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PERSPECTIVES AND INSIGHTS ON TILDRAKIZUMAB

TILDRAKIZUMAB FOR MODERATE-TO-SEVERE PLAQUE PSORIASIS: AN EVIDENCE-BASED REVIEW

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TILDRAKIZUMAB IN PATIENTS WITH METABOLIC SYNDROME: A NOVEL APPROACH

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THE ERA OF IL-23: INTRODUCTION OF TILDRAKIZUMAB

Targeting the p19 subunit of interleukin (IL)-23 has been a major development in the management of plaque psoriasis because of the durable efficacy and safety of this mechanism of action. This supplement will review the pivotal data in the tildrakizumab development program: reSURFACE-1 and reSURFACE-2. Dr. Devani and Dr. Prajapati provide a comprehensive evidence-based review of the pivotal trials including the post-hoc analyses which review specific patient subpopulations, interruption/retreatment as well as a discussion of patient-level PASI score distributions across severities. Dr. Grewal also discusses the benefit of tildrakizumab treatment in patients with the comorbidity of metabolic syndrome using a case-based approach.

Since this supplement was prepared, there have been updates presented at the late-breaking session of the virtual EADV 2020 meeting. Specifically, the 5-year efficacy and safety data of the long-term extension trials of the reSURFACE clinical trial program were presented. The long-term durable relative PASI responses were reported with PASI75 rates of 89%, PASI90 rates of 66% and PASI100 rates of 33% in subjects receiving tildrakizumab 100 mg. The more clinically meaningful absolute achievements, including PASI <5 in 89%, PASI <3 in 79% and PASI <1 in 48% at 5 years of treatment with tildrakizumab 100 mg, based on multiple imputation analysis, were also presented.

Additional data encompassing over 5,400 patient years of exposure to tildrakizumab, included low rates of treatment emergent adverse events (TEAEs) at 27 events per 100 patient years (PY), and low rates of discontinuation due to TEAEs, at less than 2 per 100 PY was also presented. Severe infection rates were low at 1.2 per 100 PY and rates of major adverse cardiovascular events (MACE), malignancy and hypersensitivity were all less than 1 per 100 PY. Also new this year was the presentation of the Phase 2b psoriatic arthritis program at the virtual EULAR 2020 by Mease et al. showing promising efficacy that will need to be confirmed in future Phase 3 trials.

Although some patients may benefit from the high levels of response with IL-17 inhibitors for both skin and joint disease, and the broader treatment of TNF inhibitors (i.e. treating skin, joints and bowel disease) clinicians need to consider that IL-23 therapy is also simple, convenient and safe. Tildrakizumab requires 4 doses per year after the loading dose, has been proven to be both effective and safe over the long-term and data shows that targeting IL-23 is also effective in treating the joints and the bowel, with other programs investigating IL-23 inhibition in psoriatic arthritis and inflammatory bowel disease. Given the chronic nature of plaque psoriasis, these late-breaking 5-year durable efficacy and safety data are important additions to medical knowledge, thereby allowing clinicians to make informed decisions when choosing the right therapy for their patients.

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Dr. Devani completed his dermatology residency at the University of Alberta, earning certification in both Canada and the United States. Dr. Devani has received 5 major awards; authored 1 textbook chapter; published 10 peer-reviewed manuscripts in print or electronic format; and presented at numerous scientific meetings regionally and nationally. He currently practices at the Skin Health and Wellness Centre and the Dermatology Research Institute. Dr. Devani also conducts clinical trials for both adults and children and is the co-creator of The Dermatology Philosophy, as well as the co-founder and co-director of the Dermatology Learning Institute, Dermatology Research Institute, and Dermphi Therapeutics. He is an expert in acne, atopic dermatitis, psoriasis, skin cancer, and anti-aging.

