A SPECIAL SUPPLEMENT OF CANADIAN DERMATOLOGY TODAY

PERSPECTIVES AND INSIGHTS ON TILDRAKIZUMAB

TILDRAKIZUMAB IN PsA: A DATA REVIEW

Juthika Thakur, MD

ABOUT THE AUTHOR

Melinda Gooderham, MSc, MD, FRCPC

Medical Director, SKin Health Investigator, Probity
Medical Research Assistant Professor, Queen's University

TILDRAKIZUMAB FOR PsA

In a previous supplement published in March 2021, we discussed the pivotal data for the interleukin (IL)-23 p19 inhibitor, tildrakizumab, for use in plaque psoriasis. The reSURFACE-1 and reSURFACE-2 clinical trial program demonstrated the durable efficacy and safety of tildrakizumab in the moderate-to-severe plaque psoriasis population. We have also seen 5-year efficacy and safety data confirming the durability of response along with no new safety concerns having arisen in the long term. Recently, tildrakizumab (Ilumya™, Sun Pharma Canada) therapy was approved for use in Canada for plaque psoriasis. The safety, efficacy, durability and convenience of four doses a year after the loading dose, makes tildrakizumab an attractive therapy for a chronic disease such as psoriasis. We also know that one-third of our psoriasis patients will develop psoriatic arthritis over their lifetime. When choosing a therapy that can treat both skin and joints, targeting IL-23 is an important option to consider. Conventional therapies for psoriatic arthritis (methotrexate, leflunomide, sulfasalazine) are burdened with tolerability issues, adverse effects and end-organ toxicity. Current biologics, including TNF-α inhibitors and IL-17 inhibitors, are quite effective for the management of psoriatic arthritis, but also suffer from tolerability issues, loss of efficacy, and adverse effects related to their mechanism of action. Tildrakizumab, and its mechanism of targeting IL-23, is also being studied in psoriatic arthritis and inflammatory bowel disease since IL-23 plays an important role in regulating these conditions as well. Currently we have other IL-23 inhibitors which have shown the importance of blocking IL-23 in the treatment of psoriatic arthritis. Guselkumab is already approved for use and emerging phase 3 clinical trial data (KEEPsAKE-1, KEEPsAKE-2) supports the use of risankizumab in psoriatic arthritis as well.

The phase 2b data for tildrakizumab in psoriatic arthritis is presented in this supplement, highlighting the expected efficacy and safety with IL-23 inhibition. Tildrakizumab is a treatment that offers all the attributes of IL-23 inhibition: safety, efficacy, convenience, and overall improvement in quality of life. High rates of ACR20/50/70 in this early phase trial look promising but phase 3 results are needed to confirm the phase 2b data. These results, along with the impact on other important domains of disease such as improvement of dactylitis and enthesitis, quality of life and long-term use data are eagerly anticipated.

ABOUT THE AUTHOR

Juthika Thakur, MD

Dr. Thakur completed her Bachelor of Medical Sciences degree from Western University and a business degree from the Richard Ivey School of Business in 2011 with honours. She then went on to graduate from Michael G. DeGroote School of Medicine at McMaster University and completed her dermatology residency at the University of Toronto serving as a co-chief resident in her final year. Since then, Dr. Thakur has written and presented her research at several national and international conferences at Canadian Dermatology Association, EADV, The World Congress of Dermatology, and published in the Ivey Business Review. She has an interest in the intersection between e-health, machine learning, and dermatology.

TILDRAKIZUMAB IN PsA: A DATA REVIEW

Case Study:

A thirty-three-year-old male with body and scalp plaque psoriasis and a history of psoriatic arthritis with established duration of seven years presented with a flare of his joint disease. The patient's previous therapy included several TNF-α inhibitors, most recently infliximab dosed at six week intervals, with the addition of leflunomide, and oral corticosteroids due to progression of his peripheral articular disease. His past medical history included depression, hypertension, and prediabetes. He is co-managed by both a dermatologist and rheumatologist who collaborate to determine the optimal treatment approach to manage his psoriatic arthritis. The case study demonstrates the ideal patient for consideration of IL-23 inhibitors for the management of psoriasis and psoriatic arthritis.

