapsing inflammatory skin disease that affects 2%–5% of adults and 20% of children.⁴³ The efficacy of targeted immune therapy in AD has been proven by multiple studies. A recent systematic review of 60 clinical trials conducted in 16,579 patients confirms the clinical efficacy of these targeted therapies in AD.⁴⁴

Eligibility criteria

Both children and adults can be considered for targeted immune therapy if they have severe disease, defined as; involvement of greater than 10% of the total BSA, Investigator Global Assessment (IGA) of at least 3, Eczema Area and Severity Index (EASI) ≥ 16 , Scoring Atopic Dermatitis (SCORAD) ≥ 50 , and Peak Pruritus Numerical Rating Scale (PP-NRS) severity score ≥ 4 , or when it causes intractable pruritus or it has serious emotional consequences.^{45,46}

Therapy

Multiple targeted therapies are available for AD that must be selected according to different clinical criteria in each patient (Table 2). Dupilumab has demonstrated similar efficacy to higher-dose cyclosporine in patients older than 6 months with a more reliable response and superiority to methotrexate and azathioprine with considerably fewer side effects.⁴⁴ This has made targeted immune therapy very promising for AD, but the comparison of efficacy and safety between targeted therapies is difficult.^{44,47} Four systemic drugs have been approved by the FDA (dupilumab,⁴⁸ tralokinumab,⁴⁹ abrocitinib,⁵⁰ upadacitinib⁵¹) and other drugs are used off-label or in clinical trials.

Compared with dupilumab, abrocitinib, 200 mg daily, and upadacitinib, 30 mg daily, were associated with higher

Table 1 Targeted immune therapies for psoriasis.

Drug	Mechanism of action	Dosage and via of administration	Indication	Efficacy	FDA	Level of evidence	Grade of recommendation
IL-23 Risankizumab	Anti-IL-23	Induction dose: 150 mg weeks 0 and 4/SC Maintenance dose: 150 mg every 12 weeks/SC	Moderate to severe plaque psoriasis (>10% PASI, BSA or DLQI)	74% PASI 90 week 12 ^{25,26}	Yes	I	A
Guselkumab	Anti-IL-23	Induction dose: 100 mg weeks 0 and 4/SC Maintenance dose: 100 mg every 8 weeks/SC	Moderate to severe plaque psoriasis (>10% PASI, BSA or DLQI)	68% PASI 90 week 12 ^{25,26}	Yes	I	A
Tildrakizumab	Anti-IL-23	Induction dose: 100 mg weeks 0 and 4/SC Maintenance dose: 100 mg every 12 weeks/SC	Moderate to severe plaque psoriasis (>10% PASI, BSA or DLQI)	39% PASI 90 week 12 ^{25,26}	Yes	I	A
IL-17 Brodalumab	Anti-IL-17	Induction dose: 210 mg weeks 0, 1 and 2/SC Maintenance dose: 210 mg every 2 weeks/SC	Moderate to severe plaque psoriasis (>10% PASI, BSA or DLQI)	73% PASI 90 week 12 ^{25,26}	Yes	I	A
Ixekizumab	Anti-IL-17	Induction dose: 160 mg week 0 SC, 80 mg weeks 2, 4, 6, 8, 10, 12/SC Maintenance dose: 80 mg every 4 weeks/SC	Moderate to severe plaque psoriasis (>10% PASI, BSA or DLQI)	72% PASI 90 week 12 ^{25,26}	Yes	I	A
Secukinumab	Anti-IL-17	Induction dose: 300 mg weeks 0,1,2,3 and 4/SC Maintenance dose: 300 mg every month/SC	Moderate to severe plaque psoriasis (>10% PASI, BSA or DLQI)	60% PASI 90 week 12 ^{25,26}	Yes	I	A
IL-12/23 Ustekinumab	Anti-IL-12/23	Induction dose: <100 kg: 45 mg weeks 0 and 4/SC; >100 kg: 90 mg weeks 0 and 4/SC Maintenance dose: <100 kg: 45 mg weeks every 12-weeks/SC; >100 kg: 90 mg every 12-weeks/SC	Moderate to severe plaque psoriasis (>10% PASI, BSA or DLQI)	Adults: 42% PASI 90 week 12 ^{25,26}	Yes	I	A
TNF- α Infliximab	Anti-TNF- α	Induction dose: 5 mg/kg weeks 0, 2 and 6/IV Maintenance dose: 5 mg/kg every 8 weeks/IV	Moderate to severe plaque psoriasis (>10% PASI, BSA or DLQI)	53% PASI 90 week 12 ^{25,26}	Yes	I	A

Table 1 (Continued)

Drug	Mechanism of action	Dosage and via of administration	Indication	Efficacy	FDA	Level of evidence	Grade of recommendation
Adalimumab	Anti-TNF- α	Induction dose: 80 mg week 0, 40 mg week 1/SC Maintenance dose: 40 mg every 2 weeks/SC	Moderate to severe plaque psoriasis (>10% PASI, BSA or DLQI)	41% PASI 90 week 12 ^{25,26}	Yes	I	A
Certolizumab	Anti-TNF- α	Induction dose: 400 mg weeks 0, 2 and 4/SC Maintenance dose: <90 kg: 200 mg every 2-weeks/SC; >90 kg: 400 mg every 2-weeks/SC	Moderate to severe plaque psoriasis (>10% PASI, BSA or DLQI)	40% PASI 90 week 12 ^{25,26}	Yes	I	A
Golimumab	Anti-TNF- α	Induction dose: 200 mg week 0, 100 mg week 2 Maintenance dose: 50 mg mg every 4 weeks/SC	Moderate to severe plaque psoriasis (>10% PASI, BSA or DLQI)	40% PASI 75 in week 14 ²⁵	No	I	A
Etanercept	Anti-TNF- α	Induction dose: 50 mg twice a week/SC for 12 weeks Maintenance dose: 50 mg once weekly/SC	Moderate to severe plaque psoriasis (>10% PASI, BSA or DLQI)	Adults: 23% PASI 90 week 12 ^{25,26}	Yes	I	A
JAK-2i Deucravacitinib	JAK-2 inh	6 mg once daily/VO	Moderate to severe plaque psoriasis (>10% PASI, BSA or DLQI)	58% PASI 75 week 16 ^{25,30-32}	Yes	I	A

SC, Subcutaneous; VO, Orally; IV, Intravenous; yo, years old; PASI, Psoriasis Area and Severity Index; BSA, Body Surface Area; DLQI, Dermatology Life Quality Index.

Table 2 Targeted immune therapies for atopic dermatitis.

Drug	Mechanism of action	Dosage and via of administration	Indication	Efficacy	FDA	Level of evidence	Grade of recommendation
Upadacitinib	JAK 1	15–30 mg once daily/VO	Severe AD (BSA $\geq$ 10%, IGA $\geq$ 3, EASI $\geq$ 16, SCORAD $\geq$ 50, PP-NRS $\geq$ 4) refractory to other treatments	71% EASI 75 week 16 (30 mg) ⁴³	Yes	I	A
Abrocitinib	JAK 1	100–200 mg once daily/VO	Severe AD (BSA $\geq$ 10%, IGA $\geq$ 3, EASI $\geq$ 16, SCORAD $\geq$ 50, PP-NRS $\geq$ 4) refractory to other treatments	70% EASI 75 week 16 (200 mg) ⁵⁰	Yes	I	A
Dupilumab	Anti-IL-4/13	Induction dose: 600 mg single dose/SC Maintenance dose: 300 mg every 2 weeks/SC	Severe AD (BSA $\geq$ 10%, IGA $\geq$ 3, EASI $\geq$ 16, SCORAD $\geq$ 50, PP-NRS $\geq$ 4) refractory to other treatments	64% EASI 75 week 16 ⁵¹	Yes	I	A
Lebrikizumab	Anti-IL-13	Induction dose: 500 mg week 0 and 2/SC Maintenance dose: 250 mg every 2 weeks/SC	Severe AD (BSA $\geq$ 10%, IGA $\geq$ 3, EASI $\geq$ 16, SCORAD $\geq$ 50, PP-NRS $\geq$ 4) refractory to other treatments	58,8% EASI 75 at week 16 ⁵⁵	No	I	A
Baricitinib	JAK 1/2	4 mg once daily/VO	Severe AD (BSA $\geq$ 10%, IGA $\geq$ 3, EASI $\geq$ 16, SCORAD $\geq$ 50, PP-NRS $\geq$ 4) refractory to other treatments	54% EASI 75 at week 16 ⁶⁰	No	I	A
Tralokinumab	Anti-IL-13	Induction dose: 600 mg single dose/SC Maintenance dose: 300 mg every 2 weeks/SC	Severe AD (BSA $\geq$ 10%, IGA $\geq$ 3, EASI $\geq$ 16, SCORAD $\geq$ 50, PP-NRS $\geq$ 4) refractory to other treatments	25% EASI 75 week 16 ⁴⁸	Yes	I	A
Etokimab	Anti-IL-33	300 mg Week 0, 150 mg weeks 4, 8 and 12/IV	Severe AD (BSA $\geq$ 10%, IGA $\geq$ 3, EASI $\geq$ 16, SCORAD $\geq$ 50, PP-NRS $\geq$ 4) refractory to other treatments	33% EASI 75 at week 4 ⁶⁵	No	II	B
Fezakinumab	Anti-IL-22	Induction dose: 600 mg single dose/SC Maintenance dose: 300 mg every 2 weeks for 10 weeks/SC	Severe AD (BSA $\geq$ 10%, IGA $\geq$ 3, EASI $\geq$ 16, SCORAD $\geq$ 50, PP-NRS $\geq$ 4) refractory to other treatments	SCORAD decline of 14 points at week 12 ⁶³	No	II	B
Nemolizumab	Anti-IL-31	30 mg every 4 weeks/SC	Severe AD (BSA $\geq$ 10%, IGA $\geq$ 3, EASI $\geq$ 16, SCORAD $\geq$ 50, PP-NRS $\geq$ 4) refractory to other treatments	69% EASI improvement week 12 (30 mg) ⁶⁴	No	II	B
Tezepelumab	Anti-TSLP	280 mg every 2 weeks for 3 months/SC	Severe AD (BSA $\geq$ 10%, IGA $\geq$ 3, EASI $\geq$ 16, SCORAD $\geq$ 50, PP-NRS $\geq$ 4) refractory to other treatments	65% EASI 50 week 12 ⁶²	No	II	B
Topicals Tofacitinib	JAK 1/3	2% topical, once daily	IGA 2–3, BSA 2–20%	82% EASI improvement at week 4 ⁶⁷	No	II	B
Ruxolitinib	JAK 1/2	1,5% topical twice daily	IGA 2–3, BSA 2%–20%	71% EASI improvement at week 4 ⁶⁶	Yes	I	A

SC, Subcutaneous; VO, Orally; IV, Intravenous; EASI, Eczema Area and Severity Index; BSA, Body Surface Area; IGA, Investigator Global Assessment; SCORAD, SCORing Atopic Dermatitis, PP-NRS, Peak Pruritus Numerical Rating Scale; AD, Atopic Dermatitis.

reductions in EASI scores meanwhile baricitinib and tralokinumab, reductions in EASI scores were similar or slightly worse than dupilumab.⁴⁴

Dupilumab is an anti-IL-4/13 mAb approved by the FDA in 2017 for the treatment of moderate to severe AD from 6 months.⁵² The therapeutic effect of dupilumab is primarily mediated through its inhibition of the alpha subunit of the Interleukin-4 Receptor (IL-4R α).^{53,54}

