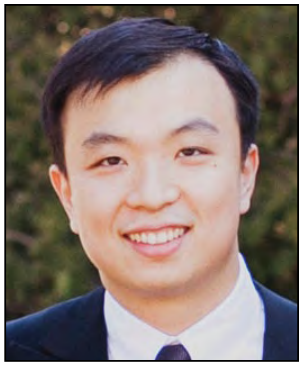

Biologics in Dermatology Beyond Psoriasis

George Han, MD, PhD

Biologic agents, or protein-based drugs derived from living cells, are becoming commonplace in dermatology for the treatment of psoriasis, but their use spans many dermatologic conditions beyond psoriasis and psoriatic arthritis. In recent years, there has been considerable interest in their use for other inflammatory skin diseases. This article will review currently available data and reports on the off-label use of biologics in the treatment of cutaneous diseases other than psoriasis, including inflammatory dermal processes, autoimmune bullous skin diseases, connective-tissue diseases, and hidradenitis suppurativa (HS).

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In the age of biologic therapy, dermatologists have become increasingly comfortable using these protein-based drugs derived from living cells for the treatment of psoriasis. Indeed, the US Food and Drug Administration–approved dermatologic indications for biologics generally fall under the realm of psoriasis or psoriatic arthritis; however, given that these agents have overall immunomodulatory effects that extend beyond psoriasis, there has been considerable interest in their use for other inflammatory skin diseases. This article will review data and reports on the use of biologics in cutaneous diseases other than psoriasis.

Biologics

The library of currently available biologic agents in dermatology is growing, with many agents in development, mostly for psoriasis therapy. Specifically, the drugs with the most reported data regarding usage in treatment of other skin conditions are the tumor necrosis factor α (TNF-α) inhibitors etanercept, infliximab, and adalimumab; the IL-12 and IL-23 blocker ustekinumab; and the anti-CD20 monoclonal antibody rituximab. By definition, these biologic agents are generated through biologic synthesis via living systems rather than a chemical process. As a result, their generation generally is quite complex and costly.[1] These agents also are administered through parenteral modalities, which can be challenging in some patients. In addition to well-publicized concerns about the reactivation of infectious processes and possible links to lymphoma, several biologic agents also are known to generate antidrug antibodies, which may limit their long-term efficacy.[2] Notwithstanding, several of these drugs have promising preliminary reports for their use in the treatment of dermatologic conditions outside the realm of psoriasis. Familiarity with these possible indications may be beneficial in challenging cases. The vast majority of uses for biologics presented in this article are considered off label, thus caveat emptor.

Inflammatory Dermal Processes

Perhaps the most logical use for biologics outside of psoriasis is the treatment of inflammatory dermal processes, encompassing both granulomatous and neutrophilic processes within the dermis. Numerous physicians have attempted to use TNF-α inhibitors against sarcoidosis as a paradigm of this application, especially given the fact that TNF-α plays a definite role in the pathogenesis of sarcoid.[3] There are numerous reports of treatment success with infliximab infusions for sarcoidosis, including cutaneous involvement.[4-9] Although there is a lack of convincing evidence to suggest that etanercept is of any benefit for patients with sarcoid and early attempts

From Albert Einstein College of Medicine/Montefiore Medical Center, New York, New York.
The author reports no conflict of interest.
Correspondence: George Han, MD, PhD (george.han@med.einstein.yu.edu).

to use adalimumab yielded modest results, a more recent double-blind, randomized, placebo-controlled trial showed some promise with adalimumab,[10] which suggests that we may not yet know the optimal approach with this class of medications toward sarcoid. However, it is important to keep in mind that numerous case reports have documented exacerbation or triggering of sarcoid associated with all of the TNF-α inhibitors.[11-13]

Other granulomatous dermal inflammatory processes that have been treated with TNF-α inhibitors include granuloma annulare and necrobiosis lipoidica, which is in line with the known role of TNF-α in the pathogenesis of these conditions, shown both in direct studies with granuloma annulare[14] and theoretically with any granulomatous process as a critical regulator of inflammatory granuloma formation.[15] Although neither of these conditions has been treated in a randomized controlled trial (RCT), many case reports have shown success in treating refractory or challenging cases of these conditions with TNF-α inhibitors. Both infliximab[16,17] and adalimumab[18-22] have been shown to improve granuloma annulare (mostly in its disseminated form), while there are reports of both improvement[23] and failure[24] in treatment with etanercept. Although they are sparse, there also are some case reports in the literature showing successful treatment of necrobiosis lipoidica with numerous TNF-α inhibitors.[25-28] With regard to granulomatous disorders, it seems that the best and most robust data exist for infliximab, followed by adalimumab and etanercept, respectively.