Introduction

Psoriasis is a prevalent skin disease with several associated comorbidities including depression, cardiovascular disease, metabolic syndrome, and psoriatic arthritis with personal and economic implications[1]. The economic burden of psoriasis in the USA alone is estimated to be over $112 billion USD[2]. Psoriatic arthritis has an estimated global prevalence of 0.2-0.3%[3], and likely has a similar economic burden due to effects on physical function and quality of life.

The pathogenesis of psoriasis is a result of dysregulation of T lymphocytes and dendritic cells contributing to aberrant keratinocyte proliferation. Particularly, T-helper 17 (Th17) cells are key to the overproduction of IL-17 and IL-22 which drive the pathogenesis of psoriasis and psoriatic arthritis. IL-22, along with TNF-α and IL-23 has been implicated in activating resident cells (chondrocytes, osteoblasts, osteoclasts) in the joint and at the enthesis ultimately upregulating RANKL and inducing osteoclast formation contributing to bone erosion and new bone formation[4,5]. Upstream to Th17 activation is dendritic cell driven IL-23 production, that amplifies further differentiation of Th17[4]. As such, targeting IL-23 can ablate aberrant production of IL-23, decreasing Th17 activation.

The American College of Rheumatology-National Psoriasis Foundation joint guidelines for the treatment of PsA recommend TNF-α inhibitors, and DMARDs prior to the initiation of IL-23 inhibitors; Currently, the only IL-23 inhibitor that has been approved by the FDA in patients with psoriatic arthritis is guselkumab[6]. Recently published GRAPPA treatment guidelines strongly recommended use of IL-23 inhibitors in line with other bDMARDs for the treatment of peripheral arthritis, enthesitis, and dactylitis[7].

The reSURFACE1 and reSURFACE2 trials as well as studies investigating tildrakizumab for psoriatic arthritis demonstrated similar safety profiles for tildrakizumab. Nasopharyngitis, headache and injection site reactions were the most common treatment emergent adverse events reported[8,9]. As of May 2021, tildrakizumab is Health Canada approved for the treatment of moderate-to-severe plaque psoriasis.

Pivotal Study Design

Tildrakizumab was evaluated for the treatment of psoriatic arthritis in a recent phase IIb study conducted in 8 countries across 74 sites over 52 weeks with placebo crossover at week 24. Patients over the age of 18, with a diagnosis of PsA meeting CASPAR (ClASsification criteria for Psoriatic ARthritis) criteria for > 6 months, with ≥ 3 tender or swollen joints as evaluated by an independent assessor were screened for study entry. Randomisation was computer-generated before the study and patients were stratified by prior anti-TNF-α therapy use (yes/no; prior anti-TNF-α use capped at 30% of total patients) and baseline body weight (≤ 90 kg/> 90 kg). Key inclusion criteria included stable use of NSAIDs, acceptable concomitant use of conventional systemic disease modifying antirheumatic drugs (csDMARDs) or prednisone, and the ability to maintain current background treatment for the first 24 weeks.[9] Conventional systemic DMARDs allowed included methotrexate < 25 mg per week or leflunomide < 20 mg per day for > 3 months and on a stable dose for > 8 weeks prior to the start of treatment with tildrakizumab. Patients were excluded if they had more than 1 biologic treatment or any prior use of IL-18, IL24 or IL12/23 p40 biologic therapies. Patients who were on anti-TNF-α therapy, B-cell and T-cell depleting agents, or apremilast use were excluded. Five hundred patients were screened of whom 391 patients met inclusion criteria. These patients with psoriatic arthritis were randomized and assigned 1:1:1:1:1 to receive tildrakizumab 200 mg subcutaneous every 4 weeks, tildrakizumab 200 mg, 100 mg or 20 mg every 12 weeks or placebo every 4 weeks (**Figure 1**). At 24 weeks, patients receiving tildrakizumab 20 mg or placebo were switched to receive tildrakizumab 200mg every 12 weeks.[9]

The primary end point was ACR20 response at week 24. The secondary and exploratory end points were prespecified as well, notably minimal disease activity, and ACR50/70. Additional end points are listed in **Table 1**. Patients were allowed to enroll and continue concomitant antirheumatic medications. Patients who failed to show minimal response to treatment (<10% improvement from baseline in swollen and tender joint counts) at week 16 could have background csDMARDs or oral corticosteroids adjusted according to the maximum permitted daily dose and continue in the study as a non-responder. At baseline, demographics were matched for age, sex, body mass. Patients had psoriatic arthritis for a median range of 4.4 years since diagnosis.