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TILDRAKIZUMAB FOR MODERATE-TO-SEVERE PLAQUE PSORIASIS: AN EVIDENCE-BASED REVIEW

Introduction

Tildrakizumab is a fully human monoclonal antibody that selectively targets the p19 subunit of interleukin-23 (IL-23). It has been approved for the treatment of adults with moderate-to-severe plaque psoriasis in several

countries. The standard dose is 100 mg by subcutaneous injection at weeks 0 and 4, then every 12 weeks thereafter, although a 200 mg dosage at the same interval does have approval in some jurisdictions.[1,2]

The aim of this article is to review the available evidence for tildrakizumab in treating moderate-to-severe chronic plaque psoriasis. In-depth discussion will be limited to pivotal studies and post hoc analyses.

Pivotal Studies

In the pivotal phase 2b study, tildrakizumab was compared to placebo.[3] This was a three-part, double-blind, randomized controlled trial. The primary endpoint was PASI 75 at week 16, while key secondary endpoints included PASI 75 at weeks 12 and 52, PASI 90 at week 16, PGA response at weeks 16 and 52, time to PASI 75, and mean change in DLQI at week 16. Safety was assessed in the all-participants-as-treated population.

A total of 355 subjects were randomized (1:2:2:2:1) to tildrakizumab 5 mg (n=42), tildrakizumab 25 mg (n=92), tildrakizumab 100 mg (n=89), tildrakizumab 200 mg (n=86), and placebo (n=46).[3] At week 16, tildrakizumab 5 mg, tildrakizumab 25 mg, tildrakizumab 100 mg, and tildrakizumab 200 mg were superior to placebo for PASI 75 (33%, 64%, 66%, and 74%, respectively, versus 4%; p≤0.001) and PGA 0/1 (33%, 58%, 62%, and 74%, respectively, versus 2%; p<0.001). At week 16, tildrakizumab 25 mg, tildrakizumab 100 mg, and tildrakizumab 200 mg were also superior to placebo for PASI 90 (25%, 39%, and 52%, respectively, versus 2%; p<0.001). In addition, the proportion of subjects achieving PASI 75 at week 12 was significantly greater (p≤0.001) for tildrakizumab 5 mg (24%), tildrakizumab 25 mg (59%), tildrakizumab 100 mg (61%), and tildrakizumab 200 mg (72%) compared with placebo (4%). The median time to PASI 75 in subjects receiving tildrakizumab was 85 days (25 mg), 84 days (100 mg), and 57 days (200 mg). Improvements in DLQI were noted for all tildrakizumab treatment groups compared with placebo. For PASI 75 responders at week 16, over 90% of these subjects continuing to receive doses of either 100 mg or 200 mg of tildrakizumab maintained PASI 75 through week 52. Furthermore, 96% and 93% of subjects receiving doses of 100 mg and 200 mg of tildrakizumab, respectively, maintained PASI 75 at week 72 following treatment discontinuation at week 52, with only 4% (8/222) of the PASI 75 responders at week 52 experiencing relapse.

With respect to safety, the most common adverse events (AEs) were nasopharyngitis and headache.[3] The frequency of serious AEs was low. One patient receiving tildrakizumab 100 mg died. This individual had a history of alcohol abuse. Adjudication was unable to determine the cause of death. AEs of special interest, such as severe infections, malignancies, and major adverse cardiac events (MACE), were rare.

In the two pivotal phase 3 studies (reSURFACE 1 and reSURFACE 2), tildrakizumab was compared to placebo and etanercept.[4] These were parallel group, double-blind, randomized controlled trials. Each had three parts. For both reSURFACE 1 and reSURFACE 2, the co-primary endpoints were PASI 75 and PGA response (score of 0 or 1 with ≥2 grade score reduction from baseline) at week 12, while key secondary endpoints included PASI 90, PASI 100, and DLQI 0/1 at week 12. For reSURFACE 2, PASI 75, PGA response, and DLQI 0/1 at week 28 were also key secondary endpoints. Safety was assessed in the all-participants-as-treated population.