Tralokinumab is an anti-IL-13 mAb approved by the FDA in 2021 for the treatment of moderate-to-severe AD in adults. In 2 RCTs, tralokinumab 300mg every 2 weeks achieved an EASI 75 in 25%–33.2% of patients at 16 weeks of treatment. These RCTs also showed early improvements in pruritus, sleep interference, and DLQI. Patients maintained these responses after 52 weeks of treatment with tralokinumab without any rescue medication.^{49,55} Lebrikizumab, a mAb that targets IL-13 in two randomized, double-blind, placebo-controlled, phase 3 trials in >12-years old patients with moderate to severe AD showed an EASI-75 response in 58.8% and 52.1% of patients respectively at week 16.⁵⁶

Abrocitinib is a JAK-1 inhibitor approved by the FDA for the treatment of AD in adults in 2022. In moderate to severe AD, abrocitinib showed consistent responses to treatment and presented no new safety concerns compared with dupilumab.^{46,57–59} It is used at a dose of 200 mg daily, achieving 70% of EASI 75 at week 12 of treatment.⁵⁸

Upadacitinib is a JAK-1 inhibitor approved by the FDA (2022) for the treatment of AD in patients >12 years old. It shows an improvement in EASI 75 of 71% at week 16 with a dose of 30 mg per day orally.⁶⁰

Recently baricitinib, a first-generation inhibitor of JAK 1–2 not yet approved by FDA in AD, has completed phase 2 and 3 RCTs in combination with topical corticosteroids in adults with moderate-to-severe AD. At 16 weeks baricitinib 4mg provided 54.9% and 59.4% improvement in EASI score in BREEZE-AD1 and BREEZE-AD2 respectively.⁶¹

Tezepelumab is a human mAb that binds thymic stromal lymphopoietin (TSLP, an epithelial cell-derived cytokine that induces the production of Th2 cytokines, including IL-4, IL-5, and IL-13)⁶² used for the treatment of asthma. It has been tested at doses of 280mg every 2 weeks in phase 2 studies, achieving an EASI 50 in 65% of patients at week 12 of treatment.⁶³ Fezakinumab, a human mAb against IL-22 is in phase 2 studies, induction doses of 600mg followed by 300mg every 2 weeks have demonstrated an improvement in IGA score from 12 weeks of use.⁶⁴ Nemolizumab is an experimental anti-IL-31RA mAb in phase 2 studies. It was reported that 42% of patients treated showed an improvement in the EASI score at 12 weeks of use.⁶⁵ Etokimab is another experimental mAb that binds IL-33 in the initial phase of development. At the moment, studies have tested doses of 300mg IV once, achieving EASI 50 in 100% of the participants at 140 days.⁶⁶

New topical targeted immune therapy for AD has recently appeared as a therapeutic tool. Ruxolitinib 1.5% cream (approved by FDA in 2021) for patients >12 years old shows improvements of 71.6% in EASI score after 4 weeks of use.⁶⁷ Tofacitinib 2% cream had shown improvements of 82% on EASI score after 4 weeks of use and is awaiting FDA approval.^{68,69}

The safety profile of targeted immune therapy for AD

The most common adverse events were upper respiratory tract infections and injection site reactions for all classes.^{44,45} General considerations should be taken in relation to the reactivation of tuberculosis, and hepatitis B, and in the case of JAKis also consider infections by viruses of the Herpes family.^{58,60} Another common adverse effect in all classes was eye symptoms (conjunctivitis, keratitis, blepharitis, ocular pruritus, dryness and discomfort in the eye). Dupilumab and tralokinumab do not require laboratory monitoring but abrocitinib, baricitinib, and upadacitinib need laboratory follow-up. It can produce creatine phosphokinase elevation, thrombocytopenia, and neutropenia.⁴⁵ Other adverse effects reported for JAKis are nausea, headache, diarrhea, fatigue, acne, abdominal pain, and myalgias.⁷⁰

Recently it has been observed an increased risk of seronegative inflammatory arthritis and psoriasis in patients using dupilumab.⁷¹ Based on current evidence, it appears that the use of anti-TNF- α for psoriasis and anti-IL-4/13 for atopic dermatitis are inversely related. The dual blockade with dupilumab is associated with psoriasiform diseases, while biologics for psoriasis can cause a phenotypic switch to eczema.⁷²

For topicals, mild local irritation was the most common adverse effect.^{67,68}

There are insufficient data to determine whether any targeted immune therapy is safer than another for AD. Abrocitinib, 100 mg daily, was associated with 2.6 times the odds of serious adverse events compared with dupilumab, but with a higher dose (i.e., abrocitinib, 200 mg daily) the odds were lower (1.4).⁴⁴

Lower rates of serious adverse events were observed for dupilumab compared with placebo.⁴⁴ Dupilumab is also associated with a non-significant increase in Herpes infection. The reason for a decrease in cutaneous infections, including eczema herpeticum is unknown, but improvement in the skin barrier and microbiome caused by targeted immune therapy may explain this observation.⁷³

Hidradenitis suppurativa

Hidradenitis Suppurativa (HS) is an autoinflammatory disease of the pilosebaceous follicle with a prevalence ranging from 0.05% to 4.1%.⁷⁴ There are at least 9 clinical guidelines that consider the use of biologics in the management of HS.^{75–83}

Eligibility criteria

Management with targeted immune therapy should be considered early in severe cases. International guidelines recommend starting a targeted treatment for recalcitrant moderate-to-severe HS, defined as Hurley stage II–III, or total abscess and inflammatory-nodule count ≥ 3 at baseline and an inadequate response to oral antibiotic treatment for at least 90 days.

Therapy

There are a few targeted therapies for HS that must be selected according to different clinical criteria in each patient (Table 3). Adalimumab⁸⁴ is the only biologic treatment approved by the FDA for HS (2015) and it is

Table 3 Targeted immune therapies for hidradenitis suppurativa.

Drug	Mechanism of action	Dosage and via of administration	Indication	Efficacy	FDA	Level of evidence	Grade of recommendation
Adalimumab	Anti-TNF- α	Induction dose: 160 mg day 0, 80 mg day 15/SC Maintenance dose: 40 mg every week/SC or 80 mg every two weeks/SC	Recalcitrant moderate-to-severe HS (Hurley stage II–III)	42%–59% HiSCR improvement in 50% of patients at week 12 ⁸³	Yes	I	A
Anakinra	Anti-IL-1	100 mg once daily/SC for 12 weeks	Recalcitrant moderate-to-severe HS (Hurley stage II–III)	78% of patients showed an HiSCR improvement at week 12 ⁸⁶	No	II	B
Bermekimab	Anti-IL-1	400 mg every week/SC for 12 weeks	Recalcitrant moderate-to-severe HS (Hurley stage II–III)	60% of patients showed an HiSCR improvement at week 12 ⁸⁷	No	II	B
Infliximab	Anti-TNF- α	Induction dose: 5 mg/kg weeks 0, 2 and 6/IV Maintenance dose: 5 mg/kg every 8 weeks/IV	Recalcitrant moderate-to-severe HS (Hurley stage II–III)	25%–50% HSSI improvement at week 8 ⁸⁴	No	II	B

SC, Subcutaneous; IV, Intravenous; HiSCR, Hidradenitis Suppurativa Clinical Response; HSSI, Hidradenitis Suppurativa Severity Index.

recommended as the first-line biologic drug in all guidelines, making infliximab the second option.⁷⁴ Anakinra and bermekimab may be considered following failure of anti-TNF- α agents but evidence to support their efficacy in HS is limited.⁷⁴

Adalimumab showed a 41.8%–58.9% improvement in Hidradenitis Suppurativa Clinical Response (HiSCR) in 50% of patients at 12 weeks.⁸⁴ Infliximab demonstrated a 25%–50% improvement in Hidradenitis Suppurativa Severity Index (HSSI) in 60% of patients at 8 weeks.⁸⁵ Other anti-TNFs are not used to treat HS such as etanercept or golimumab since paradoxical reactions of worsening or inducing the disease.^{74,86}

Anti-IL-1 drugs have proven their efficacy in small placebo-controlled-RCT.^{87,88} Anakinra showed a >50% of improvement in Disease Activity Score (DAS) in 78% of patients at 12 weeks of treatment.⁸⁷ Bermekimab showed a 60% of improvement in HiSCR at 12 weeks of treatment.⁸⁸ These drugs should be considered when patients are not candidates for anti-TNF- α therapy.

Clinical guidelines also mention other biologics that have been used in case series successfully for the treatment of HS (guselkumab, risankizumab, secukinumab, bimekizumab, and upadacitinib), but the results in patients who have been treated with these drugs are based mainly on isolated case reports, which is not sufficient to recommend their use in the clinical setting.⁸⁶

The safety profile of targeted immune therapy for HS

The safety profile of anti-TNF- α drugs has been discussed in a previous section (see Psoriasis). For anti-IL-1 drugs, the general considerations are similar between them. The

most common adverse effects are injection site reactions and upper respiratory tract infections. Other adverse effects reported are headache, abdominal pain, diarrhea, and flu-like symptoms.⁸⁹

Pyoderma gangrenosum

Pyoderma Gangrenosum (PG) is a neutrophilic dermatosis characterized by chronic and recurrent skin ulcers with a necrolytic border with an estimated incidence of 3–10/1,000,000 cases yearly.⁹⁰ There are currently no FDA-approved drugs for this disease. New targeted immune therapies have been used with some success lately to treat refractory cases of PG, but clinical trials are needed to establish the real efficacy of these therapies.^{91–93}

Eligibility criteria

We suggest considering targeted immune therapy in PG after a thorough study to establish the diagnosis of this condition.⁹⁴ The disease must be recalcitrant or with moderate-severe intensity (BSA > 10%, complex anatomical sites, or excruciating pain).

Therapy

There are a few targeted therapies for PG that must be selected according to different clinical criteria for each patient (Table 4). The drug with more data for PG treatment is infliximab.⁹⁴ Infliximab demonstrated improvement of lesions at week 4 (20/29 patients), with complete remission in 21% at week 6.⁹⁴ Infliximab has also been used successfully in combination with other drugs (oral systemic

Table 4 Targeted immune therapies for pyoderma gangrenosum.

