

Biologics in patients with skin diseases



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Biologic agents are important therapeutic options for treating multiple moderate-to-severe cutaneous diseases. Monoclonal antibodies already in use or under investigation are targeted for psoriasis, atopic dermatitis, melanoma, hidradenitis suppurativa, and pemphigus vulgaris. (J Allergy Clin Immunol 2017;139:1423-30.)

Key words: *Biologics, mAbs, pemphigus, psoriasis, eczema, hidradenitis suppurativa, melanoma*

Biologic agents are important therapeutic options for treating multiple moderate-to-severe cutaneous diseases. With the major advances in understanding the pathophysiology of diverse dermatologic conditions, many new molecules binding to specific extracellular or cell-surface targets are being developed. Monoclonal antibodies already in use or under investigation are targeted for psoriasis, atopic dermatitis, melanoma, hidradenitis suppurativa (HS), and pemphigus vulgaris.

PSORIASIS

Globally, the prevalence of psoriasis is around 2.5%.¹ Traditional oral systemic treatments include acitretin, cyclosporine, and methotrexate.² With the discovery of key cells and mediators in psoriasis (Fig 1),³ mAbs have become important targeted treatment options for moderate-to-severe plaque psoriasis.⁴ Classically, *TNF-α* was considered the main cytokine in patients with psoriasis. The clinically beneficial *TNF-α* inhibitors etanercept (Enbrel; Amgen, Thousand Oaks, Calif), infliximab (Remicade; Janssen Biotech, Horsham, Pa), and adalimumab (Humira; Abbvie, Lake Bluff, Ill) received US Food and Drug Administration (FDA) approval for psoriasis in 2004, 2006, and 2008, respectively.⁵

Abbreviations used

CTLA-4: Cytotoxic T lymphocyte-associated antigen 4
FDA: US Food and Drug Administration
HS: Hidradenitis suppurativa
NK: Natural killer
PAPA: Pyogenic (sterile) arthritis, pyoderma gangrenosum, acne
PASH: Pyoderma gangrenosum, acne, suppurative hidradenitis
PASI: Psoriasis Area Severity Index
PD-1: Programmed cell death 1
PD-L1: Programmed cell death ligand 1

Nonetheless, the *IL-23/IL-17A* axis has recently been recognized as also playing an important role in plaque psoriasis.¹ This led to the development of novel drugs, such as the human mAb targeting *IL-12/23* ustekinumab (Stelara; Janssen Biotech) and the *IL-17A* inhibitors. Two of the anti-*IL-17* mAbs have obtained FDA approval for plaque psoriasis: secukinumab (Cosentyx; Novartis Pharmaceuticals Corp, Basel, Switzerland) in 2015 and ixekizumab (Taltz; Eli Lilly and Co, Indianapolis, Ind) in 2016.⁶⁻⁸ Head-to-head clinical studies evaluating the efficacy of anti-*IL-17A* versus anti-*TNF-α* (ixekizumab vs etanercept) or anti-p40 *IL-12/23* (secukinumab vs ustekinumab) showed a higher efficacy of the anti-*IL-17A* drugs based on Psoriasis Area Severity Index (PASI) 75, PASI-90, and PASI-100 scores (ie, 75% or greater, 90% or greater, and 100% reduction in PASI scores from baseline).⁹⁻¹² PASI is a widely used tool to assess the severity of psoriasis, providing a score in the range of 0 (no disease) to 72 (maximal disease), taking into account body surface area, as well as erythema, induration, and scaling of the plaques.

Also, ixekizumab and secukinumab were more effective than placebo in patients with arthritic psoriasis in phase III trials.^{13,14} Consequently, secukinumab received FDA approval for arthritic psoriasis in 2016.⁷

Patients with inborn impairment of the *T_H17* pathway present with increased susceptibility to *Candida* species infections, which characterizes chronic mucocutaneous candidiasis. Thus it was not surprising that *Candida* species infections were observed more frequently with secukinumab and ixekizumab than with etanercept or placebo.⁶ Apart from 3 severe mucocutaneous cases reported in the UNCOVER-2 trial (1 affecting the external ear during the induction period and 2 affecting the oral mucosa between 12 and 60 weeks of treatment), all cases reported were mild to moderate.¹² No systemic *Candida* species infection has been reported with the anti-*IL-17* mAbs. Neutropenia and inflammatory bowel diseases were also objectivized with these drugs. Nonetheless, they are considered overall safe treatment options for psoriasis.¹⁵

