The Post-PASI Era: Considering Comorbidities to Select Appropriate Systemic Psoriasis Treatments

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Psoriasis treatments have come a long way in the past 20 years. We now have more than a dozen systemic targeted treatments for psoriatic disease, with more on the way; however, with each successive class of medications introduced, the gap has narrowed in terms of increasing efficacy. In an era of medications reporting complete clearance rates in the 70% range, the average improvement in Psoriasis Area and Severity Index (PASI) for most biologics has remained at 90% to 95% in the past half-decade. While this is a far cry from the mean PASI improvements of 70% seen with the first biologics,[1] it is becoming more challenging to base our treatment decisions solely on PASI outcome measures.

How, then, do we approach rational selection of a systemic psoriasis treatment? We could try to delineate based on mechanism of action, but it may be disingenuous to dissect minor differences in pathways (eg, IL-17 vs IL-23) that are fundamentally related and on the same continuum in psoriasis pathophysiology. Therefore, the most meaningful way to select an appropriate therapeutic may be to adopt a patient-centered approach that accounts for both individual preferences and specific medical needs by evaluating for other comorbidities[2] to exclude or select certain medicines or types of treatments. We have long known to avoid tumor necrosis factor (TNF) α inhibitors in patients with congestive heart failure or a history of demyelinating disorders while regularly considering the presence of psoriatic arthritis and family planning when making treatment decisions. Now, we can be more nuanced in our approaches to psoriasis biologics. Specifically, the most important comorbidities to consider broadly encompass cardiometabolic disorders, gastrointestinal conditions, and psychiatric conditions.

Cardiometabolic Disorders

Possibly the hottest topic in psoriasis for some years now, the relationship between cardiometabolic disorders and psoriasis is of great interest to clinicians, scientists, and patients alike. There is a clear link between development of atherosclerosis and Th17-related immune mechanisms that also are implicated in the pathogenesis of psoriasis.[3] Furthermore, the incidence of cardiovascular disease is markedly increased in patients with psoriasis, which is an independent risk factor for myocardial infarction, particularly among younger patients.[4,5] Although several retrospective studies[6-8] have shown that TNF-α inhibitors are associated with a reduction in cardiovascular outcomes, it is yet to be seen whether biologic treatment actually has a direct impact on cardiovascular outcomes, multiple studies investigating the effect of biologics on arterial inflammation markers notwithstanding.[9]

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There are some direct factors to keep in mind when considering cardiometabolic comorbidities in patients with psoriasis. Obesity is common in the psoriasis population and can have a direct negative effect on cardiovascular health.[10] However, the data on obesity and psoriasis are somewhat mixed with regard to treatment outcomes. In general, with increased volumes of distribution for biologics in patients with obesity, it has been shown that treatment success is more difficult to achieve in those with a body mass index greater than 30.[11] Rather surprisingly, a separate nationwide study in South Korea found that patients on biologics for psoriasis were more likely to experience weight gain, even after controlling for factors such as exercise, smoking, and drinking,[12] but it is unclear whether this is driven mostly by a known connection between weight gain and TNF-α inhibitors.[13] These contrasting results point to the need for further studies in this area, as our intuitive approach would involve promoting weight loss while starting on a systemic treatment for psoriasis—but perhaps it is important not to assume that one will come with the other in tow, reinforcing the need to discuss a healthy diet with our patients with psoriasis regardless of treatment decisions.