Drug	Mechanism of action	Dosage and via of administration	Indication	Efficacy	FDA	Level of evidence	Grade of recommendation
Infliximab	Anti-TNF- α	Induction dose: 5 mg/kg weeks 0, 2 and 6/IV Maintenance dose: 5 mg/kg every 8 weeks/IV	Recalcitrant and late stage with moderate-severe disease	68% complete response, 19% partial response ⁹¹	No	I	B
Etanercept	Anti-TNF- α	25–50 mg every week/SC	Recalcitrant and late stage with moderate-severe disease (under research context)	68% complete response, 30% partial response ⁹⁴	No	III	C
Adalimumab	Anti-TNF- α	Induction dose: 80 mg week 0/SC Maintenance dose: 40 mg every week/SC	Recalcitrant and late stage with moderate-severe disease (under research context)	77% complete response, 14% partial response ⁹⁴	No	III	C
Anakinra	Anti-IL-1	100 mg once daily/SC	Recalcitrant and late stage with moderate-severe disease (under research context)	38% complete response, 21% partial response ⁹⁰	No	III	C
Canakinumab	Anti-IL-1 β	150–300 mg every 4–8 weeks/SC	Recalcitrant and late stage with moderate-severe disease (under research context)	55% complete response, 9% partial response ⁹⁵	No	III	C
Ustekinumab	Anti-IL-12/23	Induction dose: 90 mg week 0/SC Maintenance dose: 45 mg weeks 4 and 8/SC	Recalcitrant and late stage with moderate-severe disease (under research context)	71% complete response, 8% partial response ⁹⁶	No	III	C
Ruxolitinib	JAK 1/2	10 mg twice daily/VO	Recalcitrant and late stage with moderate-severe disease (under research context)	2/2 complete response after 1–15 months ⁹⁰	No	III	C

SC, Subcutaneous; VO, Orally.

corticosteroids, azathioprine, mycophenolate mofetil and cyclosporine).^{92,93,95}

There are case reports of PG treated with adalimumab and etanercept.⁹⁵ Based on these observational data, no significant differences in the partial or complete response rates to infliximab, adalimumab, and etanercept were found. In a semi-systematic review for TNF- α inhibitors, an 87% partial response rate and a 67% complete response were found.⁹⁵ Corticosteroids and cyclosporine can achieve 90% of partial response rates and only 47% complete response rates after 6 months.⁹⁵

Anti-IL-1 drugs have also been used to treat PG.⁹¹ There are 29 cases reported in the literature of the use of anakinra in patients with comorbidities such as rheumatoid arthritis, psoriasis, PASH and PAPA syndrome at a dose of 100 mg per day.^{91,92} In an uncontrolled trial canakinumab was used in five steroid-refractory PG patients. Four showed a decrease in target-lesion size and three achieved complete remission.⁹⁶

Other targeted immune therapies used successfully are ustekinumab (anti-IL-12/23)⁹⁷ and ruxolitinib (anti-JAK1-2).^{91,92}

The safety profile of targeted immune therapy for PG

There are reported cases of paradoxical induction of PG with the use of adalimumab, etanercept and to a lesser extent with infliximab.⁹⁰

Specific adverse reactions for canakinumab are worsening of rheumatoid arthritis, pyrexia, vomiting, sinusitis, and arthralgia and for anakinra weight gain, musculoskeletal pain and vertigo.⁹⁶

Chronic spontaneous urticaria

Chronic Spontaneous Urticaria (CSU) is defined by the appearance of transient pruritic wheals and/or angioedema for at least 6-weeks without a recognizable trigger.⁹⁸ The

global prevalence of CSU is 1.1% according to the Global Burden of Disease.⁹⁹

Eligibility criteria

Adults and adolescents 12 years of age and older can be considered for targeted immune therapy if they remain symptomatic despite H1 antihistamine treatment up to 4 times of standard dose, or if they persist symptomatic with combination therapy (H1 antihistamines 4-times the standard dose plus H2-antihistamines and/or leukotriene receptor antagonist).^{98,100}

Therapy

There is only one targeted immune therapy currently approved for CSU, and other options must be selected in refractory cases or research contexts (Table 5). Omalizumab, an anti-IgE mAb, was approved by the FDA in 2014 for use in patients >12 years old for CSU. This authorization was based on two RCTs (ASTERIA I and ASTERIA II).¹⁰¹ RCTs showed that at 40 weeks, 75.3% of CSU patients achieved complete response and 14.6% had partial response.¹⁰²

Ligelizumab an anti-IgE mAb is still under study but recent clinical trials for CSU treatment are showing an efficacy similar to omalizumab.^{103,104}

Lirentelimab is an anti-Sialic acid-binding Immunoglobulin-Like Lectin 8 mAb (anti-SIGLEC-8, an inhibitory receptor presents on eosinophils and mast cells). Ligation to Siglec-8 induces eosinophils death, inhibits mast cells IgE-mediated degranulation and *de novo* synthesis of prostaglandin D2. Results of a phase 2 trial with lirentelimab for the treatment of CSU and for the treatment of inducible urticaria demonstrated a 92% complete response at week 22 and only 36% complete response in patients previously refractory to omalizumab treatment.¹⁰⁵

Dupilumab has demonstrated partial response in case reports.¹⁰⁶ Benralizumab and mepolizumab, both experimental anti-IL-5R and anti-IL-5 respectively molecules, have also been used.¹⁰⁷ In both cases treated patients had clinical improvement.¹⁰⁸ Secukinumab has been used in case reports for the treatment of CSU in refractory patients to H1-antihistaminics and omalizumab treatment, showing a significant reduction in disease activity from baseline.¹⁰⁹

The safety of targeted immune therapy for CSU

The most common but manageable side effects of omalizumab are headache, upper abdominal pain, pyrexia, and local reaction at the injection site. More serious side effects such as anaphylactic reaction, syncope and angioedema have been reported with a frequency of less than 1/1000.⁹⁸

For lirentelimab the most common adverse events included infusion-related reactions, nasopharyngitis, and headache. No treatment-related serious adverse events occurred.¹⁰⁵

Alopecia areata

Alopecia Areata (AA) is an autoimmune disease due to the loss of the immune privilege of the hair follicle. Recently FDA approved baricitinib for AA treatment (2022) and many others JAKis are under advanced study for approval.

Eligibility criteria

Patients should be considered for JAKis treatment if they have moderate or severe disease ($\geq 30\%$ total scalp hair loss for at least 3–6 months as measured using Severity of Alopecia Tool (SALT) score) or refractory response to conventional treatment for the last 6 months. There is no limitation for previous duration of alopecia and trials have considered patients with a wide range of duration of AA as candidates for JAKis treatment.^{110,111}

Therapy

There is only one targeted immune therapy currently approved for AA, but other options have been used with success and must be selected according to different clinical criteria in each patient (Table 6). The FDA has approved baricitinib (2022) a JAK 1-2i for the treatment of AA in adults. Its efficacy was evaluated in two randomized, double-blind, placebo-controlled trials (BRAVE AA-1 and BRAVE AA-2).¹¹⁰ Patients in these studies received 2 or 4 mg of baricitinib per day. Final results at week 36 showed a 22% adequate response with 2 mg and 38% with 4 mg. Similar results were observed in BRAVE AA-2 (19% adequate response with 2 mg and 35% with 4 mg).¹¹⁰ Tofacitinib, a JAK 1-3i has been used to treat moderate to severe cases of AA with >50% of scalp hair loss in adults, achieving complete response in 20% of treated patients and 77% of partial response at 4–18-months of treatment.¹¹² In 2023 the FDA approved Ritlecitinib for the treatment of AA in people over 12 years of age based on the results of ALLEGRO, where 23% of patients achieved hair recovery of at least 80% after 6 months of treatment.¹¹³ Ruxolitinib is the last JAKi used for the treatment of AA achieving overall responses in 93% of patients and complete response in 21% of patients treated at 6 months of follow-up.¹¹¹

The safety profile of targeted immune therapy for AA

The safety profile of JAK inhibitor drugs has extensively been studied and in general, all JAKis used for AA treatment are well tolerated. Upper respiratory tract infections, hypercholesterolemia, elevated creatine phosphokinase, headache, diarrhea, and nasopharyngitis are the most frequently reported adverse reactions. Less common side effects included other infections such as herpes zoster, herpes simplex, urinary tract infections, and gastroenteritis.^{110–112}

Bullous autoimmune diseases

Autoimmune bullous diseases are a group of diseases characterized by production of autoantibodies against adhesion molecules of the skin.¹¹⁴ In this review we will discuss targeted immune therapy for Pemphigus Vulgaris (PV), Pemphigus Foliaceus (PF) and Bullous Pemphigoid (BP).

Eligibility criteria

Patients are candidates for targeted immune therapy as a first-line option in cases of new-onset moderate to severe PV/PF or previously treated patients who do not achieve clinical remission with systemic corticosteroids or immunosuppressive adjuvants.¹¹⁴ The severity of the disease must be measured with the Pemphigus Disease and Area Index (PDAI)

Table 5 Targeted immune therapies for chronic spontaneous urticaria.

Drug	Mechanism of action	Dosage and via of administration	Indication	Efficacy	FDA	Level of evidence	Grade of recommendation
Omalizumab	Anti-IgE	150–300 mg every 4 weeks /SC If refractory, consider 600 mg every 4 weeks/SC	Patients remaining symptomatic despite anti-H1 4× dose	75.3% complete response at 40 weeks ¹⁰⁰	Yes	I	A
Ligelizumab	Anti-IgE	72–240 mg every 4 weeks/SC	Patients remaining symptomatic despite anti-H1 4× dose	44% complete response at week 12 ^{102,103}	No	I	B
Secukinumab	Anti-IL-17	Induction dose: 150 mg weeks 0, 1, 2 and 3/SC Maintenance: 150 mg every two weeks/SC	Refractory to omalizumab (under reseach context)	Reduction in UAS7 of 82% at week 12 ¹⁰⁸	No	III	C
Dupilumab	Anti-IL-4/13	Induction dose: 600 mg week 0/SC Maintenance dose: 300 mg every 2 weeks/SC	Refractory to omalizumab (under reseach context)	Improvement in a case series of 6 patients ¹⁰⁵	No	III	C
Lirentelimab	Anti-SIGLEC-8	Initial dose: 0.3 mg/kg on day 0 Subsequent doses: 1 mg/kg on days 29, 57, 85, 113 and 141/IV	Patients remaining symptomatic despite anti-H1 4× dose (under reseach context)	92% of complete response at 22 weeks ¹⁰⁴	No	I	B
Benralizumab	Anti-IL-5	Induction dose: 30 mg every 4 weeks for 3 doses/SC Maintenance dose: 30 mg every 8 weeks/SC	Ongoing phase 2 studies in CSU refractory to antiH1	56% of complete response at 20 weeks ¹⁰⁶	No	II	B
Mepolizumab	Anti-IL-5	100–300 mg every 4 weeks/SC	Ongoing phase 2 studies in CSU refractory to antiH1	Ongoing phase 2 studies ¹⁰⁶	No	III	C

SC, Subcutaneous; IV, Intravenous; UAS7, Urticaria Activity Score summed over 7-days.

score. Multiple mucosal involvement (oral, nasopharyngeal, conjunctival, genital) or a PDAI ≥ 15 are considered moderate disease. Patients with PDAI score ≥ 45 or oral lesions, dysphagia and weight loss belong to a severe state of the disease.^{115,116}

Therapy

Rituximab is the only biologic approved by the FDA (2018) for bullous diseases and is considered the first therapeutic option for PV and PF by international guidelines.¹¹⁶ This approval was based on the results of Rituxi3,¹¹⁵ in which 89% of pemphigus patients treated with rituximab and oral prednisolone were disease-free and without requirement of any further treatment after 24 months, compared to 34% with prednisolone alone. Rituximab treatment also reduced the dose of corticosteroids required for clinical remission, reducing the side effects associated with high-dose steroids¹¹⁷ (Table 7).

Efgartigimod is a human IgG1 antibody targeting the neonatal Fc receptor. The blockade of the neonatal Fc receptor diminishes the availability of pathogenic IgG antibodies and it has been tested for the treatment of PF and PV.¹¹⁸ In a phase 2 trial, single use of efgartigimod demonstrated early disease control in 90% of patients after 17 days. Combined with prednisone led to complete clinical remission in 64% of patients after 6 months.¹¹⁹ Two phase 3 clinical trials evaluating the efficacy and safety of efgartigimod in adults with pemphigus (NCT04598451 and NCT04598477) are underway.¹¹⁷

B-cell Activating Factor (BAFF), also known as B-lymphocyte Stimulator (BLyS) is an important B-cell activator.¹²⁰ Ianalumab is an experimental mAb that binds to BLyS. A phase 2 clinical trial was conducted to determine the doses, benefits, and safety of ianalumab in patients with PV, showing a 73% decrease in mean PDAI score at week 12 in seven patients with pemphigus compared with placebo-treated controls.¹²¹

Table 6 Targeted immune therapies for alopecia areata.