More biologics targeting the *T_H17* pathway are under evaluation for psoriasis. Brodalumab (Siliq; Valeant Pharmaceuticals, Laval, Canada) is an anti-*IL-17* receptor A mAb that has proved

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Terms in boldface and italics are defined in the glossary on page 1424.

highly effective in patients with moderate-to-severe plaque psoriasis.^{16,17} Despite the promising results, a hold was put on the 3 phase III trials (AMAGINE-1, AMAGINE-2, and AMAGINE-3) in May 2015 based on events of suicidal ideation. Brodalumab is currently prescribed in Japan, but its approval is still pending in the United States. Other anti-IL-17 mAbs, such as bimekizumab (UCB4940; UCB, Brussels, Belgium), are currently under investigation. Also, biologics selectively blocking IL-23, including guselkumab (CNT01959; Janssen Biotech), tildrakizumab (SCH 900222/MK-3222; Merck and Co, Kenilworth, NJ), and risankizumab (BI 655066/ABBV-066; Abbvie), have proved beneficial in early studies.¹⁷⁻¹⁹

Because the aforementioned FDA-approved mAbs find their utility and efficacy in patients with moderate-to-severe psoriasis, they are widely prescribed, and the associated financial burden is increasing.²⁰ The biosimilars for the 3 anti-TNF- α etanercept (Erelzi; Sandoz, Holzkirchen, Germany), adalimumab (Amjevita; Amgen), and infliximab (Inflectra; Hospira, Lake Forest, Ill) have been officially FDA approved since 2016 and represent a potential cost savings.²¹⁻²³ Biologics are large and complex molecules that can never be exactly duplicated because of their inherent variability. Hence biosimilars are not chemically identical to the original biologic. Because they cannot be considered generics, comparative clinical trials with the original biologic are necessary to determine whether there is equivalence of efficacy.²⁴ A phase III study comparing etanercept with its biosimilar was recently published, demonstrating equivalent efficacy and comparable safety between both arms.²⁵ A similar study has been

completed for adalimumab and its biosimilar, but results are still pending (clinicaltrials.gov NCT02016105). The NOR-SWITCH study, a phase 4 clinical trial assessing the worsening of disease over 52 weeks when patients are switched from the originator infliximab to its biosimilar, is also ongoing (clinicaltrials.gov NCT02148640).

It has been postulated that simultaneous neutralization of 2 targets (eg, TNF- α and IL-17A), thus blocking concurrently relevant mediators in psoriasis, would result in high responses in even more patients.¹

EXPERT OPINION: Spectacular success rates for complete clearing of and decrease in morbidity in patients, including adolescents, are experienced with the current available mAb. Yet there are still patients who are repeat failures to all therapies. We need more scientific insight into why biologics fail in some patients.

ATOPIC DERMATITIS

Atopic dermatitis is the most common chronic inflammatory pruritic skin disease, with a prevalence of 2% to 10% in adults and up to 30% in the pediatric population.²⁶ From a pathophysiologic point of view, atopic dermatitis could include genetic dysfunction of the epidermal barrier, for which emollients, topical corticosteroids, and *calcineurin* inhibitors are still a cornerstone of treatment.²⁶

More recent insights demonstrated T_H2-driven inflammation in these patients, including the implication of IL-4 and IL-13.²⁶ This finding promoted the investigation of target treatments in patients with atopic dermatitis (Table I),²⁷⁻⁴¹ such as the development of

GLOSSARY

BRAF KINASE: A serine/threonine kinase protein that is part of the mitogen-activated protein kinase signaling pathway. Mutated BRAF proteins (oncogenes) have increased kinase activity, which is known to be a cause of melanoma.

CALCINEURIN: A calcium and calmodulin-dependent serine/threonine protein phosphatase that activates T cells and can be blocked by inhibitors. Calcineurin activates cytoplasmic nuclear factor of activated T cells (NFATc), a transcription factor, through dephosphorylation. Activated NFATc upregulates IL-2 expression, stimulating growth and differentiation of the T-cell response.

CD20: An activated glycosylated phosphoprotein expressed on the surfaces of all B cells that plays a role in the development and differentiation of B cells into plasma cells.

CD22: A transmembrane protein that preferentially binds to α -2,6-linked sialic acid and mediates B cell–B cell interactions. CD22 is known to be a regulatory molecule that functions as an inhibitory receptor for B-cell receptor signaling that prevents overactivation of the immune system and development of autoimmune diseases.