Treatment Efficacy

The primary end point, ACR20 at week 24, was achieved by 71.4-79.5% of patients receiving any dose of tildrakizumab relative to placebo-treated patients (50.6%), with more responders at 200 mg every 4 weeks and 100 mg every 12 weeks (**Table 2**). At 52 weeks, the response was marginally higher at 67.5-79.5% of patients achieving ACR20. Similarly, at week 24 ACR50 was achieved by 50.6-52.6% of patients receiving tildrakizumab 200 mg either every 4 weeks or every 12 weeks relative to placebo-treated patients (24.1%).[9] Although a direct comparison cannot be made, 52.0-64.1% of patients achieved ACR 20 on guselkumab in the DISCOVER-1 and DISCOVER-2 trials.[10] With respect to tildrakizumab, patients achieving ACR70 at 24 weeks displayed more modest response at 16.7-28.2% (**Table 2**). Patients achieving ACR70 at 52 weeks had a more robust response ranging from 35.4-50.0% across all treatment arms; tildrakizumab 200 mg dosed at 4-week intervals having the highest response rate (50.0%).

With respect to minimal disease activity (**Figure 2**), a composite of physician and patient global assessments as well as quality of life measures, tildrakizumab 200 mg dosed at 12-week intervals outperformed other doses across most criteria, including tender joint count, swollen joint count, PASI, BSA, and pain visual analogue scale. However, patients had limited improvement in tender entheseal points compared to the

placebo-treated arm (71.8-80.3% on Tildrakizumab vs 74.4% on placebo treatment) as well as HAQ-DI <0.05 (**Figure 2**).[11]

Interestingly, exploratory analysis of patients on tildrakizumab with prior anti-TNF-α experience also demonstrated sustained response and met ACR20 relative to placebo but less than TNF-α-naive patients (**Figure 3**). At week 24, 52.9-70.6% of TNF-α-exposed patients with PsA had achieved ACR20 compared to patients in the placebo treated arm (36.8%) (**Figure 4**).[9]

The proportion of patients achieving very low disease activity (VLDA) (**Figure 5**) was higher in patients who received tildrakizumab 200 mg dosed at 4-week intervals (15.4%) and in patients who received tildrakizumab 200 mg dosed at 12-week intervals (16.5%) vs patients in the placebo group (1.3%) at week 24. Durable responses were noted at week 52, with responses seen in patients that switched from the placebo arm or the tildrakizumab 20 mg every 4 weeks arm to the tildrakizumab 200 mg every 4 weeks arm.[12]

Safety

This study demonstrated a similar safety profile for tildrakizumab as was observed in the reSURFACE trials in plaque psoriasis. In a pooled analysis of reSURFACE 1 and reSURFACE 2 trials over a 148-week period, tildrakizumab was shown to be safe and effective with treatment emergent AEs at 35.2-37.2 per 100 patient years compared to placebo at 148.6 events per 100 patient years[8]. Nasopharyngitis, headache and injection site reactions were the most common treatment emergent adverse events reported. A low incidence of serious adverse events was noted in this study similar to the reSURFACE trial[13]. The safety profile of tildrakizumab compared to other IL-23 inhibitors is also similar with respect to overall adverse events including serious adverse events. In this study, there were no reports of deaths, systemic candidiasis, inflammatory bowel disease, major adverse cardiac event, or significant transaminitis through week 52[9]. There was one case each of pyelonephritis and UTI in the tildrakizumab 100 mg arm, but none in the 200 mg every 12-week arm (**Table 3**). One malignancy (intraductal proliferative breast lesion) was reported in a patient who started on tildrakizumab 20 mg every 12 weeks and then crossed over to tildrakizumab 200 mg every 12 weeks.