In reSURFACE 1 (n=772), subjects were randomized (2:2:1) to tildrakizumab 200 mg (n=308), tildrakizumab 100 mg (n=309), or placebo (n=155).[4] At week 12, tildrakizumab 200 mg and tildrakizumab 100 mg were superior to placebo (p<0.0001) for PASI 75 (62% and 64%, respectively, versus 6%), PASI 90 (35% and 35%, respectively, versus 3%), PASI 100 (14% and 14%, respectively, versus 1%), PGA response (59% and 58%, respectively, versus 7%), and DLQI 0/1 (44% and 42%, respectively, versus 5%). In reSURFACE 2 (n=1090), subjects were randomized (2:2:1:2) to tildrakizumab 200 mg (n=314), tildrakizumab 100 mg (n=307), placebo (n=156), or etanercept 50 mg twice weekly (n=313). At week 12, tildrakizumab 200 mg and tildrakizumab 100 mg were superior to placebo and etanercept for PASI 75 (66% and 61%, respectively, versus 6% and 48%, respectively; p<0.0001 for both tildrakizumab groups versus placebo; p<0.0001 for tildrakizumab 200 mg versus etanercept; p=0.0010 for tildrakizumab 100 mg versus etanercept). In addition, tildrakizumab 200 mg was superior to placebo and etanercept for PGA response (59% versus 4% and 48%, respectively; p<0.0001 for tildrakizumab 200 mg versus placebo; p=0.0031 for tildrakizumab 200 mg versus etanercept), while tildrakizumab 100 mg was superior to placebo,

but not significantly different than etanercept, for PGA response (55% versus 4% and 48%, respectively; p<0.0001 for tildrakizumab 100 mg versus placebo; p=0.0663 for tildrakizumab 100 mg versus etanercept). In both studies, a higher proportion of subjects achieved PASI 75, PASI 90, PASI 100, PGA response, and DLQI 0/1 with both doses of tildrakizumab at week 28 compared to week 12. Additionally, subjects initially assigned to placebo but subsequently re-randomized to receive either dose of tildrakizumab improved from week 12 to week 28 and had similar levels of response to those receiving either dose of tildrakizumab continuously from baseline **(Figure 1 and 2).**

With respect to safety, the most common AE in both reSURFACE 1 and reSURFACE 2 was nasopharyngitis.[4] The frequency of serious AEs was low and similar across treatment groups. One patient receiving tildrakizumab 100 mg died in reSURFACE 2. This individual had alcoholic cardiomyopathy and steatohepatitis. Adjudication was unable to determine the cause of death. For AEs of special interest, such as severe infections, malignancies, and MACE, no significant differences were noted between the treatment groups.

A long-term extension of the pivotal phase 3 studies (reSURFACE 1 and reSURFACE 2) evaluated efficacy and safety of both tildrakizumab doses at week 148.[5] Efficacy was assessed for responders (PASI ≥75) and partial responders (PASI =50 to <75) to tildrakizumab 200 mg and tildrakizumab 100 mg at week 28. Responders were subsequently maintained on the same dose of tildrakizumab (every 12 weeks) while partial responders either stayed on the same dose of 200 mg tildrakizumab or were titrated to 200 mg tildrakizumab if they had been initiated on the 100 mg dose. Efficacy was also assessed for partial responders and non-responders (PASI <50) to etanercept 50 mg at week 28 who were subsequently (after 4-week washout) switched to tildrakizumab 200 mg (at weeks 32 and 36, then every 12 weeks). Safety was assessed in the all- patients-as-treated population.

	Tildrakizumab 200 mg (n=308)	Tildrakizumab 100 mg (n=309)	Placebo (n=154)
PASI 75	**62%**	**64%**	**6%**
% difference from placebo (95% CI; p value)	56.6% (49.6-62.8; p<0.0001)	58.0% (51.0-64.1; p<0.0001)	N/A
Clear or minimal PGA	**59%**	**58%**	**7%**
% difference from placebo (95% CI; p value)	52.1% (44.8-58.5; p<0.0001)	50.9% (43.6-57.4; p<0.0001)	N/A
PASI 90	**35%**	**35%**	**3%**
% difference from placebo (95% CI; p value)	32.9% (26.8-38.8; p<0.0001)	32.1% (25.9-38.0; p<0.0001)	N/A
PASI 100	**14%**	**14%**	**1%**
% difference from placebo (95% CI; p value)	12.7% (8.3-17.2; p<0.0001)	12.7% (8.0-17.3; p<0.0001)	N/A
DLQI score 0 or 1	**44%**	**42%**	**5%**
% difference from placebo (95% CI; p value)	38.9% (31.9-45.4; p<0.0001)	36.1% (26.3-42.5; p<0.0001)	N/A