CYTOTOXIC T LYMPHOCYTE-ASSOCIATED PROTEIN 4 (CTLA-4): A receptor that functions as an inhibitory signal that downregulates immune responses. CTLA4 is constitutively expressed in regulatory T cells but is only upregulated in conventional T cells after activation.

DESMOGLEIN 1 AND 3 (Dsg1 AND Dsg3): Calcium-binding transmembrane glycoproteins of desmosomes in vertebrate epithelial cells and members of the cadherin cell adhesion molecule superfamily. Furthermore, Dsg1 and Dsg3 proteins have been identified as autoantigens of the autoimmune skin-blistering disease pemphigus vulgaris.

IL-1 α : A cytokine of the IL-1 family responsible for the regulation of inflammation, as well as the promotion of fever and sepsis. IL-1 α is involved in TNF- α activation.

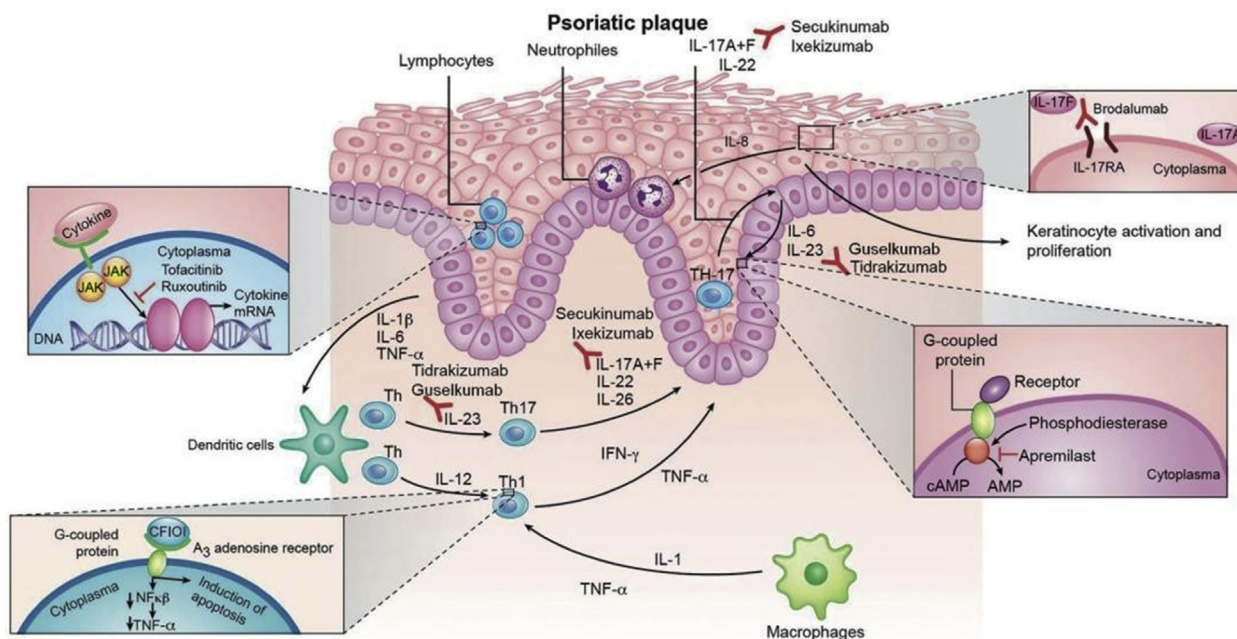
IL-17A: A proinflammatory cytokine that regulates nuclear factor κ B and mitogen-activated protein kinase expression. IL-17A has been shown to stimulate IL-6 and COX-2 (PTGS2/COX-2) expression, as well as nitric oxide production. Furthermore, increased levels of this cytokine are known to be associated with chronic inflammatory diseases, including rheumatoid arthritis, psoriasis, and multiple sclerosis.

IL-23: A cytokine secreted by activated dendritic cells and activated macrophages, IL-23 functions in both innate and adaptive immunity to regulate T_H17 function and proliferation. In addition, IL-23 induces CD8⁺ memory T cells to proliferate and produce IL-17. As such, IL-23 has been described as a key cytokine controlling inflammation in peripheral tissues.