The data that we have do not directly answer the big questions about biologic treatment and cardiovascular health, but we are starting to see interesting signals. For example, in a report of tildrakizumab treatment in patients with and without metabolic syndrome, the rates of major adverse cardiovascular events as well as cardiac disorders were essentially the same in both groups after receiving treatment for up to 244 weeks.[14] This is interesting, more because of the lack of an increase in cardiovascular adverse events in the metabolic syndrome group, who entered the trial on average 25 kg to 30 kg heavier than those without metabolic syndrome. There is an increased risk for adverse cardiovascular events among patients with metabolic syndrome, a roughly 2-fold relative risk in as few as 5 to 6 years of follow-up.[15] While the cohorts in the tildrakizumab study[14] were too small to draw firm conclusions, the data are interesting and a step in the right direction; we need much larger data sets for analysis. Among other agents, similar efficacy and safety have been reported for guselkumab in a long-term psoriasis study; as a class, IL-23 inhibitors also tend to perform well from an efficacy standpoint in patients with obesity.[16]

Overall, when assessing the evidence for cardiometabolic disorders, it is reasonable to consider starting a biologic from the IL-17 or IL-23 inhibitor classes—thus avoiding both the potential downside of weight gain and contraindication in patients with congestive heart failure associated with TNF-α inhibitors. It is important to counsel patients about weight loss in conjunction with these treatments, both to improve efficacy and reduce cardiovascular risk factors. There may be a preference for IL-23 inhibitors in patients with obesity, as this class of medications maintains efficacy particularly well in these patients. Patients with psoriasis should be counseled to follow up with a primary care physician given their higher risk for metabolic syndrome and adverse cardiovascular outcomes.

Gastrointestinal Conditions

Psoriasis and inflammatory bowel disease (IBD) have a bidirectional association, and patients with psoriasis are about 1.7 times more likely to have either Crohn disease or ulcerative colitis.[17,18] This association may be related to a shared pathogenesis with regard to immune dysregulation and overactivated inflammatory pathways, but there are some important differences to consider from a therapeutic standpoint. Given the increased expression of IL-17 in patients with IBD,[19] a phase II trial of secukinumab yielded surprising results—not only was secukinumab ineffective in treating Crohn disease, but there also were higher rates of adverse events[20] (as noted on the product label for all IL-17 inhibitors). We have come to understand that there are regulatory subsets of IL-17 cells that are important in mucosal homeostasis and also regulate IL-10, which generally is considered an anti-inflammatory cytokine.[21] Thus, while IL-17 inhibition can reduce some component of inflammatory signaling, it also can increase inflammatory signaling through indirect pathways while increasing intestinal permeability to microbes. Importantly, this process seems to occur via IL-23–independent pathways; as such, while direct inhibition of IL-17 can be deleterious, IL-23 inhibitors have become important therapeutics for IBD.[22]

One further nuance is that, of the 6 members of the IL-17 family, IL-17A clearly is the culprit for worsening colitis as evidenced by both human and animal models. On the contrary, IL-17F blockade has been shown to ameliorate colitis in a murine model, whereas IL-17A inhibition worsens it.[23] Furthermore, dual blockade of IL-17A and IL-17F has a protective effect against colitis, suggesting that the IL-17F inhibition is dominant. This interesting finding has some mechanistic backing, since blockade of IL-17F induces Treg cells that serve to maintain gut epithelium homeostasis and integrity.[24]

Overall, IL-17A inhibitors should be avoided in patients with a history of IBD—namely, secukinumab and ixekizumab. While there may be theoretical reasons that brodalumab or bimekizumab may confer a somewhat different risk for IBD exacerbation, there may be better choices that would be expected to effectively treat both the psoriasis and IBD manifestations. Given the US Food and Drug Administration approval of IL-23 inhibitors for IBD and their high levels of efficacy in treating psoriasis, these likely will be the best choice for most patients. Another mainstay of IBD treatment is TNF-α inhibitors, but they come with other risks such as increased immunosuppression and increased risk for nonmelanoma skin cancer.

An important question remains: What about patients who do not have known IBD? Do we proactively change our treatment choice due to fear of IBD development given the higher incidence of both Crohn disease and

ulcerative colitis in patients with psoriasis? What about patients with a family history of IBD? First-degree relatives of patients with Crohn disease and ulcerative colitis have an 8- and 4-fold higher risk for those same conditions, respectively.[25] Postmarketing surveillance and database findings of low rates of IBD development with IL-17 inhibitors gives only modest reassurance, as dermatologists generally know to avoid these medications for patients with even questionable IBD symptoms. It is important to emphasize to our patients that in no case do we believe that a psoriasis medication actually will cause IBD—rather, someone with subclinical IBD could experience a flare and a first manifestation of colitis. The drug is not the culprit in inducing IBD but rather may serve to unmask existing disease.