Summary and Conclusion

Compared with the placebo group, more patients in the tildrakizumab groups achieved an ACR20 or ACR50 response, minimal disease activity responses at week 24 and maintained their response through week 52. The molecule's safety profile is consistent with other IL-23 inhibitors and the medication was generally well tolerated. Shortening the dosing interval from every 12 weeks to every 4 weeks for the 200 mg dose did not result in a measurable increase in skin or joint response scores. Some of the practical considerations to utilizing tildrakizumab include convenience, safety with concomitant csDMARDs, and sustained improvement in PASI scores, which make tildrakizumab a favourable option in the clinician's therapeutic armamentarium.

Acronyms

PsA - Psoriatic Arthritis

PACE - Psoriatic Arthritis Screening and Evaluation

HAQ - Health Assessment Questionnaire

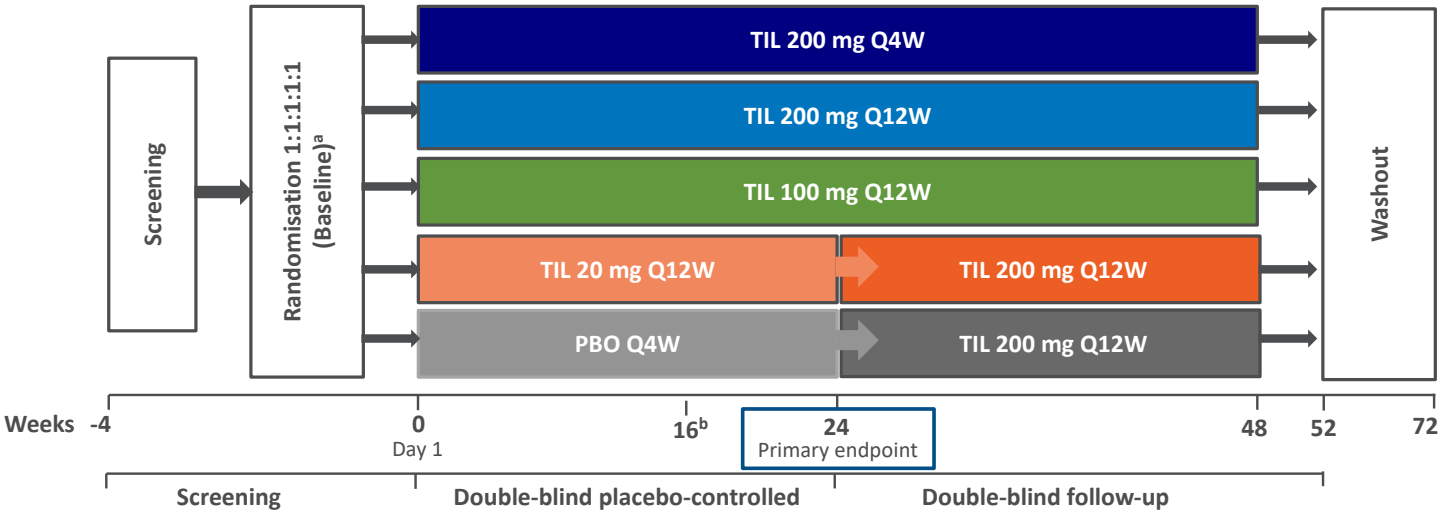
hsCRP - high sensitivity C-reactive protein

csDMARD - conventional systemic disease modifying antirheumatic drug

bDMARD - biologic disease modifying antirheumatic drug

GRAPPA – Group for Research and Assessment of Psoriasis and Psoriatic Arthritis

Study Design



[a]*Randomisation stratified by prior anti–TNF-α use (prior use capped at 30% of total patients) and baseline body weight (≤90 kg/>90kg).*
†Patients who failed to show minimal response to treatment (<10% improvement from baseline in swollen and tender joint counts) at week 16 could have background medications (MTX, leflunomide, or oral corticosteroids) adjusted according to the maximum permitted daily dose and continue in the study as a nonresponder.
MTX, methotrexate; PBO, placebo; Q4W, every 4 weeks; Q12W, every 12 weeks; TIL, tildrakizumab; TNF, tumour necrosis factor.