MITOGEN-ACTIVATED PROTEIN KINASE (RAS-RAF-MEK-ERK): Cascades that are key signaling pathways involved in the regulation of normal cell proliferation, survival, and differentiation. Aberrant regulation of mitogen-activated protein kinase cascades has been shown to cause cancer and other human diseases, which have led to the development of pharmacologic inhibitors.

PROGRAMMED CELL DEATH 1 (PD-1): A cell-surface receptor that plays an important role in downregulating the immune system and suppressing inflammatory T-cell activation. PD-1 is an immune checkpoint that serves a dual role of promoting apoptosis in antigen-specific T cells while simultaneously reducing apoptosis in regulatory T cells.

TNF- α : Secreted primarily by macrophages, this cytokine's primary role is immune cell regulation. Moreover, it is involved in the regulation of a wide spectrum of biological processes, including cell proliferation, differentiation, apoptosis, lipid metabolism, and coagulation.



developed for its treatment. Adapted from Kofoed et al.³

SOLO 1 and SOLO 2 phase 3 clinical trials bring hope for severe cases that are not well controlled by the classic systemic immunosuppressive medications used in atopic dermatitis, such as cyclosporine, methotrexate, mycophenolate mofetil, and azathioprine. In patients aged 6 years or older to less than 18 years with atopic dermatitis, a phase 2 trial to determine the safety and tolerability of dupilumab was completed but remains unpublished

EXPERT OPINION: The use of biologics is new but very much needed for patients with chronic resistant atopic dermatitis. The field of investigating novel immunologic molecules thought to be relevant in patients with atopic dermatitis is currently very active, which might result in another promising target therapy in patients with this common disease in the near future.

MELANOMA

A new era began when prolonged survival was reported with targeted therapies blocking the mitogen-activated protein kinase pathway (the RAS-RAF-MEK-ERK signaling pathway, which normal function is to regulate cell proliferation, growth, and migration) and immunotherapy with checkpoint inhibitors.^{47,48} In 2010, a phase 3 study demonstrated improved survival with ipilimumab (Yervoy; Bristol-Myers Squibb Co, New York, NY), a fully human mAb (IgG₁) that blocks *cytotoxic T lymphocyte-associated antigen 4 (CTLA-4)*, thus limiting T-cell activation and promoting antitumor immunity.^{49,50} In 2011, vemurafenib (Zelboraf; Genentech, San Francisco, Calif), a *BRAF kinase* inhibitor, also showed a survival benefit for the treatment of metastatic melanoma with the BRAF V600E mutation.⁵¹ Dabrafenib (Tafinlar; Novartis Pharmaceuticals Corp) and trametinib (Mekinist; Novartis Pharmaceuticals Corp), targeting BRAF and MEK,

TABLE I. Novel immunologic approaches in the therapy of AD²⁷

Target	Biological agent	Level of evidence	Key outcome/reference
T_H2 immunity			
IL-4Rα chain	Dupilumab (further substances: AMG 317, pitakinra)	Phase III	EASI-50: 47/55 ^{28,29}
IL-5	Mepolizumab	Phase II	EASI-50: 0/18 ³⁰
IL-13	Tralokinumab, lebrikizumab	Phase II	Unpublished
IgE	Omalizumab (further substances: MEDI4212, QGE031)	Stopped after proof of concept	Heterogeneous reports ranging from EASI or SCORAD-50: 0/20 ³¹ to 21/21 ³²
CD20	Rituximab	Case series	EASI-50: 6/6 ³³ ; long-term: 0/211
IL-31	BMS-981164	Phase I	Study completed but unpublished
IL-31R	Nemolizumab (CIM331)	Phase II ongoing	
TSLP	AMG-157	Phase I completed	Unpublished
Histamine 4 receptor	ZPL389	Phase IIa completed	Recent congress report by Werfel et al (EAACI 2016): significant improvement of EASI and SCORAD scores over placebo
Non-T_H2 immunity			
IL-1R1	Anakinra	Phase I completed	Unpublished
IL-6	Tocilizumab	Case series	EASI-50: 3/3 ³⁵
IL-22	ILV-094	Phase II ongoing	
IL-23p40	Ustekinumab	Case series; phase II completed	Heterogeneous reports: successful ^{36,37} vs noneffective ³⁸ ; no significant clinical response over placebo ³⁹
TNF-α	Etanercept	Case series	EASI-50: 0/2 ⁴⁰
IFN-γ		Phase III	EASI-50: 18/40 ⁴¹
PDE ₄	Apremilast	Phase II completed	Unpublished
NK-1R	Tradipitant (VLY868)	Phase II ongoing	