Drug	Mechanism of action	Dosage and via of administration	Indication	Efficacy	FDA	Level of evidence	Grade of recommendation
Baricitinib	JAK 1/2	4 mg once daily/VO	Moderate to severe AA 30% scalp hair loss	35%–38% adequate hair restorage at week 36 ¹⁰⁹	Yes	I	A
Tofacitinib	JAK 1/3	5 mg twice daily/VO	Moderate to severe AA 30% scalp hair loss	20% complete response and 58% adequate hair restorage during 4–18 months of treatment ¹¹¹	No	II	B
Ritlecitinib	JAK 3	50 mg once daily/VO	Moderate to severe AA 30% scalp hair loss	23% of patients have >80% of hair restorage at 6-months ¹¹²	Yes	I	A
Ruxolitinib	JAK 1/2	20 mg twice daily/VO	Moderate to severe AA 30% scalp hair loss	21% complete response and 64% adequate hair restorage during 6-months of treatment ¹¹⁰	No	II	B

VO, Orally.

Treatment with rituximab, omalizumab and dupilumab is reported in patients with bullous pemphigoid. Cao et al.¹²² conducted a systematic review to evaluate the use of these 3 biologics in patients with BP who had been refractory to the use of other systemic therapies such as systemic corticosteroids, methotrexate, mycophenolate mofetil, azathioprine, cyclosporine and cyclophosphamide. They found that rituximab led to complete remission in 70.5% and partial remission in 23.8% of patients within 6 months of follow-up with a recurrence rate of 20.5%.¹²² Omalizumab led to complete remission in 67.9% and partial remission in 20.8% of patients within 6 months, with a recurrence rate of 5.7%.¹²² Dupilumab led to complete remission in 66.7% and partial remission in 19.4% of patients within 4.5 months of treatment, with a recurrence rate of 5.6%.^{123,124}

The safety profile of targeted immune therapy for bullous diseases

Although rituximab is an excellent drug for severe PV or PF, it is also associated with well-known severe adverse events. The most well-documented are infusion reactions, infections, cardiac disorders, and cases of fatal progressive multifocal leukoencephalopathy.¹¹⁴ Most of these adverse effects can clinically be controlled if they are recognized early stage.

A recent study showed that treatment with rituximab was associated with a lower risk of developing cardiovascular and metabolic comorbidities, so it might be particularly preferred in individuals with cardiovascular and metabolic risk factors, for whom corticosteroid-related adverse events must be strictly avoided.¹²⁵

Other dermatological diseases

We have considered in this section diseases with scant evidence (small trials or case series, indirect evidence from other diseases or ongoing trials without results) or with topical but no systemic therapy available (Table 8).

Stevens-Johnson Syndrome/Toxic Epidermal Necrolysis

Stevens-Johnson Syndrome/Toxic Epidermal Necrolysis (SJS/TEN) is a rare serious mucocutaneous disease caused by exposure to certain drugs, the most frequent being sulfonamides, anticonvulsants, non-steroidal anti-inflammatory drugs, allopurinol, and penicillins.¹²⁶ Due to its low incidence the reported use of biologics in this disease has been limited mostly to case series and only two trials.^{126–128} With current data the efficacy and safety of biologic monotherapy and combination therapy cannot be conclusively determined, and the final role of these drugs is still under research.

The largest number of cases reported are related with etanercept. The most used therapeutic regime is 25 mg (in children weighing <65 kg) and 50 mg (adults or children >65 kg) on days 0 and 3. Etanercept monotherapy achieved re-epithelialization in 13 days and a mortality rate of 7.6%, while patients treated with etanercept in combination with corticosteroids achieved re-epithelialization in 11.1 days and had a mortality rate of 7.7%.¹²⁶ Wang et al.¹²⁷ conducted a RCT in which 96 patients with SJS/TEN were enrolled to compare the effects of etanercept to traditional corticosteroids. The study demonstrated that etanercept decreased the TEN-specific severity of illness score (SCORTEN)-based predicted mortality in about 9.4% compared to traditional corticosteroids.¹²⁷ Infliximab was generally used in a dose of 5 mg/kg once.¹²⁶ In case reports of patients treated

Table 7 Targeted immune therapies for bullous diseases.

Drug	Mechanism of action	Dosage and via of administration	Indication	Efficacy	FDA	Level of evidence	Grade of recommendation
PV and PF Rituximab	Anti-CD20	1g on two occasions 2 weeks apart /IV	Steroid refractory PV and PF	Combined with prednisone 89% complete response at 24 months ¹¹⁴	Yes	I	A
Efgartigimod	Anti-neonatal receptor for Fc (FcRn)	10–25 mg weekly for 4 weeks/IV	Steroid refractory PV and PF	Combined with prednisone complete response in 64% patients at 2–41 weeks ¹¹⁸	No	II	B
Ianalumab	Anti-BLyS	3 mg/Kg IV	Steroid refractory PV and PF (under research context)	73% decrease in mean PDAI score at week 12 ¹²⁰	No	I	B
BP Rituximab	Anti-CD20	375 mg/m ² every 1–4 weeks to 500 mg weekly for 2 weeks/IV	Steroid refractory BP	70.5% complete response at 6 months ¹²¹	No	III	C
Omalizumab	Anti-IgE	100–525 mg every 1–4 weeks/SC	Steroid refractory BP	68% complete response at 6-months ¹²¹	No	III	C
Dupilumab	Anti-IL-4/13	Induction dose: 600 mg/SC single dose Maintenance dose: 300 mg every 2 weeks/SC	Steroid refractory BP	66.7% complete response at 4.5-months ¹²¹	No	III	C

SC, Subcutaneous; IV, Intravenous; PDAI, Pemphigus Disease and Area Index.

with infliximab monotherapy the average number of days to reepithelization was 10.4 and there were no cases of mortality reported.¹²⁶ In case reports of TEN treated with the combination infliximab/systemic corticosteroids the average number of days to reepithelization was 14.2 and the average mortality rate was 22.2%. A recent Cochrane review showed that etanercept 25 mg (50 mg if >65 kg) twice weekly until skin lesions healed may reduce disease-specific mortality compared to corticosteroids (RR = 0.51, 95% CI 0.16 to 1.63) however, the CIs were consistent with possible benefit and possible harm.¹²⁹

Regarding the use of targeted immune therapy used in SJS/TEN compared to corticosteroids, there was no statistical difference observed between the 2 treatment groups in the incidence of adverse events, however, there was a lower incidence of GI hemorrhage reported with biologics versus traditional corticosteroid.^{126,127,130}

DiHS/DRESS

Drug-induced Hypersensitivity Syndrome/Drug Reaction with eosinophilia and Systemic Symptoms (DiHS/DRESS) is a severe drug reaction with a 10% mortality.¹³¹ Successful cases have been published using targeted immune therapy. In a recent report studying two cases of DRESS associ-

ated with myocardial involvement, tofacitinib 5 mg/bid was used (during 3-years) sequentially associated with corticosteroids, cyclosporin, methotrexate or IVIg.¹³² The two cases demonstrated remission when tofacitinib was utilized.¹³²

A previous case report study of 10 patients with DRESS demonstrated a median healing time of 8.5 days after a 50-mg subcutaneous injection of etanercept.¹³¹ Finally there is a single case report of a patient treated successfully with mepolizumab.¹³³

Lichen planus

Adalimumab is the only targeted immune therapy recommended by international guidelines for the treatment of cutaneous and mucosal LP, in severe refractory cases.¹³⁴ Its use improves pruritus and accomplishes healing of skin lesions in a period of 6 months.¹³⁴ Another targeted immune therapy for LP is topical ruxolitinib that is in phase 2 studies to treat cutaneous LP.¹³⁵ It has been tested at 1.5% cream twice daily showing clinical and modified Composite Assessment of Index Lesion Severity (mCAILS) score improvement after 4 weeks of treatment.¹³⁵ The use of tofacitinib has been reported in case series at doses of 5 mg (bid) in follow-up periods ranging from 2 to 9 months to treat lichen planopilaris and hypertrophic LP showing

Table 8 Targeted immune therapies for other diseases.

Diagnostic	Drug	Mechanism of action	Dosage and via of administration	Indication	Efficacy	FDA	Level of evidence	Grade of recommendation
SSJ/TEN	Etanercept	Anti-TNF- α	<65 kg: 25 mg day 0 and 3/SC >65 kg: 50 mg day 0 and 3/SC	Consider use under research context	7.6% mortality ¹²⁶	No	III	C
	Infliximab	Anti-TNF- α	5 mg/kg single dose/IV	Consider use under research context	22% mortality ¹²⁷	No	III	C
Lichen planus	Adalimumab	Anti-TNF- α	Induction dose: 80 mg week 0/SC, 40 mg week 1/SC Maintenance dose: 40 mg every 2 weeks SC	2 nd line in mucosal LP, 3 rd line in cutaneous LP	Improvements in itching and healing of skin lesions over a period of 6 months ¹³³	No	III	C
	Ruxolitinib	JAK 1/2	Topical 1.5% twice daily	Cutaneous Lichen Planus	Decrease 7.6 points of mCAIS at 4 weeks ¹³⁴	No	II	B
	Tofacitinib	JAK 1/3	5 mg twice daily/VO	Lichen planopilaris and hypertrophic LP	46% improvement LPPAI at 12 weeks in lichen planopilaris ¹⁴⁵	No	III	C
Cutaneous Lupus Erythematosus	Anifrolumab	Anti-IFN- γ	300 mg/IV every 4 weeks	Cutaneous symptoms in the context of Systemic Lupus Erythematosus	49% of patients achieved reduction in CLASI score of $\geq 50\%$ ¹⁴⁰	Yes	I	A
Vitiligo	Ruxolitinib	JAK 1/2	1.5% topical twice daily	<10% BSA	75% VASI improvement in 30% of patients at week 24 ¹⁴¹	Yes	I	A
	Tofacitinib	JAK 1/3 inhibitor	2% topical twice daily	<10% BSA	70% VASI improvement at 4 months (sun-exposed areas) ¹⁴²	No	III	C
	Tofacitinib	JAK 1/3	5 mg twice daily/VO	>10% BSA	5.4% decrease in BSA in 50% patients ¹⁴³	No	II	B
Granuloma annulare	Tofacitinib	JAK 1/3	5 mg bid/VO	Steroid refractory	CR (only case reports) ¹⁴⁶	No	III	C
Sarcoidosis	Tofacitinib	JAK 1/3	5 mg twice daily/VO	Steroid refractory	Improvement in case series ¹⁴⁶	No	III	C
DiHS/DRESS	Tofacitinib	JAK 1/3	5 mg twice daily/VO	Steroid refractory	CR (only case reports) ^{131,132}	No	III	C
	Etanercept	Anti-TNF- α	50 mg single dose/SC	First line	CR (only case reports) ^{131,132}	No	III	C
Hypereosinophilic syndrome	Tofacitinib	JAK 1/3	5 mg twice daily/VO	Steroid refractory	CR (only case reports) ¹⁴⁷	No	III	C
	Ruxolitinib	JAK 1/2	25 mg AM-10 mg PM/VO	Steroid refractory	CR (only case reports) ¹³⁷	No	III	C
Morphea	Tofacitinib	JAK 1/3	10 mg twice daily/VO	Steroid refractory	Improvement in case report ¹⁴⁹	No	III	C

SC, Subcutaneous; VO, Orally; CR, Complete Response.

clinical and LPAAI score improvement.¹³⁶ The use of other JAKis such as upadacitinib or baricitinib is scarce. There are 13 patients reported in case series and case reports using baricitinib for lichen planopilaris, with 5 achieving partial resolution, 7 having no resolution, and only 1 achieving complete resolution. There are only 2 case reports with the use of upadacitinib for LP both of which achieved complete resolution.¹³⁷ Finally, phase 2 studies are currently being carried out with ixekizumab (cutaneous LP, Lichen planopilaris) and secukinumab (cutaneous LP, Lichen planopilaris and oral LP).¹³⁸