The full analysis set population included all randomly assigned patients who received at least one dose of study medication. % differences and 95% CIs were calculated with the Miettinen-Nurminen method and stratified by bodyweight (≤90 kg vs >90 kg) and previous exposure to biologic therapy for psoriasis (yes or no) with sample size weights. p values were calculated with the Cochran-Mantel-Haenszel and stratified by bodyweight and exposure to biologic therapies; p values were not adjusted for multiplicity. Non-responder imputation was pre-specified and is shown for all data, except for DLQI, which were observed data. PASI=Psoriasis Area and Severity Index. N/A=not applicable. PGA=Physician's Global Assessment. DLQI=Dermatology Life Quality Index.

Figure 1. Primary and secondary efficacy endpoints at 12 weeks in reSURFACE 1 part 1 (full analysis set); adapted from Reich et al, 2020

Using the non-responder imputation (NRI) method to account for missing efficacy data, PASI 75, PASI 90, and PASI 100 responses at week 148 were: 80%, 60%, and 33%, respectively, for responders to tildrakizumab 200 mg; 73%, 54%, and 29%, respectively, for responders to tildrakizumab 100 mg; 47%, 28%, and 13%, respectively, for partial responders to tildrakizumab 200 mg; 33%, 25%, and 10%, respectively, for partial responders to tildrakizumab 100 mg; and 67%, 44%, and 15%, respectively, for partial responders or non-responders to etanercept 50 mg.[5] With respect to safety, rates of discontinuation due to AEs and exposure-adjusted serious AEs, such as severe infections, malignancies, and MACE, were low and comparable across all treatment groups, although severe infection rates tended to be higher

	Tildrakizumab 200 mg (n=314)	Tildrakizumab 100 mg (n=307)	Placebo (n=156)	Etanercept (n=313)
PASI 75	**66%**	**61%**	**6%**	**48%**
% difference from placebo (95% CI; p value)	59.8% (52.9 to 65.9; p<0.0001)	55.5% (48.3 to 61.8; p<0.0001)	N/A	N/A
% difference from etanercept (95% CI; p value)	17.4% (9.7 to 24.9; p<0.0001)	13.1 (5.3 to 20.7; p=0.001)	N/A	N/A
Clear or minimal PGA	**59%**	**55%**	**4%**	**48%**
% difference from placebo (95% CI; p value)	54.7 (47.9 to 60.8; p<0.0001)	50.2 (43.2 to 56.5; p<0.0001)	N/A	N/A
% difference from etanercept (95% CI; p value)	11.7 (4.0 to 19.3; p=0.0031)	7.3 (-0.5 to 15.0; p=0.0663)	N/A	N/A
PASI 90	**37%**	**39%**	**1%**	**21%**
% difference from placebo (95% CI; p value)	35.3% (29.2 to 41.1; p<0.0001)	37.5% (31.1 to 43.4; p<0.0001)	N/A	N/A
% difference from etanercept (95% CI; p value)	15.2% (8.3 to 22.1; p<0.0001)	17.4% (10.3 to 24.4; p<0.0001)	N/A	N/A
PASI 100	**12%**	**12%**	**0**	**5%**
% difference from placebo (95% CI; p value)	11.7% (7.8 to 16.0; p<0.0001)	12.4% (8.5 to 16.6; p<0.0001)	N/A	N/A
% difference from etanercept (95% CI; p value)	7.0% (2.8 to 11.6; p=0.0014)	7.6% (3.3 to 12.3; p=0.0006)	N/A	N/A
DLQI	**47%**	**40%**	**8%**	**36%**
% difference from placebo (95% CI; p value)	39.3% (31.8 to 46.1; p<0.0001)	32.1% (24.5 to 39.1; p<0.0001)	N/A	N/A
% difference from etanercept (95% CI; p value)	11.9% (4.1 to 19.5; p=0.0029)	4.8% (-2.9 to 12.5; p=0.2206)	N/A	N/A