Adapted from Werfel et al.²⁷

CRTH2, Chemoattractant receptor-homologous molecule expressed on T_H2 lymphocytes; EAACI, European Academy of Allergy and Clinical Immunology; EASI, Eczema Area and Severity Index; IL-4Rα, IL-4 receptor α; IL-31R, IL-31 receptor; NK-1R, neurokinin 1 receptor; PDE₄, phosphodiesterase 4.

respectively, were FDA approved in 2013. The response rate to the targeted therapies is high (45% to 53%), but their median duration is less than 1 year.⁴⁵ Even though the combination of anti-BRAF and anti-MEK showed a better response rate and duration, these inhibitors of the *mitogen-activated protein kinase* pathway are limited to the 40% of patients with the corresponding mutation.^{45,52,53} For ipilimumab, the response rate is only 10.9% but with a quite high maintained response of 60% at 2 years. However, 23% of patients receiving this immunotherapy will present with immune-related grade 3 or 4 adverse events, mostly affecting the skin and the gastrointestinal track.^{49,50} Thus, despite the enthusiasm generated by these new medications, the development of more accessible, well-tolerated, and effective drugs is awaited.

A new class of mAbs targeting the *programmed cell death 1 (PD-1)* checkpoint inhibitor has been on the market since 2014.⁵⁴ Although the role of CTLA-4 is to limit T-cell activation, PD-1 inactivates T cells reaching the tumor and is therefore a checkpoint in the immune system.⁵⁰ The anti-PD-1 antibodies nivolumab (Opdivo; Bristol-Myers Squibb Co) and pembrolizumab (Keytruda; Merck & Co) demonstrated a response rate of 30% to 40%, with the majority experiencing a long-standing response.⁵⁴ Three phase 3 clinical trials were published in 2015 on anti-PD-1 mAbs. First, nivolumab has shown superior efficacy over dacarbazine.⁴⁵ Also, pembrolizumab significantly prolonged progression-free and overall survival compared with ipilimumab in the KEYNOTE-006 study.⁵⁰ Finally, the combination of nivolumab with ipilimumab (3 mg/kg; CheckMate 067) was more effective than either agent alone. Nonetheless, more treatment-related adverse effects were noted in the group receiving both treatments. In an attempt to maintain efficacy while diminishing the secondary effects, a “low dose” of ipilimumab (1 mg/kg)

was used with the standard dose of pembrolizumab, with promising response rates and lower side effects, as shown in the KEYNOTE-029 study.⁵⁵

Studies at different phases are currently ongoing for other agents targeting PD-1 (eg, pidilizumab [CT-011; Medivation, San Francisco, Calif]) or its ligand, *programmed cell death ligand 1 (PD-L1)*; eg, atezolizumab [Tecentriq; Genentech], durvalumab [MEDI4736; AstraZeneca, Cambridge, United Kingdom], and avelumab [Bavencio; Pfizer, New York, NY]).⁵⁶ Many combinations are also under investigation, such as anti-PD-1 with anti-BRAF, anti-MEK or anti-CTLA-4, and anti-PD-L1 with anti-BRAF.⁵⁷

EXPERT OPINION: Antibodies directed against the PD-1 protein have become the preferred immune checkpoint inhibitors in patients with advanced melanoma. Ipilimumab, the CTLA-4 inhibitor, might find its utility more in combination with the PD-1 checkpoint inhibitors. There is rapid development in the field of promising novel agents for advanced melanoma, leading to hope for a better outcome in the near future for these patients.

HS

HS is a chronic, inflammatory, and possibly debilitating recurrent disease of the hair follicles.⁵⁸ According to the population affected, the prevalence varies between 1% and 4%.⁵⁹ Its onset is mainly between puberty and 40 years of age and affects women 4 times more frequently than men.⁵⁹ It presents clinically with nodules, abscesses, sinus track formation, and scarring. Commonly, it affects the intertriginous areas of the skin, such as the axillae (the most common site), inguinal, gluteal, and submammary areas.⁵⁹ Necessary conditions for this cutaneous