Cutaneous lupus erythematosus

The FDA approved anifrolumab for Systemic Cutaneous Lupus (SLE) in July 2021.¹³⁹ Anifrolumab is a fully humanized monoclonal antibody that selectively inhibits the IFN- α receptor 1.¹³⁹ In TULIP-2 RCT anifrolumab was tested for the treatment of SLE, among patients with at least moderately severe skin disease, 49% of patients achieved a reduction in CLASI score of $\geq 50\%$ compared to 25% in the placebo group.¹⁴⁰ Belimumab is another drug approved by the FDA in 2011 for the treatment of SLE. We still lack final skin-specific outcomes of this drug in CLE.¹⁴¹

Vitiligo

For vitiligo topical ruxolitinib was approved by FDA in 2022 for the treatment of nonsegmental disease compromising $<10\%$ of the body's surface area in adult and pediatric patients >12 years old. In two phase 3 trials (TRuE-V1 and TRuE-V2), subjects were randomized to treatment with ruxolitinib 1.5% cream or placebo twice daily for 2 weeks. At the end of the 24-week treatment period, 30% of ruxolitinib patients had at least 75% improvement in the facial Vitiligo Area Scoring Index (VASI), compared with 10% of placebo patients.¹⁴² Also in these studies ruxolitinib cream has shown improvement in acral pigmentation, which has historically been a refractory area for repigmentation for phototherapy, topical corticosteroids and tacrolimus.¹⁴² A pilot study of eleven patients with facial vitiligo using tofacitinib 2% cream in conjunction with narrow band UVB showed a reduction of 70% in VASI score after 2–4 months.¹⁴³ In the other hand a case series of ten patients using tofacitinib 5 mg bid for 10 months and narrow band UVB or photo-exposure had a decrease of only 5.4% in BSA (5 patients) and others (5 patients) did not achieve any repigmentation.¹⁴⁴

Cutaneous granulomatous disorders (granuloma annulare and sarcoidosis)

Granulomatous diseases can be therapeutic challenges. Management may be unsatisfactory with conventional systemic therapy.¹⁴⁵ Treatment with anti-TNF has been tried with variable results.¹⁴⁶ JAKis targeted immune therapy appears to be a promising option based on the results of a recent case series.¹⁴⁷ Tofacitinib 5 mg/bid has been used in patients who were non-responders to corticosteroids. In a case series of only 1 patient complete remission was obtained after 4 months of treatment. For sarcoidosis (3 patients) the same case series showed complete response in 2 patients and 96% improvement in 1 patient.¹⁴⁷ Further, RCT studies are needed to establish the real value of JAKis in granulomatous diseases.

Hypereosinophilic syndrome

A case series of 5 patients refractory to steroids treated with tofacitinib 5 mg/bid showed complete remission in 3 of them and near complete remission in another one.¹⁴⁸ The remaining patient was unable to complete treatment with tofacitinib due to insurance reasons and treatment was changed to ruxolitinib 25 mg in the morning and 10 mg in the evening. This patient also achieved complete remission.¹⁴⁸

Morphea

There are cases of success using targeted immune therapy for refractory cases of morphea. In two patients with generalized deep morphea associated with eosinophilic fasciitis who did not respond to corticosteroid therapy, tofacitinib (10 mg/bid) was added to phototherapy and methotrexate, achieving clinical improvement in both of them.¹⁴⁹ Tocilizumab (an anti-IL-6 drug) has been reported to be effective in the treatment of pansclerotic morphea.^{150,151} One 14-year-old girl was treated successfully with infliximab.¹⁵⁰

Conclusion

Many targeted immune therapies are currently employed in the management of inflammatory dermatological diseases. Some of these molecules have gained a major role in the treatment of chronic and disabling skin diseases that were not previously controlled with standard treatments, such as anti-IL-4/13 in AD, anti-TNF- α in HS or JAK inhibitors in AA, generating a paradigm shift in the therapeutic armamentarium of dermatology.^{44,152,153} In addition, advances in the understanding of pathophysiology of these diseases have facilitated targeted therapy approaches in inflammatory pathways such as the blockade of JAK-STAT dependent cytokines IL-5, IL-6, IL-10, and IL-13 in DIHS/DRESS.¹³²

There are some critical aspects in the development of targeted therapies for inflammatory skin diseases that must be considered. Long-term safety is a relevant aspect of all new drugs. Some adverse effects may remain latent during clinical trials, only appearing with prolonged use. Others – in very few patients – can appear from the beginning of the treatment inducing a paradoxical reaction with a worsening of the clinical condition under treatment-targeted immune therapy (e.g., PG, psoriasis).^{34,35,90} Collaboration between regulatory agencies, healthcare professionals and the pharmaceutical industry is essential in post-marketing surveillance and long-term follow-up studies to evaluate the safety and effectiveness of these new drugs.¹⁵⁴

For a drug to be considered viable, it must warrant superior clinical outcomes compared to existing treatments. This has led trials to use increasingly better clinometric variables (e.g., PASI-75 vs. PASI-90 in psoriasis),¹² but not necessarily better comparisons. To compare efficacy between drugs researchers have performed network meta-analyses, which gives some insight but has its limitations.⁴⁴ This missing head-to-head comparison with the old drugs occurs for example in the case of JAKi versus methotrexate in moderate-to-severe atopic dermatitis; JAKi vs. NB-UVB in vitiligo, and etanercept versus prednisone in DRESS.^{18,44,133,142} Studies evaluating the economic impact of

these decisions are lacking and may help to increase access to these new therapies.¹⁵⁵

Despite demonstrated efficacy in trials and real-world evidence studies, targeted therapies are still underutilized, especially in regions with lower or middle incomes due to limited availability and inadequate insurance coverage. In Chile, for instance, 92% of the population lacks coverage for targeted therapy for skin conditions, leading to out-of-pocket expenses.¹⁵⁶ A similar situation is observed in Peru and slightly better conditions in Brazil.¹⁵⁶ In a survey conducted by the International Psoriasis Council in low-resource or developing countries, including Argentina, Brazil, Chile, Colombia, Mexico, Peru, China, Egypt, Iran, India, and South Africa, dermatologists commonly cited cost as the primary barrier to accessing biological therapy for psoriasis.¹⁵⁷

Most Clinical Practice Guidelines (CPGs) for skin inflammatory diseases incorporate a logical stratification of the medical management at different stages of the disease.^{28,45,75,100,116} This stratification may not accurately reflect the socio-health conditions in various regions of the world. The majority (72.1%) of dermatological CPGs originate from countries with a high Sociodemographic Index (SDI), while only a small proportion come from high-middle (8.0%), middle (5.3%), and low-SDI countries (1.8%).¹⁵⁸ Geographically, the distribution is also nonuniform, corresponding to Europe (51.8%), North America (21.2%), Asia (15.5%), Latin America (4.9%), and Australasia (4.4%).¹⁵⁸ Thus, CPGs adapted to regional needs in developing countries are still scarce and needed for better management of patients using targeted therapy for skin inflammatory diseases.

These new immune-targeted modulators for the treatment of inflammatory skin diseases are going through the same historical steps of development as many important drugs in use today had previously undergone. The actual data and the high number of new manuscripts appearing daily in the medical literature predict a promising future for the usage of these medications in the treatment of chronic skin conditions and the improvement of the quality of life of our patients.

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Authors' contributions

Edinson Lopez: The study concept and design; data collection, analysis, and interpretation; writing of the manuscript or critical review of important intellectual content; critical review of the literature; final approval of the final version of the manuscript.

Raul Cabrera: The study concept and design; data collection, analysis, and interpretation; writing of the manuscript or critical review of important intellectual content; critical review of the literature; final approval of the final version of the manuscript.

Cristóbal Lecaros: The study concept and design; data collection, analysis, and interpretation; writing of the manuscript or critical review of important intellectual

content; critical review of the literature; final approval of the final version of the manuscript.

Conflicts of interest

None declared.

Appendix A. Supplementary material

Supplementary material related to this article can be found, in the online version, at doi:<https://doi.org/10.1016/j.abd.2023.10.002>.

References

1. Buss NAPS, Henderson SJ, McFarlane M, Shenton JM, de Haan L. Monoclonal antibody therapeutics: history and future. *Curr Opin Pharmacol*. 2012;12:615–22.
2. Duvall MR, Fiorini RN. Different approaches for obtaining antibodies from human B cells. *Curr Drug Discov Technol*. 2014;11:41–7.
3. Bologna J, Schaffer J, Cerroni L. *Dermatology*. 4th edition. Edinburgh: Elsevier; 2017. p. 2880.
4. Yeung YT, Aziz F, Guerrero-Castilla A, Arguelles S. Signaling pathways in inflammation and anti-inflammatory therapies. *Curr Pharm Des*. 2018;24:1449–84.
5. Yamauchi PS. *Biologic and systemic agents in dermatology*. 1st ed. Cham: Springer International Publishing; Imprint: Springer; 2018. p. 1.
6. Ellis CN, Krueger GG, Alefacept Clinical Study Group. Treatment of chronic plaque psoriasis by selective targeting of memory effector T lymphocytes. *N Engl J Med*. 2001;26(345):248–55.
7. Gordon KB, Papp KA, Hamilton TK, Walicke PA, Dummer W, Li N, et al. Efalizumab for patients with moderate to severe plaque psoriasis: a randomized controlled trial. *JAMA*. 2003;17(290):3073–80.
8. Leonardi CL, Powers JL, Matheson RT, Goffe BS, Zitnik R, Wang A, et al. Etanercept as monotherapy in patients with psoriasis. *N Engl J Med*. 2003;20(349):2014–22.
9. Chaudhari U, Romano P, Mulcahy LD, Dooley LT, Baker DG, Gottlieb AB. Efficacy and safety of infliximab monotherapy for plaque-type psoriasis: a randomised trial. *Lancet Lond Engl*. 2001;9(357):1842–7.
10. Moher D, Liberati A, Tetzlaff J, Altman DG, Group TP. Preferred reporting items for systematic reviews and meta-analyses: The PRISMA statement. *PLoS Med*. 2009;6:e1000097.
11. Armstrong AW, Read C. Pathophysiology, clinical presentation, and treatment of psoriasis: a review. *JAMA*. 2020;19(323):1945–60.
12. van de Kerkhof PC. From empirical to pathogenesis-based treatments for psoriasis. *J Invest Dermatol*. 2022;142:1778–85.
13. Griffiths CEM, Armstrong AW, Gudjonsson JE, Barker JNWN. Psoriasis. *Lancet*. 2021;397:1301–15.
14. Wan J, Abuabara K, Troxel AB, Shin DB, Van Voorhees AS, Bebo BF, et al. Dermatologist preferences for first-line therapy of moderate to severe psoriasis in healthy adult patients. *J Am Acad Dermatol*. 2012;66:376–86.
15. Elmetts CA, Lim HW, Stoff B, Connor C, Cordoro KM, Lebwohl M, et al. Joint American academy of dermatology–national psoriasis foundation guidelines of care for the management and treatment of psoriasis with phototherapy. *J Am Acad Dermatol*. 2019;81:775–804.