Shifting to neutrophilic processes, biologics also have been used in the treatment of both pyoderma gangrenosum (PG) and Sweet syndrome. Once again, there unfortunately is a relative paucity of RCTs to provide convincing evidence for the use of biologic agents and/or any one agent in particular. The strongest data seem to be associated with the treatment of PG with infliximab, encompassing one RCT with 30 patients showing significant (P=.025) improvement compared to the control,[29] as well as numerous case reports of successful treatment.[30-42] Reports regarding the use of etanercept and adalimumab are a bit more varied, showing treatment failures[43] and treatment successes[44-47] with both agents, and a paradoxical case of treatment failure with both infliximab and etanercept that eventually responded to adalimumab.[48] More recent evidence not only showed elevated expression of IL-23 in a recalcitrant lesion of PG but also demonstrated that treatment with ustekinumab led to complete healing in 1 case.[49]

The picture becomes a bit more complicated with Sweet syndrome. Due to concerns of underlying malignancy, there have been distinct misgivings about using TNF-α inhibitors in the treatment of this condition, particularly because other effective treatments exist. Notwithstanding, there is direct evidence that TNF-α levels are increased in the setting of Sweet syndrome,[50] and at least 2 case reports have shown the efficacy of etanercept in treating Sweet syndrome from presumed inflammatory arthritis.[51,52] With such a complex interplay of cytokines underlying the pathogenesis of these diseases, it is quite probable that we do not yet know the ideal circumstances, conditions, and dosing necessary to treat these conditions with TNF-α inhibitors. Therefore, especially in light of reports of the paradoxical exacerbation of the very underlying conditions we are treating, it would seem that the use of TNF-α inhibitors should be approached with some degree of caution.

Autoimmune Bullous Skin Diseases

Echoing the theme of "seek, and ye shall find," a review of the literature will turn up data showing that TNF-α levels are increased in blister fluid in patients with bullous pemphigoid,[53] even revealing a direct correlation with disease activity.[54] However, several other cytokines are aberrantly expressed in this environment, and it is still unknown what underlies this process. In any case, investigators have used various biologic agents in the treatment of both bullous pemphigoid and its intraepidermal counterpart, pemphigus vulgaris. Many of the case reports of TNF-α inhibitors have involved treating mucous membrane or cicatricial pemphigoid[55-57] with etanercept. Some case reports have drawn on the fortuitous coexistence of psoriasis or psoriatic arthritis with bullous pemphigoid to treat patients with etanercept, resulting in resolution of both conditions.[58-60] Similarly, a patient with psoriasis and bullous pemphigoid was treated with ustekinumab and demonstrated resolution of both conditions.[61] As a counterpoint, a few case reports have shown that bullous pemphigoid can occur while patients are receiving TNF-α therapy for other indications.[62,63] Rituximab, another biologic agent, targets CD20 and also has been used in treating bullous pemphigoid. Some case reports have cited improvement with this treatment but sometimes were limited by serious infection or short follow-up.[64]

Several biologic agents also have been used for the treatment of pemphigus vulgaris. Etanercept seems to be the most commonly used TNF-α inhibitor in this case, with reported treatment of various pemphigus-related disorders, encompassing pemphigus vulgaris, pemphigus vegetans, and pemphigus foliaceus.[65-68] Once again, however, a conflicting case report shows development of pemphigus vulgaris in a patient being treated with etanercept for psoriasis.[69] On the other hand, the data for rituximab

in the treatment of pemphigus are more robust. A meta-analysis of 153 patients showed a marked benefit with rituximab treatment, with a clinical response rate of 65% compared to prior reports of clinical response rates of approximately 30% in the treatment of pemphigus vulgaris with steroids and immunosuppressants.[70] Although there are several limitations in the data, such as concern of insufficient follow-up times from fractured case series rarely reporting more than 5 patients, the overall trend of the data definitely seems to show that rituximab should at least be considered as a steroid-sparing agent in the treatment of pemphigus vulgaris.