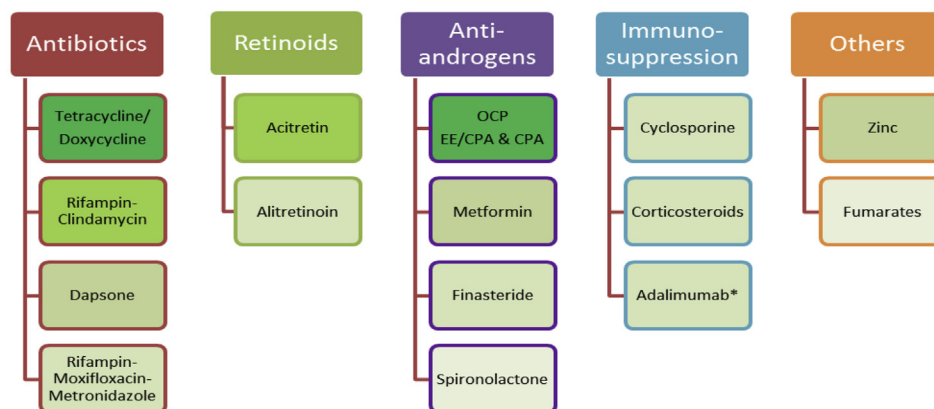


FIG 2. List of current systemic therapies with reported efficacy in patients with HS. CPA, Cyproterone acetate; EE, ethinyl estradiol; OCP, oral contraceptive pills. *Adalimumab is the only FDA-approved drug for HS. Adapted from Alhusayen et al.⁶¹

disease to develop are follicular occlusion, followed by follicular rupture with a subsequent immune response.⁵⁸ Many cytokines implicated in HS are still under investigation, but TNF- α , IL-1 β , IL-17, and IL-23 have been identified as driving the inflammation.⁵⁸ Increased IL-10 levels have also been recognized as playing a role in HS, probably acting as a negative feedback signal in the severe proinflammatory context.⁵⁸ Other recognized contributing factors are cigarette smoking, microbial colonization, obesity, and a specific genetic background.⁵⁸ Pathologic investigation showed that HS is an inflammatory disease of the hair follicles associated with the follicular occlusion tetrad (HS, pilonidal cyst, acne conglobata, and dissecting cellulitis of the scalp) and pyoderma gangrenosum (independently or with pyogenic [sterile] arthritis, pyoderma gangrenosum, acne [PAPA]; pyoderma gangrenosum, acne, suppurative hidradenitis [PASH]; and psoriatic arthritis, pyoderma gangrenosum, acne, suppurative hidradenitis [PsAPASH] syndromes).⁶⁰ Moreover, convincing associations with HS in the literature have been made with metabolic syndrome.⁶⁰

The traditional systemic therapies (Fig 2, excluding adalimumab)⁶¹ are frequently insufficient in providing a significant improvement in the treatment of HS.⁶² Thus, research investigators have gained interest in biologics as a possible effective avenue for these patients. Adalimumab (Humira; AbbVie, Lake Bluff, Ill) is the first FDA-approved treatment for moderate-to-severe HS in adults since September 2015.⁶² This occurred after the results of 2 phase 3 randomized trials, PIONEER 1 (307 patients) and PIONEER 2 (326 patients), which were similarly designed.⁶³ The primary end point in these studies was defined as an at least 50% reduction in the abscess and inflammatory nodule, with no increase in abscess and draining fistula counts at 12 weeks compared with baseline. Half of the group was assigned to receive a placebo, and the remaining received 160 mg subcutaneously at week 0, 80 mg at week 2, and 40 mg every week from week 4 to week 12. The clinical response was significantly higher in the group receiving 40 mg/wk of adalimumab when compared with the placebo group (PIONEER I: 41.8% vs 26.0%, $P = .003$; PIONEER II: 58.9% vs 27.6%, $P < .001$), and the adverse effects were mainly mild to moderate, with no significant increase in serious adverse events between groups.⁶³ However, compared with the efficacy of adalimumab in patients with other skin diseases (eg, psoriasis), the improvement observed in patients with

HS is only modest, and they were unlikely to present a complete resolution of their lesions.⁶³ Also, a decrease in the response rate over time was noted in all treatment groups.