16. Smith CH, Anstey AV, Barker JNWN, Burden AD, Chalmers RJG, Chandler D, et al. British Association of Dermatologists guidelines for use of biological interventions in psoriasis 2005. *Br J Dermatol.* 2005;153:486–97.
17. Imafuku S, Kanai Y, Murotani K, Nomura T, Ito K, Ohata C, et al. Utility of the dermatology life quality index at initiation or switching of biologics in real-life Japanese patients with plaque psoriasis: results from the ProLOGUE study. *J Dermatol Sci.* 2021;101:185–93.
18. Sbidian E, Chaimani A, Garcia-Doval I, Doney L, Dressler C, Hua C, et al. Systemic pharmacological treatments for chronic plaque psoriasis: a network meta-analysis. *Cochrane Database Syst Rev.* 2022;23:5. CD011535.
19. Armstrong AW, Puig L, Joshi A, Skup M, Williams D, Li J, et al. Comparison of biologics and oral treatments for plaque psoriasis: a meta-analysis. *JAMA Dermatol.* 2020;125:258–69.
20. Armstrong AW, Soliman AM, Betts KA, Wang Y, Gao Y, Stakias V, et al. Long-term benefit-risk profiles of treatments for moderate-to-severe plaque psoriasis: a network meta-analysis. *Dermatol Ther (Heidelb).* 2022;12:167–84.
21. Blauvelt A, Armstrong AW, Langley RG, Gebauer K, Thaçi D, Bagel J, et al. Efficacy of guselkumab versus secukinumab in subpopulations of patients with moderate-to-severe plaque psoriasis: results from the ECLIPSE study. *J Dermatol Treat.* 2022;33:2317–24.
22. Drakos A, Vender R. A review of the clinical trial landscape in psoriasis: an update for clinicians. *Dermatol Ther (Heidelb).* 2022;12:2715–30.
23. Gómez-García F, Gómez-Arias PJ, Montilla-López A, Hernández-Parada J, Sanz-Cabanillas JL, Ruano J, et al. A scoping review on use of drugs targeting the JAK/STAT pathway in psoriasis. *Front Med (Lausanne).* 2022;9:754116.
24. Armstrong AW, Gooderham M, Warren RB, Papp KA, Strober B, Thaçi D, et al. Deucravacitinib versus placebo and apremilast in moderate to severe plaque psoriasis: efficacy and safety results from the 52-week, randomized, double-blinded, placebo-controlled phase 3 POETYK PSO-1 trial. *J Am Acad Dermatol.* 2023;88:29–39.
25. Strober B, Thaçi D, Sofen H, Kircik L, Gordon KB, Foley P, et al. Deucravacitinib versus placebo and apremilast in moderate to severe plaque psoriasis: efficacy and safety results from the 52-week, randomized, double-blinded, phase 3 POETYK PSO-2 trial. *J Am Acad Dermatol.* 2023;88:29–39.
26. Xie X, Wang Y, Yao S, Xia Y, Luo H, Li L, et al. Biologics recommendations for patients with psoriasis: a critical appraisal of clinical practice guidelines for psoriasis. *J Dermatol Treat.* 2022;33:2038–50.
27. Sun HY, Keller E, Suresh H, Sebaratnam DF. Biologics for severe, chronic plaque psoriasis: an Australian cost-utility analysis. *JAAD Int.* 2021;5:1–8.
28. Smith CH, Yiu ZZN, Bale T, Burden AD, Coates LC, Edwards W, et al. British association of dermatologists guidelines for biologic therapy for psoriasis 2020: a rapid update. *Br J Dermatol.* 2020;183:628–37.
29. Chat VS, Uppal SK, Kearns DG, Wu JJ. Comparison of guidelines for the use of Ustekinumab for psoriasis in the United States, Europe, and the United Kingdom: a critical appraisal and comprehensive review. *Dermatol Ther.* 2021;34:e14974.
30. Torres T, Tavares Bello R, Paiva Lopes MJ, Menezes Brandão F, Ferreira A, Ferreira P, et al. Portuguese recommendations for the treatment of psoriasis with biologic therapy. *Eur J Dermatol.* 2020;30:645–54.
31. Carrascosa JM, Puig L, Belinchón Romero I, Salgado-Boquete L, Del Alcázar E, Andrés Lencina JJ, et al. Practical update of the recommendations published by the Psoriasis Group of the Spanish Academy of Dermatology and Venereology (GPS) on the treatment of psoriasis with biologic therapy. Part 1. concepts and general management of psoriasis with biologic therapy. *Actas Dermosifiliogr.* 2022;113:261–77.
32. Prignano F, Pescitelli L, Trovato E, Di Cesare A, Cuccia A, Mazzatenta C, et al. Tuscany consensus for the treatment of moderate-severe psoriasis: update and focus on practical guidelines for place in therapy of anti-IL-17 and anti-IL-23 biologics. *Ital J Dermatol Venereol.* 2022;157:469–79.
33. Yim RM, Singh I, Armstrong AW. Updates on treatment guidelines for psoriasis, atopic dermatitis (eczema), hidradenitis suppurativa, and acne/rosacea during the COVID-19 pandemic. *Dermatol Online J.* 2020;26, 13030/qt0j5150df.
34. Shear NH, Betts KA, Soliman AM, Joshi A, Wang Y, Zhao J, et al. Comparative safety and benefit-risk profile of biologics and oral treatment for moderate-to-severe plaque psoriasis: a network meta-analysis of clinical trial data. *J Am Acad Dermatol.* 2021;85:572–81.
35. Afach S, Chaimani A, Evrenoglou T, Penso L, Brouste E, Sbidian E, et al. Meta-analysis results do not reflect the real safety of biologics in psoriasis. *Br J Dermatol.* 2021;184:415–24.
36. D'Urso DF, Chiriccozi A, Pirro F, Calabrese L, Caldarola G, Fossati B, et al. New JAK inhibitors for the treatment of psoriasis and psoriatic arthritis. *G Ital Dermatol Venereol.* 2020;155:411–20.
37. Kamata M, Tada Y. Safety of biologics in psoriasis. *J Dermatol.* 2018;45:279–86.
38. Rungapiromnan W, Yiu ZZN, Warren RB, Griffiths CEM, Ashcroft DM. Impact of biologic therapies on risk of major adverse cardiovascular events in patients with psoriasis: systematic review and meta-analysis of randomized controlled trials. *Br J Dermatol.* 2017;176:890–901.
39. Peleva E, Exton LS, Kelley K, Kleyn CE, Mason KJ, Smith CH. Risk of cancer in patients with psoriasis on biological therapies: a systematic review. *Br J Dermatol.* 2018;178:103–13.
40. Al-Janabi A, Yiu ZZN. Biologics in psoriasis: updated perspectives on long-term safety and risk management. *Psoriasis (Auckl).* 2022;12:1–14.
41. Saunte DM, Mrowietz U, Puig L, Zachariae C. Candida infections in patients with psoriasis and psoriatic arthritis treated with interleukin-17 inhibitors and their practical management. *Br J Dermatol.* 2017;177:47–62.
42. Sun HY, Phan K, Paller AS, Sebaratnam DF. Biologics for pediatric psoriasis: a systematic review and meta-analysis. *Pediatr Dermatol.* 2022;39:42–8.
43. Barbarot S, Auziere S, Gadkari A, Girolomoni G, Puig L, Simpson EL, et al. Epidemiology of atopic dermatitis in adults: results from an international survey. *Allergy.* 2018;73:1284–93.
44. Drucker AM, Morra DE, Prieto-Merino D, Ellis AG, Yiu ZZN, Rochweg B, et al. Systemic immunomodulatory treatments for atopic dermatitis: update of a living systematic review and network meta-analysis. *JAMA Dermatol.* 2022;158:523–32.
45. Wollenberg A, Kinberger M, Arents B, Aszodi N, Avila Valle G, Barbarot S, et al. European guideline (EuroGuiDerm) on atopic eczema: part I – systemic therapy. *J Eur Acad Dermatol Venereol.* 2022;36:1409–31.
46. Reich K, Thyssen JP, Blauvelt A, Eyerich K, Soong W, Rice ZP, et al. Efficacy and safety of abrocitinib versus dupilumab in adults with moderate-to-severe atopic dermatitis: a randomised, double-blind, multicentre phase 3 trial. *Lancet.* 2022;400:273–82.
47. Sawangjit R, Dilokthornsakul P, Lloyd-Lavery A, Lai NM, Dellavalle R, Chaiyakunapruk N. Systemic treatments for eczema: a network meta-analysis. *Cochrane Database Syst Rev.* 2020;9:CD013206.
48. Agache I, Song Y, Posso M, Alonso-Coello P, Rocha C, Solà I, et al. Efficacy and safety of dupilumab for moderate-to-severe atopic dermatitis: a systematic review for the EAACI biological guidelines. *Allergy.* 2021;76:45–58.

