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TILDRAKIZUMAB IN PATIENTS WITH METABOLIC SYNDROME: A NOVEL APPROACH

Tildrakizumab is a high-affinity, humanized, IgG1 k antibody targeting interleukin 23 p19 to treat patients with chronic plaque psoriasis.[1] The Food and Drug Administration (FDA) approved ILUMYA™ (tildrakizumab-asmn) for the treatment of adults with moderate-to-severe plaque psoriasis who are candidates for systemic therapy or phototherapy in March 2018 and it has also been approved in Australia, Japan and numerous European countries. The approved recommended dosage of ILUMYA™ in the United States is a subcutaneous injection of 100 mg at Weeks 0, 4, and every 12 weeks thereafter.[2] In Canada, tildrakizumab has not yet been approved for the treatment of moderate-to-severe plaque psoriasis.

This article presents a fictitious case study of a patient who may be a good candidate for tildrakizumab and provides an underlying rationale for the choice of tildrakizumab in this clinical scenario.

A 39-year-old male presents to the office for a repeat visit for severe psoriasis. He has had psoriasis for 6 years and has failed topical therapy, and oral systemic agents. His past medical history is significant for obesity, hypertension, and impaired fasting glucose tolerance. His current medications include a multi-vitamin and an angiotensin receptor blocker. His family history is significant for obesity, hypertension, diabetes, and myocardial infarction. He travels quite frequently for work and, therefore is not able to commit to a phototherapy schedule. In choosing a biologic therapy, the new class of anti-IL23p19 agents have distinct

clinical advantages that may be beneficial for this type of patient.

Injection Frequency and Injection Site Reactions

Anti-IL23p19 agents, such as risankizumab and tildrakizumab, and anti-IL12/23 agents, like ustekinumab, have the longest interval between injections. All are dosed at week 0, week 4 and then every 12 weeks thereafter.[2-4] As well, anti-IL23p19 agents have a lower incidence of injection site reactions (<0.5%) in comparison to agents like ixekizumab (7.7 to 10% from UNCOVER-3) and adalimumab[5,6]

Efficacy

Anti-IL23p19 agents have high rates of clinical efficacy and durability. In reSURFACE 1 and reSURFACE 2, with tildrakizumab 100mg dosing, up to 64% of patients achieved a PASI 75 score, 35% achieved a PASI 90 score, 14% achieved a PASI 100 score and 59% achieved a PGA score of 0 or 1 at week 12 after 2 doses of drug.[7] Over time, the durability of responses to tildrakizumab are very stable with most patients maintaining their responses and others achieving an even higher level of psoriasis clearance. At 148 weeks, using non-responder imputation, patients on tildrakizumab 100 mg dosing achieved a PASI 75 rate of 72.6%, a PASI 90 rate of 53.8% and a PASI 100 rate of 28.9%. These results are comparable to other anti-IL23p19 and anti-IL17 agents.[5]

Cardiometabolic Effects

Patients with psoriasis have a higher degree of obesity (OR = 1.8), hypertension (OR = 1.58), diabetes (OR = 1.76) and dyslipidemia (OR = 1.04 to 5.55).[8] Severe psoriasis by itself can also confer a 6.2% increased absolute risk of developing a major adverse cardiovascular event (MACE) compared to the general population.[9] All of these factors combined, greatly increase the risk of cardiac and cerebrovascular events leading to significantly more morbidity and mortality in psoriasis patients.

The concern with using biologic therapy in this group of patients, is that metabolic syndrome itself can lower the patient's response to these biologic agents resulting in lower PASI responses and more long-term drug failure.[10] However, the efficacy of tildrakizumab was the same, irrespective of patients having pre-existent metabolic syndrome. In general, patients with metabolic syndrome had higher body weight, BMI, cardiovascular disease and diabetes mellitus, compared with patients without metabolic syndrome in tildrakizumab studies. The efficacy of both tildrakizumab 100- and 200-mg doses was maintained over 148 weeks of the study without evidence of reduced drug survival in patients with metabolic syndrome.[11-14]

Recent studies using biologic therapy have sought to elucidate the relationship between the reduction of systemic inflammation and by extension the mitigation of cardiometabolic events associated with untreated psoriasis. A recent study in *JAMA Cardiology*, that followed psoriasis patients from 2013-2019, analyzed 134 patients (82 on biologic therapy and 52 with skin-directed therapy). The investigators measured coronary inflammation via computed tomography angiography (CTA) by assessing fat attenuation index (FAI). The results demonstrated that patients on biologic therapy had greater improvements in PASI scores and only they had reduction of high sensitivity CRP scores (HS-CRP) as evaluated by FAI.[15] Another recent publication by Elbanawi et al in 2019 followed 121 patients who were all biologic naïve at baseline (89 biologic, 32 topical/light) and at 1 year of follow up, found a 5% reduction in coronary plaque build-up in the biologic group.[16]

A recent paper by Mehta (2019) showed clinically relevant numerical decreases in fasting glucose, triglycerides, and systolic blood pressure over time in patients treated with tildrakizumab.[17] Cautious extrapolation would suggest that using tildrakizumab might be efficacious regardless of underlying metabolic syndrome status. Lebwohl et al (2020) came to a similar conclusion after a post-hoc analysis of reSURFACE 1 and reSURFACE 2 noting that the efficacy, safety and drug survival of tildrakizumab was comparable in psoriasis irrespective of underlying metabolic syndrome.[18]

A recent study presented at the 28th European Academy of Dermatology and Venereology Congress (EADV) illustrated the benefits of tildrakizumab for patients with psoriasis with comorbid metabolic syndrome. Over 3 years, 75% to 100% skin clearance was reached and sustained equally in patients with and without metabolic syndrome. Metabolic syndrome is determined by elevated blood pressure, body mass index/obesity, triglycerides, glucose, and low HDL cholesterol levels.[19]

In reSURFACE 1, 69% and 71% of patients with and without metabolic syndrome achieved PASI 75, respectively; 42% and 51% of patients with and without metabolic syndrome achieved PASI 90, respectively; and 27% and 23% of patients with and without metabolic syndrome achieved PASI 100, respectively at week 12.

In reSURFACE 2, 73% and 79% of patients achieved PASI 75; 57% and 60% achieved PASI 90; and 34% and 32% achieved PASI 100, respectively at week 12.[5]

In our fictitious patient case, there would be confidence in using an agent that works in spite of metabolic syndrome and works to perhaps lower risk factors at the same time.

Safety

Over 148 weeks of therapy, the rate of treatment emergent adverse events for tildrakizumab 100 mg, tildrakizumab 200 mg, placebo and etanercept were 35.2, 37.2, 148.6 and 148.6 events per 100 patient years. The most common adverse events were nasopharyngitis, upper respiratory tract infection, influenza, bronchitis, and sinusitis. Overall, there were low rates of severe infections, malignancies, and MACE for treatment with tildrakizumab over a 148-week period. All adverse events were comparable to placebo and there were no new or unexpected adverse events concerning *candida* infections, exacerbation of inflammatory bowel disease, suicidal ideation or behavior or any other treatment emergent adverse event.[5]

Summary

In conclusion, tildrakizumab is an effective, durable, and safe therapy with a convenient injection frequency. There is robust data to suggest that tildrakizumab works well in those with metabolic syndrome and may lower the risk of metabolic disease itself leading to improved patient outcomes. Based on these known facts, our patient may greatly benefit from tildrakizumab therapy.

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