Regarding the use of other biologic TNF- α inhibitors in patients with HS, etanercept does not appear to be effective⁶³ and is thus not recommended. On the other hand, the only randomized placebo-controlled trial for infliximab⁶⁴ has shown a beneficial effect in a trial of 38 patients with moderate-to-severe HS. In the treatment group 26% of patients presented with a 50% or greater decrease in severity compared with 6% in the placebo arm. Moreover, infliximab was associated with statistically significant improvements in the patient's Dermatology Life Quality Index, pain, and Physician's Global Assessment scores.⁶⁴

Newer therapies that might be of benefit in patients with HS are ustekinumab and anakinra (Kineret; Amgen). Although more studies are warranted, a positive response was seen in patients with HS treated with ustekinumab, an IL-12/23 inhibitor, in case reports^{65,66} and a retrospective cohort.⁶⁷ Tzanetakou and al⁶⁸ have recently published a randomized trial of 10 patients with Hurley stage II or III, which demonstrates the efficacy of anakinra, an antagonist of IL-1 receptor, over placebo.⁶⁹ Of note, this drug has also shown to be beneficial in patients with PAPA syndrome and is thought to be effective in those with PASH syndrome because inflammation through IL-1 secretion is in part responsible for these autoimmune syndromes.⁷⁰

Investigations are currently ongoing or recruiting for diverse biologics, such as CJM112 (a fully human anti-IL-17A mAb [NCT02421172]) and MABp1 (human anti-IL-1 α antibody in patients with HS refractory to adalimumab [NCT02643654]).

EXPERT OPINION: Adalimumab is a major breakthrough in patients with severe HS. Nonetheless, more investigations could be beneficial because a high morbidity is often the fate of these patients despite current treatment options. There is still a lot to learn about this condition to understand it better and provide more efficient drugs.

PEMPHIGUS VULGARIS

Pemphigus refers to a group of rare autoimmune bullous diseases that can be fatal.⁷¹ The main condition in this category is pemphigus vulgaris, which is characterized by blisters and

TABLE II. Some mAbs in use for psoriasis, atopic dermatitis, melanoma, hidradenitis suppurativa, and pemphigus vulgaris

Biologics	Isotype	Mechanism of action	Diseases
Secukinumab	Human IgG _{1κ}	Neutralizes IL-17A ¹⁰	● Plaque psoriasis ● Psoriatic arthritis ● Ankylosing spondylitis
Ixekizumab	Humanized IgG _{4κ}	Neutralizes IL-17A ⁹	Plaque psoriasis
Dupilumab	Human IL-4 receptor α	Inhibits signaling of IL-4 and IL-13 ⁴³	Ongoing studies for: ● Atopic dermatitis ● Eosinophilic esophagitis ● Nasal polyposis ● Chronic sinusitis
Nivolumab	Human IgG ₄	Blocks the interaction of the PD-1 receptor with its 2 known programmed death ligands: PD-L1 and PD-L2 ⁴⁵	● Melanoma, unresectable or metastatic ● Non-small cell lung cancer, metastatic ● Renal cell cancer, clear cell (advanced) ● Hodgkin lymphoma, classical ● Squamous cell carcinoma (head and neck, recurrent or metastatic; off-label) ● Small cell lung cancer, progressive (off-label)
Pembrolizumab	Humanized IgG ₄	Blocks the interaction of the PD-1 receptor with its 2 known programmed death ligands: PD-L1 and PD-L2 (NCI drug dictionary pembrolizumab; 2016. Available at: https://www.cancer.gov/publications/dictionaries/cancer-drug?cdrid=695789 . Accessed November 6, 2016)	● Melanoma, unresectable or metastatic ● Non-small cell lung cancer, metastatic ● Squamous cell carcinoma (head and neck, recurrent or metastatic) ● Merkel cell carcinoma, advanced (off-label)
Adalimumab	Human IgG ₁	Binds TNF-α and thus inhibits TNF binding to p55 and p75 transmembrane TNF receptor ⁸²	● HS ● Plaque psoriasis ● Psoriatic arthritis ● Ankylosing spondylitis ● Rheumatoid arthritis ● Crohn disease ● Ulcerative colitis ● Uveitis ● Pyoderma gangrenosum (off-label)
Rituximab	Chimeric murine-human IgG ₁	Binds to CD20 surface molecule on B cells ⁷⁸	● Pemphigus vulgaris and other bullous dermatoses (off-label) ● Autoimmune connective tissue diseases : dermatomyositis and cutaneous lupus erythematosus/lupus nephritis (off-label) ● Graft-versus-host disease (off-label) ● Vasculitis: Wegener granulomatosis, microscopic polyangiitis ● Cutaneous B-cell lymphoma (off-label) ● Many non-Hodgkin lymphoma ● Chronic lymphocytic leukemia ● Etc