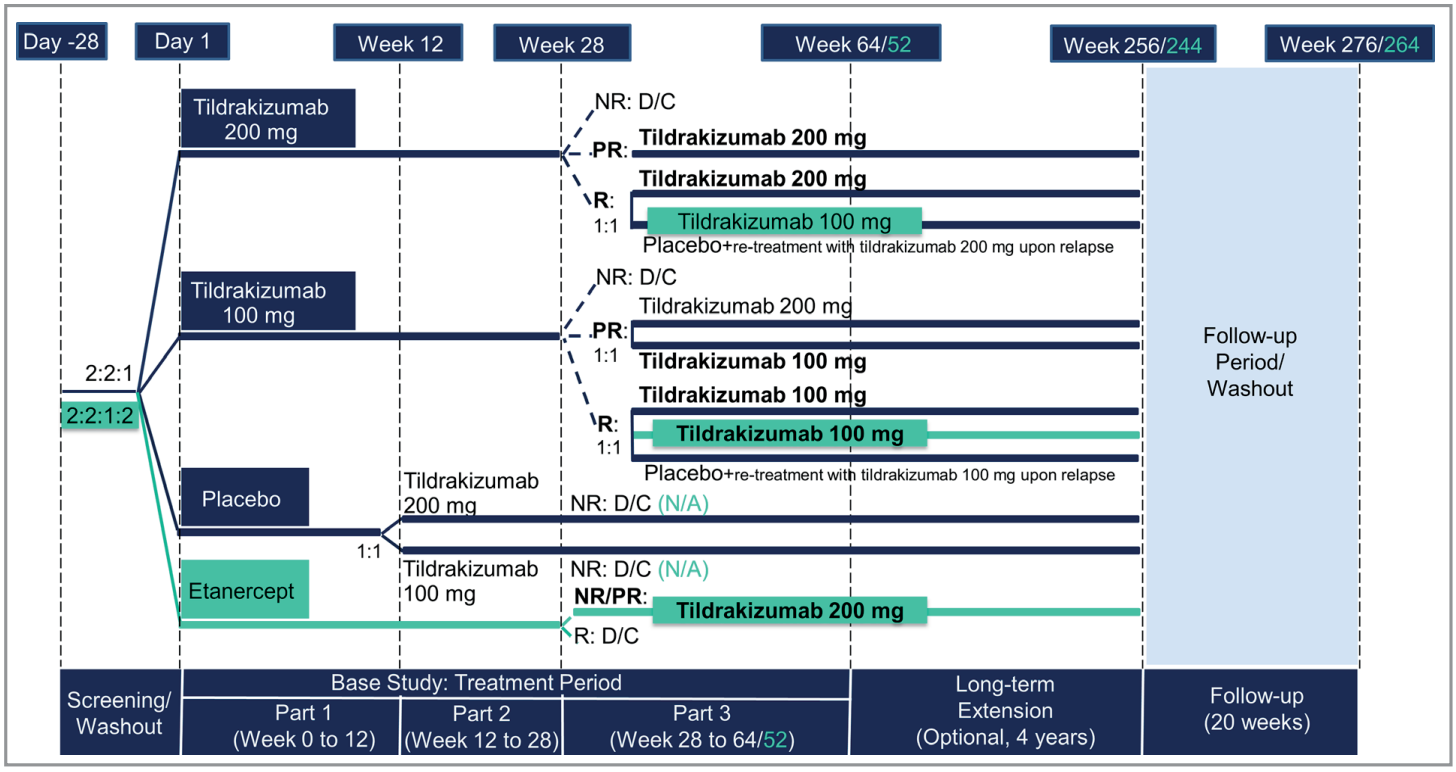
The full analysis set population included all randomly assigned patients who received at least one dose of study medication. % differences and 95% CIs were calculated with the Miettinen-Nurminen method and stratified by bodyweight (≤90 kg vs >90 kg) and previous exposure to biologic therapy for psoriasis (yes or no) with sample size weights. p values were calculated with the Cochran-Mantel-Haenszel (CMH) and stratified by bodyweight and exposure to biologic therapies; p values were not adjusted for multiplicity. Non-responder imputation was pre-specified and is shown for all data, except for DLQI, for which were observed data are shown. PASI=Psoriasis Area and Severity Index. N/A=not applicable. PGA=Physician's Global Assessment. DLQI=Dermatology Life Quality Index.