Connective-Tissue Diseases

With the many therapeutic options for systemic lupus erythematosus (SLE) and other connective-tissue diseases such as scleroderma/morphea and dermatomyositis to manage the cutaneous and systemic manifestations of these disease processes, difficult-to-treat recalcitrant cases still are common, and the therapeutic ladder would benefit from new treatment options. It is important to remember that when left untreated, SLE can easily become a fatal disease resulting in multiorgan failure. Tumor necrosis factor α inhibitors have certainly been considered and successfully used in the treatment of SLE, along with rituximab and tocilizumab, the monoclonal antibody to the IL-6 receptor.[71] One large study (N=107) illustrated the efficacy of rituximab in patients with SLE and other systemic autoimmune disorders.[72] More recently, a targeted approach was taken with belimumab, a human monoclonal antibody to the soluble B-lymphocyte stimulator. In this study encompassing 867 patients, belimumab showed significant improvement according to the SLE Responder Index (defined as a ≥4-point improvement on a validated scale of SLE, the SELENA-SLEDAI [safety of estrogen in lupus erythematosus national assessment–SLE disease activity index]) versus the control ($P<.02$ in both treatment groups of 1 mg/kg and 10 mg/kg) in patients with active SLE.[72] Further data are pending, but US Food and Drug Administration approval has been granted for the treatment of SLE and it may prove valuable in the treatment of active SLE. Data regarding biologic treatment of scleroderma/morphea or dermatomyositis are relatively sparse. Although treatment of generalized morphea with infliximab may sound promising in case reports,[73] another study failed to demonstrate clinically significant improvement at 26 weeks in a group of 16 patients, half who dropped out with many adverse events likely due to the drug.[74] Similarly, there are case reports outlining successful treatment of dermatomyositis with infliximab,[75] while in stark contrast there also is a report of what can only be described as a massive treatment failure in a patient who developed sepsis after an infliximab infusion and then lymphoma a few months thereafter.[76] This finding underscores the fact that care must be taken in putting too much stock in sparse case reports, which must be balanced with the ideal that trying new therapies may be necessary in difficult cases.

Disorders of Follicular Occlusion

Hidradenitis suppurativa (HS) is considered a disorder of follicular occlusion, classically grouped into the follicular occlusion tetrad along with acne conglobata, dissecting cellulitis of the scalp, and pilonidal cysts. It also is an extremely morbid condition, both painful and distressing, and often is difficult to manage.[77] The treatment of HS with TNF-α inhibitors also illustrates a clear relationship between clinical treatment success and pathophysiologic mechanisms of disease. One study showed elevated levels of TNF-α in patients with HS; the title of the report asked is there a basis for treatment with anti–TNF-α agents, and the answer to this question is definitively yes.[78] A phase 2 trial of 154 patients with moderate to severe HS (who did not have success with oral antibiotics) showed a significantly improved clinical response among patients who were treated with weekly adalimumab versus control ($P=.025$).[79] Phase 3 trials are in progress, but the preliminary data are very promising and echo earlier results among smaller series.[80] Also, and importantly, these studies looked at patients with long-term severe disease (average duration of HS in the latter series, 22.5 years) in whom prior treatments had failed to control the disease. Two smaller open-label studies showed efficacy in treating HS with etanercept, but both studies only recruited 10 patients each[81,82]; thus the data with adalimumab are undoubtedly more robust. The earliest and most complete data on treatment of HS with TNF-α inhibitors though lies with infliximab.[83] A PubMed search of articles indexed for MEDLINE using the search terms *infliximab* and *hidradenitis suppurativa* yielded more than 80 results as of May 2014. A small RCT that included 38 participants further reinforced this concept, demonstrating statistically significant improvement in HS severity index scores at 8 weeks ($P<.005$) with infliximab treatment (5 mg/kg at 0, 2, and 6 weeks) compared to control.[84] Although a meta-analysis of 5 RCTs suggested that both infliximab and adalimumab are effective in treating HS, infliximab may have a better early response.[85] Extending on this idea, other entities that may be grouped into disorders of follicular occlusion combined with other inflammatory conditions (eg, PASH [pyoderma gangrenosum,

acne, suppurative hidradenitis]) also may respond to treatment with TNF-α inhibitors.[86]

Other Skin Diseases

The aforementioned entities may be thought of as only the tip of the iceberg when it comes to biologic agents in dermatology. A wide variety of other conditions have been reported to respond to biologics such as TNF-α inhibitors and IL-12/IL-23 blockers, likely related to their far-reaching interactions in the inflammatory cascade. These conditions include vasculitides such as granulomatosis with polyangiitis and microscopic polyangiitis,[87] graft-versus-host disease,[88] pityriasis rubra pilaris,[89-91] multicentric reticulohistiocytosis,[92,93] and atopic dermatitis.[94,95] A complete review of these indications is beyond the scope of this column, but hopefully the discussion will support at least a search of available treatments when the next patient with an intractable inflammatory dermatosis comes into the office.

Conclusion

If the last 10 to 20 years serve as any indication, dermatologists likely will find innovative and inventive ways to use new biologics as they emerge for skin diseases that were previously difficult to treat. Although the most well-known and commonly used indication for biologic therapies remains psoriasis, for the TNF-α inhibitors and the IL-12/IL-23 blocker ustekinumab, these medications along with rituximab and other novel agents have found use in other difficult-to-treat skin diseases. Becoming comfortable with the use of biologics in general and being familiar with possible applications in recalcitrant inflammatory skin disease will greatly enhance a practicing dermatologist's pharmaceutical arsenal; however, serious side effects can occur, and the risk for paradoxical exacerbation or triggering of other skin diseases with use of biologics is very real. As we come to understand the exact situations where biologic therapy can be helpful and improve our patient selection for treatment with biologics, hopefully these occurrences will diminish and we can continue to use these novel medications to improve our patients' lives.

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