erosions of the mucous membranes and frequently of the skin, which is mediated by autoantibodies against **desmoglein 3 (Dsg3)** and, to a lesser extent, **desmoglein 1 (Dsg1)**.⁷² Even though it occurs worldwide, it is more frequently seen among Jews.⁷³ It affects predominantly adults between 40 and 60 years old.⁷⁴ This condition might require many months of treatments with systemic glucocorticoids, other immunosuppressive drugs (eg, azathioprine, mycophenolate mofetil, and cyclophosphamide), or both. These medications carry potential serious side effects in long-term use,⁷⁵ including death, which is today more frequently associated with the treatment than the disease itself.^{76,77} Also, although these drugs have improved the control of pemphigus vulgaris, relapse is always a concern when they are tapered or stopped.⁷²

Rituximab (Rituxan; Genentech, and Biogen, Cambridge, Mass) has revolutionized the treatment of pemphigus vulgaris, providing a target anti-B-cell therapy. It is a murine-human IgG_{1κ}

mAb that targets the **CD20** transmembrane glycoprotein, which depletes B cells while maintaining the terminally differentiated plasma cells, as well as stem cells.⁷⁸ It is mainly used in 2 different regimens, namely 375 mg/m² through 4 weekly infusions (lymphoma protocol) or 1000 mg/d administered as 2 intravenous infusions 2 weeks apart (rheumatoid arthritis protocol).^{75,79} Cumulative data of patients treated with rituximab, with a majority having received corticosteroids and immunosuppressive therapy before, during, or after this anti-B-cell treatment, have shown clinical remission in 90% to 95% of patients within 6 weeks, with a complete remission within 3 to 4 months.⁸⁰ Recurrence occurs in as much as 50% to 80% of patients,⁸⁰ with a benefit of further cycles of rituximab.⁷⁹ Treating patients with this mAb has helped decrease the cumulative doses of corticosteroids and immunosuppressive drugs,⁸⁰ thus potentially decreasing the long-term adverse effects. In a study of 433 patients with recalcitrant pemphigus vulgaris treated with rituximab, serious adverse

effects are seen in about 1%, mainly infections (frequently associated with septicemia⁸⁰). Clinical studies comparing rituximab with glucocorticoids (phase 3 clinical trial; [clinicaltrials.gov](https://clinicaltrials.gov/NCT02383589) NCT02383589) and mycophenolate mofetil (phase 3 clinical trial; [clinicaltrials.gov](https://clinicaltrials.gov/NCT00784589) NCT00784589) are ongoing.

Promising anti-CD20 biologics are currently under study, with the advantage over rituximab (administered intravenously in hospitals) of using a subcutaneous route of administration and thus reducing the cost burden of these treatments, as well as making it more convenient for patients.⁷⁵ Ofatumumab (Arzerra; Novartis Pharmaceuticals Corp), which is currently in a phase 3 clinical trial (studies are still pending), is a human mAb that binds to an epitope of CD20 that is different from the binding site of rituximab.⁷⁵ Veltuzumab (hA20; Immunomedics, Morris Plains, NJ) is a humanized anti-CD20 mAb with complementarity-determining regions identical to those of rituximab apart from 1 amino acid residue in the variable heavy chain (the framework regions are of epratuzumab, a humanized anti-CD22 antibody).⁷⁵ Clinical trials are still needed to monitor the side effects and determine the dosing and efficacy of these promising drugs. In addition to the new anti-CD20 mAb, other therapeutics against B-cell survival factors (B cell-activating factor and a proliferation-inducing ligand) and CD22 are currently under development.⁸¹

EXPERT OPINION: Rituximab has been a major advance because of its high efficacy, excellent safety profile, and decreased use of high-dose corticosteroids. This anti-CD20 therapy is the best biological agent currently available for treating recalcitrant pemphigus. Nonetheless, to aim for a more sustained remission with rituximab, further investigations on protocols with different doses and intervals of rituximab infusions would be needed.

CONCLUSION

Biologic agents are widely used to treat different cutaneous diseases (Table II).^{9,10,43,45,78,82} Many promising target therapies are under study, including biosimilars, to limit the financial burden associated with these originator mAbs. With the continuous fundamental research ongoing in the dermatologic field, better understanding of the pathophysiology of diverse skin conditions will lead to new and more targeted therapeutic avenues.

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