49. Wollenberg A, Howell MD, Guttman-Yassky E, Silverberg JI, Kell C, Ranade K, et al. Treatment of atopic dermatitis with tralokinumab, an anti-IL-13 mAb. *J Allergy Clin Immunol*. 2019;143:135–41.
50. Simpson EL, Sinclair R, Forman S, Wollenberg A, Aschoff R, Cork M, et al. Efficacy and safety of abrocitinib in adults and adolescents with moderate-to-severe atopic dermatitis (JADE MONO-1): a multicentre, double-blind, randomised, placebo-controlled, phase 3 trial. *Lancet*. 2020;396:255–66.
51. Guttman-Yassky E, Teixeira HD, Simpson EL, Papp KA, Pangan AL, Blauvelt A, et al. Once-daily upadacitinib versus placebo in adolescents and adults with moderate-to-severe atopic dermatitis (Measure Up 1 and Measure Up 2): results from two replicate double-blind, randomised controlled phase 3 trials. *Lancet*. 2021;397:2151–68.
52. Noda S, Krueger JG, Guttman-Yassky E. The translational revolution and use of biologics in patients with inflammatory skin diseases. *J Allergy Clin Immunol*. 2015;135:324–36.
53. 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*. 2017;389:2287–303.
54. Deleuran M, Thaçi D, Beck LA, de Bruin-Weller M, Blauvelt A, Forman S, et al. Dupilumab shows long-term safety and efficacy in patients with moderate to severe atopic dermatitis enrolled in a phase 3 open-label extension study. *J Am Acad Dermatol*. 2020;82:377–88.
55. Wollenberg A, Blauvelt A, Guttman-Yassky E, Worm M, Lynde C, Lacour JP, et al. Tralokinumab for moderate-to-severe atopic dermatitis: results from two 52-week, randomized, double-blind, multicentre, placebo-controlled phase III trials (ECZTRA 1 and ECZTRA 2). *Br J Dermatol*. 2021;184:437–49.
56. Silverberg JI, Guttman-Yassky E, Thaçi D, Irvine AD, Stein Gold L, Blauvelt A, et al. Two phase 3 trials of lebrikizumab for moderate-to-severe atopic dermatitis. *N Engl J Med*. 2023;388:1080–91.
57. Gooderham MJ, Forman SB, Bissonnette R, Beebe JS, Zhang W, Banfield C, et al. Efficacy and safety of oral janus kinase 1 inhibitor abrocitinib for patients with atopic dermatitis: a phase 2 randomized clinical trial. *JAMA Dermatol*. 2019;155:1371–9.
58. Bieber T, Simpson EL, Silverberg JI, Thaçi D, Paul C, Pink AE, et al. Abrocitinib versus placebo or dupilumab for atopic dermatitis. *N Engl J Med*. 2021;384:1101–12.
59. Silverberg JI, Simpson EL, Thyssen JP, Gooderham M, Chan G, Feeney C, et al. Efficacy and safety of abrocitinib in patients with moderate-to-severe atopic dermatitis: a randomized clinical trial. *JAMA Dermatol*. 2020;156:863–73.
60. Guttman-Yassky E, Thaçi D, Pangan AL, Hong HCH, Papp KA, Reich K, et al. Upadacitinib in adults with moderate to severe atopic dermatitis: 16-week results from a randomized, placebo-controlled trial. *J Allergy Clin Immunol*. 2020;145:877–84.
61. Simpson EL, Lacour JP, Spelman L, Galimberti R, Eichenfield LF, Bissonnette R, et al. Baricitinib in patients with moderate-to-severe atopic dermatitis and inadequate response to topical corticosteroids: results from two randomized monotherapy phase III trials. *Br J Dermatol*. 2020;183:242–55.
62. Gittler JK, Shemer A, Suárez-Fariñas M, Fuentes-Duculan J, Gulewicz KJ, Wang CQF, et al. Progressive activation of T(H)2/T(H)22 cytokines and selective epidermal proteins characterizes acute and chronic atopic dermatitis. *J Allergy Clin Immunol*. 2012;130:1344–54.
63. Simpson EL, Parnes JR, She D, Crouch S, Rees W, Mo M, et al. Tezepelumab, an anti-thymic stromal lymphopoietin monoclonal antibody, in the treatment of moderate to severe atopic dermatitis: a randomized phase 2a clinical trial. *J Am Acad Dermatol*. 2019;80:1013–21.
64. Guttman-Yassky E, Brunner PM, Neumann AU, Khattri S, Pavel AB, Malik K, et al. Efficacy and safety of fezakinumab (an IL-22 monoclonal antibody) in adults with moderate-to-severe atopic dermatitis inadequately controlled by conventional treatments: a randomized, double-blind, phase 2a trial. *J Am Acad Dermatol*. 2018;78:872–81, e6.
65. Silverberg JI, Pinter A, Pulka G, Poulin Y, Bouaziz JD, Wollenberg A, et al. Phase 2B randomized study of nemolizumab in adults with moderate-to-severe atopic dermatitis and severe pruritus. *J Allergy Clin Immunol*. 2020;145:173–82.
66. Chen YL, Gutowska-Owsiak D, Hardman CS, Westmoreland M, MacKenzie T, Cifuentes L, et al. Proof-of-concept clinical trial of etokimab shows a key role for IL-33 in atopic dermatitis pathogenesis. *Sci Transl Med*. 2019;11, eaax2945.
67. Kim BS, Howell MD, Sun K, Papp K, Nasir A, Kuligowski ME, et al. Treatment of atopic dermatitis with ruxolitinib cream (JAK1/JAK2 inhibitor) or triamcinolone cream. *J Allergy Clin Immunol*. 2020;145:572–82.
68. Bissonnette R, Papp KA, Poulin Y, Gooderham M, Raman M, Mallbris L, et al. Topical tofacitinib for atopic dermatitis: a phase IIa randomized trial. *Br J Dermatol*. 2016;175:902–11.
69. Purohit VS, Ports WC, Wang C, Riley S. Systemic tofacitinib concentrations in adult patients with atopic dermatitis treated with 2% tofacitinib ointment and application to pediatric study planning. *J Clin Pharmacol*. 2019;811–20.
70. Miao M, Ma L. The efficacy and safety of JAK inhibitors for atopic dermatitis: a systematic review and meta-analysis. *J Dermatol Treat*. 2022;33:1869–77.
71. Bridgwood C, Wittmann M, Macleod T, Watad A, Newton D, Bhan K, et al. T Helper 2 IL-4/IL-13 dual blockade with dupilumab is linked to some emergent T helper 17-type diseases, including seronegative arthritis and enthesitis/enthesopathy, but not to humoral autoimmune diseases. *J Invest Dermatol*. 2022;142:2660–7.
72. Al-Janabi A, Foulkes AC, Mason K, Smith CH, Griffiths CEM, Warren RB. Phenotypic switch to eczema in patients receiving biologics for plaque psoriasis: a systematic review. *J Eur Acad Dermatol Venereol*. 2020;34:1440–8.
73. Fleming P, Drucker AM. Risk of infection in patients with atopic dermatitis treated with dupilumab: a meta-analysis of randomized controlled trials. *J Am Acad Dermatol*. 2018;78:62–9, e1.
74. Hendricks AJ, Hsiao JL, Lowes MA, Shi VY. A comparison of international management guidelines for hidradenitis suppurativa. *Dermatology*. 2021;237:81–96.
75. Ingram JR, Collier F, Brown D, Burton J, Chin MF, et al. British association of dermatologists guidelines for the management of hidradenitis suppurativa (acne inversa) 2018. *Br J Dermatol*. 2019;180:1009–17.
76. Alikhan A, Sayed C, Alavi A, Alhusayen R, Brassard A, Burkhart C, et al. North American clinical management guidelines for hidradenitis suppurativa: a publication from the United States and Canadian hidradenitis suppurativa foundations: Part II: topical, intralesional, and systemic medical management. *J Am Acad Dermatol*. 2019;81:91–101.
77. Zouboulis CC, Bechara FG, Dickinson-Blok JL, Gulliver W, Horváth B, Hughes R, et al. Hidradenitis suppurativa/acne inversa: a practical framework for treatment optimization - systematic review and recommendations from the HS ALLIANCE working group. *J Eur Acad Dermatol Venereol*. 2019;33:19–31.
78. Zouboulis CC, Desai N, Emtestam L, Hunger RE, Ioannides D, Juhász I, et al. European S1 guideline for the treatment of hidradenitis suppurativa/acne inversa. *J Eur Acad Dermatol Venereol*. 2015;29:619–44.

79. Gulliver W, Zouboulis CC, Prens E, Jemec GBE, Tzellos T. Evidence-based approach to the treatment of hidradenitis suppurativa/acne inversa, based on the European guidelines for hidradenitis suppurativa. *Rev Endocr Metab Disord*. 2016;17:343–51.
80. Gulliver W, Landells IDR, Morgan D, Pirzada S. Hidradenitis suppurativa: a novel model of care and an integrative strategy to adopt an orphan disease. *J Cutan Med Surg*. 2018;22:71–7.
81. Magalhães RF, Rivitti-Machado MC, Duarte GV, Souto R, Nunes DH, Chaves M, et al. Consensus on the treatment of hidradenitis suppurativa - Brazilian Society of Dermatology. *An Bras Dermatol*. 2019;94:7–19.
82. Hunger RE, Laffitte E, Lächli S, Mainetti C, Mühlstädt M, Schiller P, et al. Swiss practice recommendations for the management of hidradenitis suppurativa/acne inversa. *Dermatol Basel Switz*. 2017;233:113–9.
83. Alavi A, Lynde C, Alhusayen R, Bourcier M, Delorme I, George R, et al. Approach to the management of patients with hidradenitis suppurativa: a consensus document. *J Cutan Med Surg*. 2017;21:513–24.
84. Kimball AB, Okun MM, Williams DA, Gottlieb AB, Papp KA, Zouboulis CC, et al. Two phase 3 trials of adalimumab for hidradenitis suppurativa. *N Engl J Med*. 2016;375:422–34.
85. Grant A, Gonzalez T, Montgomery MO, Cardenas V, Kerdel FA. Infliximab therapy for patients with moderate to severe hidradenitis suppurativa: a randomized, double-blind, placebo-controlled crossover trial. *J Am Acad Dermatol*. 2010;62:205–17.
86. Aarts P, Dudink K, Vossen ARJV, van Straalen KR, Ardon CB, Prens EP, et al. Clinical implementation of biologics and small molecules in the treatment of hidradenitis suppurativa. *Drugs*. 2021;81:1397–410.
87. Tzanetakou V, Kanni T, Giatrakou S, Katoulis A, Papadavid E, Netea MG, et al. Safety and efficacy of anakinra in severe hidradenitis suppurativa: a randomized clinical trial. *JAMA Dermatol*. 2016;152:52–9.
88. Kanni T, Argyropoulou M, Spyridopoulos T, Pistiki A, Stecher M, Dinarello CA, et al. MABp1 targeting IL-1 α for moderate to severe hidradenitis suppurativa not eligible for adalimumab: a randomized study. *J Invest Dermatol*. 2018;138:795–801.
89. Huang CH, Huang IH, Tai CC, Chi CC. Biologics and small molecule inhibitors for treating hidradenitis suppurativa: a systematic review and meta-analysis. *Biomedicines*. 2022;10:1303.
90. Ahn C, Negus D, Huang W. Pyoderma gangrenosum: a review of pathogenesis and treatment. *Expert Rev Clin Immunol*. 2018;14:225–33.
91. Ben Abdallah H, Fogh K, Vestergaard C, Bech R. Pyoderma gangrenosum and interleukin inhibitors: a semi-systematic review. *Dermatology*. 2022;238:785–92.
92. McKenzie F, Cash D, Gupta A, Cummings LW, Ortega-Loayza AG. Biologic and small-molecule medications in the management of pyoderma gangrenosum. *J Dermatol Treat*. 2019;30:264–76.
93. Partridge ACR, Bai JW, Rosen CF, Walsh SR, Gulliver WP, Fleming P. Effectiveness of systemic treatments for pyoderma gangrenosum: a systematic review of observational studies and clinical trials. *Br J Dermatol*. 2018;179:290–5.
94. Brooklyn TN, Dunnill MGS, Shetty A, Bowden JJ, Williams JDL, Griffiths CEM, et al. Infliximab for the treatment of pyoderma gangrenosum: a randomised, double blind, placebo controlled trial. *Gut*. 2006;55:505–9.
95. Ben Abdallah H, Fogh K, Bech R. Pyoderma gangrenosum and tumour necrosis factor alpha inhibitors: a semi-systematic review. *Int Wound J*. 2019;16:511–21.
96. Kolios AGA, Maul JT, Meier B, Kerl K, Traidl-Hoffmann C, Hertl M, et al. Canakinumab in adults with steroid-refractory pyoderma gangrenosum. *Br J Dermatol*. 2015;173:1216–23.
97. Guenova E, Teske A, Fehrenbacher B, Hoerber S, Adamczyk A, Schaller M, et al. Interleukin 23 expression in pyoderma gangrenosum and targeted therapy with ustekinumab. *Arch Dermatol*. 2011;147:1203–5.
98. Maurer M, Khan DA, Elieh Ali Komi D, Kaplan AP. Biologics for the use in chronic spontaneous urticaria: when and which. *J Allergy Clin Immunol Pract*. 2021;9:1067–78.
99. Peck G, Hashim MJ, Shaughnessy C, Muddasani S, Elsayed NA, Fleischer AB Jr. Global epidemiology of urticaria: increasing burden among children, females and low-income regions. *Acta Derm Venereol*. 2021;101, adv00433.
100. Zuberbier T, Aberer W, Asero R, Abdul Latiff AH, Baker D, Ballmer-Weber B, et al. The EAACI GALEN EDF WAO guideline for the definition, classification, diagnosis and management of urticaria. *Allergy*. 2018;73:1393–414.
101. Saini SS, Bindslev-Jensen C, Maurer M, Grob JJ, Bülbül Baskan E, Bradley MS, et al. Efficacy and safety of omalizumab in patients with chronic idiopathic/spontaneous urticaria who remain symptomatic on H1 antihistamines: a randomized, placebo-controlled study. *J Invest Dermatol*. 2015;135:67–75.
102. Chen Y, Yu M, Huang X, Tu P, Shi P, Maurer M, et al. Omalizumab treatment and outcomes in Chinese patients with chronic spontaneous urticaria, chronic inducible urticaria, or both. *World Allergy Organ J*. 2021;14:100501.
103. Maurer M, Giménez-Arnau AM, Sussman G, Metz M, Baker DR, Bauer A, et al. Ligelizumab for chronic spontaneous urticaria. *N Engl J Med*. 2019;381:1321–32.
104. Maurer M, Giménez-Arnau A, Bernstein JA, Chu CY, Danilycheva I, Hide M, et al. Sustained safety and efficacy of ligelizumab in patients with chronic spontaneous urticaria: a one-year extension study. *Allergy*. 2022;77:2175–84.
105. Altrichter S, Staubach P, Pasha M, Singh B, Chang AT, Bernstein JA, et al. An open-label, proof-of-concept study of liletekimab for antihistamine-resistant chronic spontaneous and inducible urticaria. *J Allergy Clin Immunol*. 2022;149:1683–90, e7.
106. Lee JK, Simpson RS. Dupilumab as a novel therapy for difficult to treat chronic spontaneous urticaria. *J Allergy Clin Immunol Pract*. 2019;7:1659–61, e1.
107. Bernstein JA, Singh U, Rao MB, Berendts K, Zhang X, Mutasim D. Benralizumab for chronic spontaneous urticaria. *N Engl J Med*. 2020;383:1389–91.
108. Magerl M, Terhorst D, Metz M, Altrichter S, Zuberbier T, Maurer M, et al. Benefit of mepolizumab treatment in a patient with chronic spontaneous urticaria. *J Dtsch Dermatol Ges*. 2018;16:477–8.
109. Sabag DA, Matanes L, Bejar J, Sheffer H, Barzilai A, Church MK, et al. Interleukin-17 is a potential player and treatment target in severe chronic spontaneous urticaria. *Clin Exp Allergy*. 2020;50:799–804.
110. King B, Ohyama M, Kwon O, Zlotogorski A, Ko J, Mesinkovska NA, et al. Two phase 3 trials of baricitinib for alopecia areata. *N Engl J Med*. 2022;386:1687–99.
111. Almutairi N, Nour TM, Hussain NH. Janus kinase inhibitors for the treatment of severe alopecia areata: an open-label comparative study. *Dermatology*. 2019;235:130–6.
112. Liu LY, Craiglow BG, Dai F, King BA. Tofacitinib for the treatment of severe alopecia areata and variants: a study of 90 patients. *J Am Acad Dermatol*. 2017;76:22–8.
113. Blair HA. Ritlecitinib: first approval. *Drugs*. 2023;83:1315–21.
114. Di Lernia V, Casanova DM, Goldust M, Ricci C. Pemphigus vulgaris and bullous pemphigoid: update on diagnosis and treatment. *Dermatol Pract Concept*. 2020;10:e2020050.
115. Joly P, Maho-Vaillant M, Prost-Squarcioni C, Hebert V, Houivet E, Calbo S, et al. First-line rituximab combined with short-term prednisone versus prednisone alone for the treatment of pemphigus (Ritux 3): a prospective, multicentre,