Figure 1: Study Design illustrating randomization stratified by prior TNF-α use, baseline body weight.

	TIL 200 mg Q4W (N = 78)	TIL 200 mg Q12W (N = 79)	TIL 100 mg Q12W (N = 77)	TIL 20 → 200 mg Q12W (N = 78)	PBO 200 mg (N = 79)
ACR20, % ± SE (*P* value)	79.5 ± 4.6 (0.0001)	77.2 ± 4.7 (0.0006)	71.4 ± 5.2 (0.0088)	73.1 ± 5.0 (0.0041)	50.61 ± 5.6
ACR50, % ± SE (*P* value)	52.6 ± 5.7 (0.0002)	50.6 ± 5.76 (0.0006)	45.5 ± 5.7 (0.0059)	39.7 ± 5.5 (0.0364)	24.1 ± 4.8
ACR270, % ± SE (*P* value)	28.2 ± 5.1 (0.0040)	29.1 ± 5.1 (0.0033)	22.1 ± 4.7 (0.0550)	16.7 ± 4.2 (0.2495)	10.1 ± 3.4

Response rates are shown for randomized patients who received ≥ 1 dose of study drug.
P values are for comparison of each tildrakizumab treatment vs placebo.
ACR, American Collete of Rheumatology response criteria; PBO, placebo; Q4W, every 4 weeks; Q12W, every 12 weeks; SE, standard

Table 2: Review of ACR20/50/70 across all treatment arms at week 24 and week 52.

Primary End Point:
Disease activity: ACR20. ACR20 criteria required a > 20% reduction in the tender joint count, a >20% reduction in the swollen joint count and a >20% reduction in 3 of 5 measures including a) patient assessment of pain, b) patient global assessment of disease activity, c) physician global assessment of disease activity d) disability index of the HAQ and e) acute phase reactant. ACR 50 and 70% are the same criteria as above, with use of a higher percentage improvement instead of 20%.
Secondary End Point:
Disease Activity: ACR50/70 at week 52
Disease Activity: Disease Activity Score in 28 joints with C Reactive Protein (DAS28-CRP)
Disease Activity: Minimal Disease Activity at week 24 and 52. Minimal disease activity was achieved if patients met 5 out of 7 criteria which include: TJC68<1, SJC66<1, Psoriasis Area and Severity Index <1 or Body surface area <3, patient pain visual analogue scale <15, patient global disease activity <1, VAS <20, HAQ-DI <0.5 and tender entheseal points <1.
Disease Activity: Leeds Dactylitis Index (LDI in patients with LDI>1)
Disease Activity: Leeds Enthesitis Index (LEI; in patients with baseline LEI>1)
Bath Ankylosing Spondylitis Disease Activity (BASDAI)
Exploratory End Points
PASI75/90/100
PsA Impact of Disease (PsAID) change from baseline, week 24 and week 52
Post Hoc Analysis
Proportion of patients achieving very low disease activity (VLDA)
Psoriatic arthritis disease activity score (PASDAS) <3.2
Disease Activity in Psoriatic Arthritis (DAPSA) remission - score 0 to 4
Complete LDI/LEI resolution

Table 1: Primary and Secondary End Points

TIL 200 mg Q4W (N = 78)	TIL 200 mg Q12W (N = 79)	TIL 100 mg Q12W (N = 77)	TIL 20 → 200 mg Q12W (N = 78)	PBO 200 mg (N = 79)
79.5 ± 4.6	72.2 ± 5.04	67.5 ± 5.3	78.2 ± 4.7	77.2 ± 4.7
68.0 ± 5.3	608. ± 5.5	57.1 ± 5.6	65.4 ± 5.4	59.5 ± 5.5
50.0 ± 5.7	39.2 ± 5.5	31.2 ± 5.3	38.5 ± 5.5	35.4 ± 5.4

error; TIL, tildrakizumab.