Figure 2. Primary and secondary efficacy endpoints at 12 weeks in reSURFACE 2 part 1 (full analysis set); adapted from Reich et al, 2020

for etanercept 50 mg. A total of nine deaths occurred during the 148-week study period—none were deemed related to the medication by the investigators.

Post Hoc Analyses

In a post hoc analysis of the efficacy data from the combined pivotal phase 2 and 3 studies (n=2081), it was found that tildrakizumab 200 mg (n=708) and tildrakizumab 100 mg (n=705) were superior to placebo (n=355) at week 12 (p<0.0001) for PASI 75 (65% and 62%, respectively, versus 6%), PASI 90 (37% and 36%, respectively, versus 2%), PASI 100 (13% and 13%, respectively, versus 1%), and PGA 0/1 (60% and 57%, respectively, versus 6%).[6] Responses to tildrakizumab 200 mg (n=581) and tildrakizumab 100 mg (n=575) increased from week 12 to week 28 for PASI 75 (78% and 77%, respectively), PASI 90 (58% and 54%, respectively), PASI 100 (29% and 23%, respectively), and PGA 0/1 (70% and 66%, respectively). In the same publication, results of additional subgroup analyses were also reported.[6] The efficacy of tildrakizumab was greater in subjects with lower baseline weight versus higher baseline weight at week 12. Additionally, responses to tildrakizumab were numerically higher with the 200 mg dose compared to the 100 mg dose in those with higher baseline weight at week 12. The difference in proportion of subjects achieving PASI 75, PASI 90, PASI 100, and PGA 0/1 at week 12 with either dose of tildrakizumab was significant compared with placebo across the weight cut-offs that were investigated. The efficacy of tildrakizumab was also typically numerically greater in biologic-naïve versus biologic-experienced subjects but the difference was not statistically significant. Although PASI 75 responses with either dose of tildrakizumab versus placebo were similar in both populations, compared to those with prior biologic exposure, the PASI 90, PASI 100, and PGA 0/1 responses were generally higher in subjects without prior biologic exposure—the exception being that PASI 100 responses were similar for the 200 mg dose in biologic-naïve and biologic-experienced subjects. Lastly, baseline PASI, PGA, and BMI were not found to be predictive of PASI 90 response to tildrakizumab at weeks 12 and 28, while achievement of PASI ≥50 by week 8 with tildrakizumab was predictive of PASI ≥90 at weeks 12 and 28.



Integrated design of the reSURFACE 1 and reSURFACE 2 trials. Differences in design for reSURFACE 2 vs. reSURFACE 1 are shown in turquoise colour. Groups of interest for efficacy analyses are marked in bold. D/C, discontinued; N/A, not applicable; NR, nonresponders [< 50% improvement in Psoriasis Area and Severity Index PASI <50]; PR, partial responders PASI ≥ 50 to < 75); R, responders (PASI ≥ 75); adapted from Reich et al, 2020

Another post hoc analysis of the pivotal phase 3 studies evaluated the impact of body weight on the efficacy of tildrakizumab.[7] Data were stratified by weight deciles. At week 12, a slightly greater median percentage improvement in PASI was observed in the lower weight deciles: 87.4%, 86.6%, 83.6%, 88.9%, 81.5%, 84.3%, 83.1%, 78.0%, 76.7%, and 77.5% (lowest to highest decile). However, by week 28, these differences had narrowed: 91.6%, 91.9%, 92.6%, 90.4%, 91.1%, 90.6%, 91.2%, 87.7%, 87.0%, and 86.0% (lowest to highest decile). Treatment responses were subsequently maintained across all weight deciles: 100%, 96.9%, 96.9%, 96.6%, 96.6%, 97.2%, 95.3%, 93.4%, 93.5%, and 90.8% (lowest to highest decile).