- parallel-group, open-label randomised trial. *Lancet Lond Engl*. 2017;389:2031–40.
116. Joly P, Horvath B, Patsatsi A, Uzun S, Bech R, Beissert S, et al. Updated S2K guidelines on the management of pemphigus vulgaris and foliaceus initiated by the european academy of dermatology and venereology (EADV). *J Eur Acad Dermatol Venereol*. 2020;34:1900–13.
 117. Yanovsky RL, McLeod M, Ahmed AR. Treatment of pemphigus vulgaris: part 2 - emerging therapies. *Expert Rev Clin Immunol*. 2019;15:1061–71.
 118. Heo YA. Efgartigimod: first approval. *Drugs*. 2022;82:341–8.
 119. Goebeler M, Bata-Csörgő Z, De Simone C, Didona B, Remenyik E, Reznichenko N, et al. Treatment of pemphigus vulgaris and foliaceus with efgartigimod, a neonatal Fc receptor inhibitor: a phase II multicentre, open-label feasibility trial. *Br J Dermatol*. 2022;186:429–39.
 120. Eberhard Y, Burgos E, Gagliardi J, Vullo CM, Borosky A, Pessoa S, et al. Cytokine polymorphisms in patients with pemphigus. *Arch Dermatol Res*. 2005;296:309–13.
 121. Ellebrecht CT, Maseda D, Payne AS. Pemphigus and pemphigoid: from disease mechanisms to druggable pathways. *J Invest Dermatol*. 2022;142:907–14.
 122. Cao P, Xu W, Zhang L. Rituximab, omalizumab, and dupilumab treatment outcomes in bullous pemphigoid: a systematic review. *Front Immunol*. 2022;13:928621.
 123. Saleh M, Reedy M, Torok H, Weaver J. Successful treatment of bullous pemphigoid with dupilumab: a case and brief review of the literature. *Dermatol Online J*. 2021;27, 13030/qt0dv3f9h6.
 124. Kremer N, Snast I, Cohen ES, Hodak E, Mimouni D, Lapidot M, et al. Rituximab and omalizumab for the treatment of bullous pemphigoid: a systematic review of the literature. *Am J Clin Dermatol*. 2019;20:209–16.
 125. Kridin K, Mruwat N, Ludwig RJ. Association of rituximab with risk of long-term cardiovascular and metabolic outcomes in patients with pemphigus. *JAMA Dermatol*. 2023;159:56–61.
 126. Sachdeva M, Maliyar K, Ponzo MG. A systematic review of efficacy and safety of monotherapy and combination therapy with biologic for Stevens-Johnson syndrome and toxic epidermal necrolysis. *J Cutan Med Surg*. 2021;25:598–615.
 127. Wang CW, Yang LY, Chen CB, Ho HC, Hung SI, Yang CH, et al. Randomized, controlled trial of TNF- α antagonist in CTL-mediated severe cutaneous adverse reactions. *J Clin Invest*. 2018;128:985–96.
 128. Paquet P, Jennes S, Rousseau AF, Libon F, Delvenne P, Piérard GE. Effect of N-acetylcysteine combined with infliximab on toxic epidermal necrolysis. A proof-of-concept study. *Burns*. 2014;40:1707–12.
 129. Jacobsen A, Olabi B, Langley A, Beecker J, Mutter E, Shelley A, et al. Systemic interventions for treatment of Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), and SJS/TEN overlap syndrome. *Cochrane Database Syst Rev*. 2022;3:CD013130.
 130. Woolridge KF, Boler PL, Lee BD. Tumor necrosis factor alpha inhibitors in the treatment of toxic epidermal necrolysis. *Cutis*. 2018;101:E15–21.
 131. Zhang J, Lei Z, Xu C, Zhao J, Kang X. Current perspectives on severe drug eruption. *Clin Rev Allergy Immunol*. 2021;61:282–98.
 132. Damsky WE, Vesely MD, Lee AI, Choi J, Meyer AC, Chen M, et al. Drug-induced hypersensitivity syndrome with myocardial involvement treated with tofacitinib. *JAAD Case Rep*. 2019;5:1018–26.
 133. Ange N, Alley S, Fernando SL, Coyle L, Yun J. Drug reaction with eosinophilia and systemic symptoms (DRESS) syndrome successfully treated with mepolizumab. *J Allergy Clin Immunol Pract*. 2018;6:1059–60.
 134. Husein-ElAhmed H, Gieler U, Steinhoff M. Lichen planus: a comprehensive evidence-based analysis of medical treatment. *J Eur Acad Dermatol Venereol J EADV*. 2019;33:1847–62.
 135. Brumfiel CM, Patel MH, Severson KJ, Zhang N, Li X, Quillen JK, et al. Ruxolitinib cream in the treatment of cutaneous lichen planus: a prospective, open-label study. *J Invest Dermatol*. 2022;142:2109–16, e4.
 136. Seiringer P, Lauffer F, Pilz AC, Boehmer D, Biedermann T, Eyreich K. Tofacitinib in hypertrophic lichen planus. *Acta Derm Venereol*. 2020;100:adv00220.
 137. Abdulmulla A, Bagit A, Mufti A, Yeung KCY, Yeung J. The use of janus kinase inhibitors for lichen planus: an evidence-based review. *J Cutan Med Surg*. 2023;27:271–6.
 138. Boch K, Langan EA, Kridin K, Zillikens D, Ludwig RJ, Bieber K. Lichen planus. *Front Med (Lausanne)*. 2021;8:737813.
 139. Sprow G, Dan J, Merola JF, Werth VP. Emerging therapies in cutaneous lupus erythematosus. *Front Med (Lausanne)*. 2022;9:968323.
 140. Morand EF, Furie R, Tanaka Y, Bruce IN, Askanase AD, Richez C, et al. Trial of anifrolumab in active systemic lupus erythematosus. *N Engl J Med*. 2020;382:211–21.
 141. Manzi S, Sánchez-Guerrero J, Merrill JT, Furie R, Gladman D, Navarra SV, et al. Effects of belimumab, a B lymphocyte stimulator-specific inhibitor, on disease activity across multiple organ domains in patients with systemic lupus erythematosus: combined results from two phase III trials. *Ann Rheum Dis*. 2012;71:1833–8.
 142. Rosmarin D, Passeron T, Pandya AG, Grimes P, Harris JE, Desai SR, et al. Two phase 3, randomized, controlled trials of ruxolitinib cream for vitiligo. *N Engl J Med*. 2022;387:1445–55.
 143. McKesey J, Pandya AG. A pilot study of 2% tofacitinib cream with narrowband ultraviolet B for the treatment of facial vitiligo. *J Am Acad Dermatol*. 2019;81:646–8.
 144. Liu LY, Strassner JP, Refat MA, Harris JE, King BA. Repigmentation in vitiligo using the Janus kinase inhibitor tofacitinib may require concomitant light exposure. *J Am Acad Dermatol*. 2017;77:675–82, e1.
 145. Dai C, Shih S, Ansari A, Kwak Y, Sami N. Biologic therapy in the treatment of cutaneous sarcoidosis: a literature review. *Am J Clin Dermatol*. 2019;20:409–22.
 146. Chen A, Truong AK, Worswick S. The role of biologics in the treatment of chronic granuloma annulare. *Int J Dermatol*. 2019;58:622–6.
 147. Damsky W, Thakral D, McGeary MK, Leventhal J, Galan A, King B. Janus kinase inhibition induces disease remission in cutaneous sarcoidosis and granuloma annulare. *J Am Acad Dermatol*. 2020;82:612–21.
 148. King B, Lee AI, Choi J. Treatment of Hypereosinophilic Syndrome with Cutaneous Involvement with the JAK Inhibitors Tofacitinib and Ruxolitinib. *J Invest Dermatol*. 2017;137:951–4.
 149. Kim SR, Charos A, Damsky W, Heald P, Girardi M, King BA. Treatment of generalized deep morphea and eosinophilic fasciitis with the Janus kinase inhibitor tofacitinib. *JAAD Case Rep*. 2018;4:443–5.
 150. George R, George A, Kumar TS. Update on management of morphea (localized scleroderma) in children. *Indian Dermatol Online J*. 2020;11:135–45.
 151. Zhang A, Nocton J, Chiu Y. A case of pansclerotic morphea treated with tocilizumab. *JAMA Dermatol*. 2019;155:388–9.
 152. Yan D, Fan H, Chen M, Xia L, Wang S, Dong W, et al. The efficacy and safety of JAK inhibitors for alopecia areata: a systematic review and meta-analysis of prospective studies. *Front Pharmacol*. 2022;13:950450.
 153. Scala E, Cacciapuoti S, Garzorz-Stark N, Megna M, Marasca C, Seiringer P, et al. Hidradenitis suppurativa: where we are and where we are going. *Cells*. 2021;10:2094.

154. Lima XT, Seidler EM, Lima HC, Kimball AB. Long-term safety of biologics in dermatology. *Dermatol Ther.* 2009;22:2–21.
155. Hamilton MP, Ntais D, Griffiths CEM, Davies LM. Identification and Management of Psoriasis-Associated Comorbidity (IMPACT) Team. Psoriasis treatment and management - a systematic review of full economic evaluations. *Br J Dermatol.* 2015;172:574–83.
156. Bravo FG. Assessing the use of biologic therapy for psoriasis in Latin America. *Br J Dermatol.* 2023;188:454.
157. De la Cruz C. Psoriasis treatment in Latin America: The Access Issue. 24th World Congress of Dermatology; 2019. Milan, Italy.
158. Haw WY, Al-Janabi A, Arents BWM, Asfour L, Exton LS, Grindlay D, et al. Global Guidelines in Dermatology Mapping Project (GUIDEMAP): a scoping review of dermatology clinical practice guidelines. *Br J Dermatol.* 2021;185:736–44.