One study suggested that for patients who move on to the IL-17 inhibitor secukinumab after being treated with TNF-α inhibitors for psoriasis, the rates of IBD development are higher (4.8%) than in those who start IL-17A inhibition without prior treatment (1%)(OR, 8.38; P=.018).[26] This begs the question of whether subclinical IBD in many patients with psoriasis who are treated with TNF-α inhibitors can be unmasked later when they are transitioned to a treatment that either does not treat the IBD or could worsen it. There may be a mechanistic drive behind this sequencing of treatments that predisposes patients to colitis, which would suggest selecting an IL-23 inhibitor after failing/trying a TNF-α inhibitor. However, the data are very preliminary, and in real practice, other concerns such as severe psoriatic arthritis may outweigh these considerations, as the IL-17 inhibitor class still is considered to be more effective than IL-23 inhibition at treating psoriatic arthritis overall. For most patients with no personal history of IBD and no strong family history of IBD (ie, first-degree relatives), the choice of biologic should not be affected by concern over gastrointestinal issues.

Psychiatric Conditions

It has been well established that psoriasis is linked to higher rates of depression, anxiety, and suicidality.[27] How do we take this into account when treating patients with psoriasis, especially when we have biologics with a warning label for suicidality and a Risk Evaluation and Mitigation Strategies program (brodalumab) and language around suicidal ideation in the label (bimekizumab)? While it is challenging to discuss mental health, it is not a conversation that we as dermatologists should shy away from. Appropriate treatment of psoriasis is an important tool to get our patients on the path to better mental health. A recent database study of more than 4000 patients showed that patients with psoriasis treated with biologics had a 17% lower risk for depression than those treated with conventional disease-modifying drugs such as methotrexate.[28] The comparator of the conventional disease-modifying drug class is important as it serves as a control for disease severity. Too often, a higher rate of depression, anxiety, or suicidality can be attributed to a medication when we in fact may just be capturing the background of higher incidence of all 3 in patients with severe psoriasis.

Indeed, even with the medication that many worry about on this front (brodalumab), multiple studies have confirmed that the effect on mental health generally is a positive one, with decreases in depressive symptoms.[29] In a cohort switched from TNF-α inhibitors to brodalumab, symptoms of depression actually improved,[30] so attributing a direct treatment effect to negative mental health outcomes does not seem to be justified, especially in light of the low number of suicide events in global postmarketing surveillance for brodalumab, comparable to or lower than other biologics for psoriasis.[31] Similarly, bimekizumab has language in the label about discussing suicidality with patients, although the rates of suicidal ideation and behavior are no different from other biologics and rates of depression improved with its use.[32]

Heightened awareness of our patients' mental health is something that we as providers should embrace, even when it seems that we do not have much time to see each patient. The priority when a patient comes in with mental health symptoms should be to treat what is within our scope (ie, psoriasis) as quickly and effectively as possible—with a newer-generation biologic such as an IL-17 or IL-23 inhibitor—while encouraging the patient to seek care from a mental health professional. In these cases, one might even argue that the rapidity of action of IL-17 inhibitors may be of additional benefit.

Final Thoughts

We as dermatologists generally are tasked with seeing high volumes of patients, and an initial psoriasis consultation can be a lengthy visit; however, it is rewarding to establish this relationship with patients and a reminder of why we practice medicine to begin with. Psoriasis can be satisfying to treat, and we have so many highly effective medicines that can completely transform our patients' lives. Applying an understanding of the interplay between psoriasis, its related comorbidities, and treatment choices can be a fulfilling exercise that captures the essence of shared decision-making, which can lead to better outcomes and satisfaction for both providers and patients.

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