In a post hoc analysis of the efficacy data from the pivotal phase 3 studies (n=1862), different treatment scenarios, such as continuous long-term dosing of tildrakizumab, interruption/reinitiation of tildrakizumab, dose adjustment of tildrakizumab, and switching from etanercept to tildrakizumab, were investigated.[8] For week 28 partial responders (PASI ≥50 to <75) receiving the same dosage of either 100 mg or 200 mg tildrakizumab from baseline to the end of study, continuous long-term dosing allowed a greater proportion of subjects to become responders (PASI ≥75) over time. In addition, among subjects experiencing a relapse following withdrawal of either 100 mg or 200 mg tildrakizumab (defined as a 50% reduction in the maximum PASI response), reinitiation resulted in 86% (tildrakizumab 100 mg) and 83% (tildrakizumab 200 mg) achieving PASI 75 by week 64, usually within 12 weeks of re-instituting therapy. Furthermore, PASI 75 responses to tildrakizumab increased for week 28 partial responders when the dose was subsequently adjusted from 100 mg to 200 mg, but remained consistent for week 28 responders when the dose was subsequently adjusted from 200 mg to 100 mg. Lastly, for subjects receiving 50 mg etanercept from baseline who were classified as partial responders or non-responders (PASI <50) at week 28, switching to tildrakizumab 200 mg allowed a greater proportion of subjects to become responders (PASI ≥75) over time. In all four of the above treatment scenarios, the PASI 90, PASI 100, and PGA 0/1 responses were generally consistent with the PASI 75 results.

In another post hoc analysis of the efficacy data from the pivotal phase 3 studies, patient-level PASI score distributions were used to investigate how disease activity varied across the study population before and after treatment with tildrakizumab 100 mg (n=616) and placebo (n=309).[9] Median baseline PASI was 17.9 for subjects receiving tildrakizumab 100 mg.

At week 12, median PASI was 2.9, with a dichotomous PASI 90 response rate of 37%, while 64%, 51%, and 23% achieved absolute PASI <5.0, <3.0, and <1.0, respectively. At week 28, median PASI was 1.7, with a dichotomous PASI 90 response rate of 52%, while 75%, 63%, and 38% achieved absolute PASI <5.0, <3.0, and <1.0, respectively. DLQI and PASI scores were correlated through week 28 (r=0.51, p≤0.0001). This study showed that post-treatment disease activity was more reliably estimated by absolute PASI scores compared to percentage PASI improvement, which may partially explain disparities between clinical trial efficacy and real-world effectiveness.

Several other post hoc analyses have been performed. These found that treatment with tildrakizumab resulted in rapid and progressive improvement of scalp, face, and neck involvement as evidenced by decreases in PASI scores[10]; pre-existing metabolic syndrome did not alter the efficacy, safety, and drug survival of tildrakizumab[11]; tildrakizumab was well-tolerated with low rates of serious AEs, discontinuations due to AEs, and AEs of special interest[12]; tildrakizumab did not have any additional risk of candidiasis[12], inflammatory bowel disease[12,13], MACE[12,14], malignancy[12], or suicide[12]; injection-site reactions with tildrakizumab were infrequent (tildrakizumab 200 mg: 4%; tildrakizumab 100 mg: 3%)[12]; exposure to tildrakizumab was not associated with new safety signals concerning increased rates of spontaneous abortions or birth defects/anomalies.[15]

Conclusion

Tildrakizumab has sustained efficacy, convenient dosing, and favorable safety profile. Improvements in quality of life have also been observed. Robust clinical trial data supports use of this IL-23 inhibitor for treating moderate-to-severe plaque psoriasis in adults.

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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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PERSPECTIVES AND INSIGHTS ON TILDRAKIZUMAB

TILDRAKIZUMAB FOR MODERATE-TO-SEVERE PLAQUE PSORIASIS: AN EVIDENCE-BASED REVIEW

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