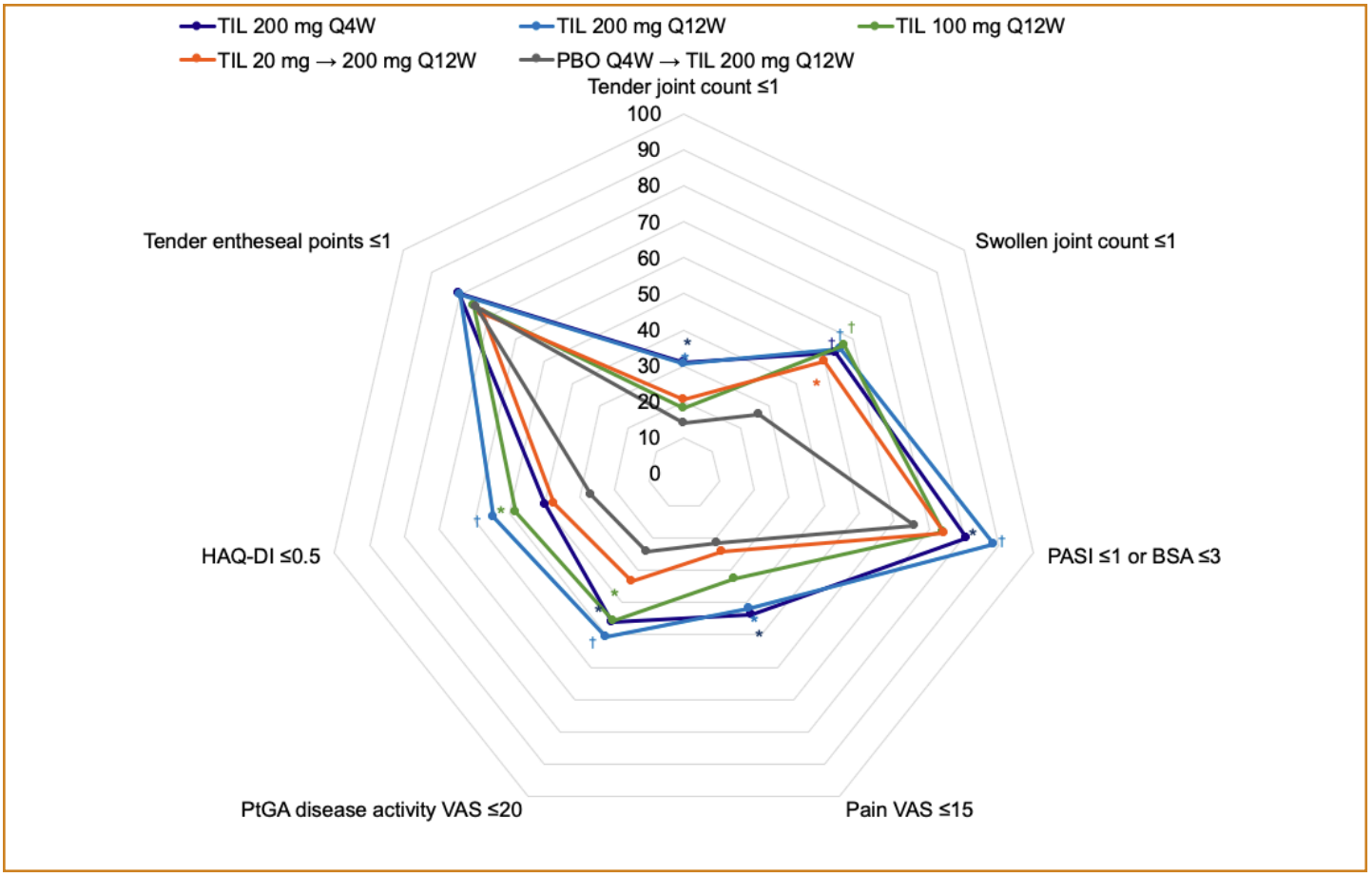


Figure 2: Tildrakizumab and impact on minimal disease activity composite at Week 24. Tender joint count (TJC) <1, Swollen Joint Count (SJC) <1, Psoriasis Area and Severity Index <1 or Body surface area <3%, patient pain visual analogue scale <15, patient global disease activity <1, VAS <20, HAQ-DI <0.5 and tender5 entheseal points <1.

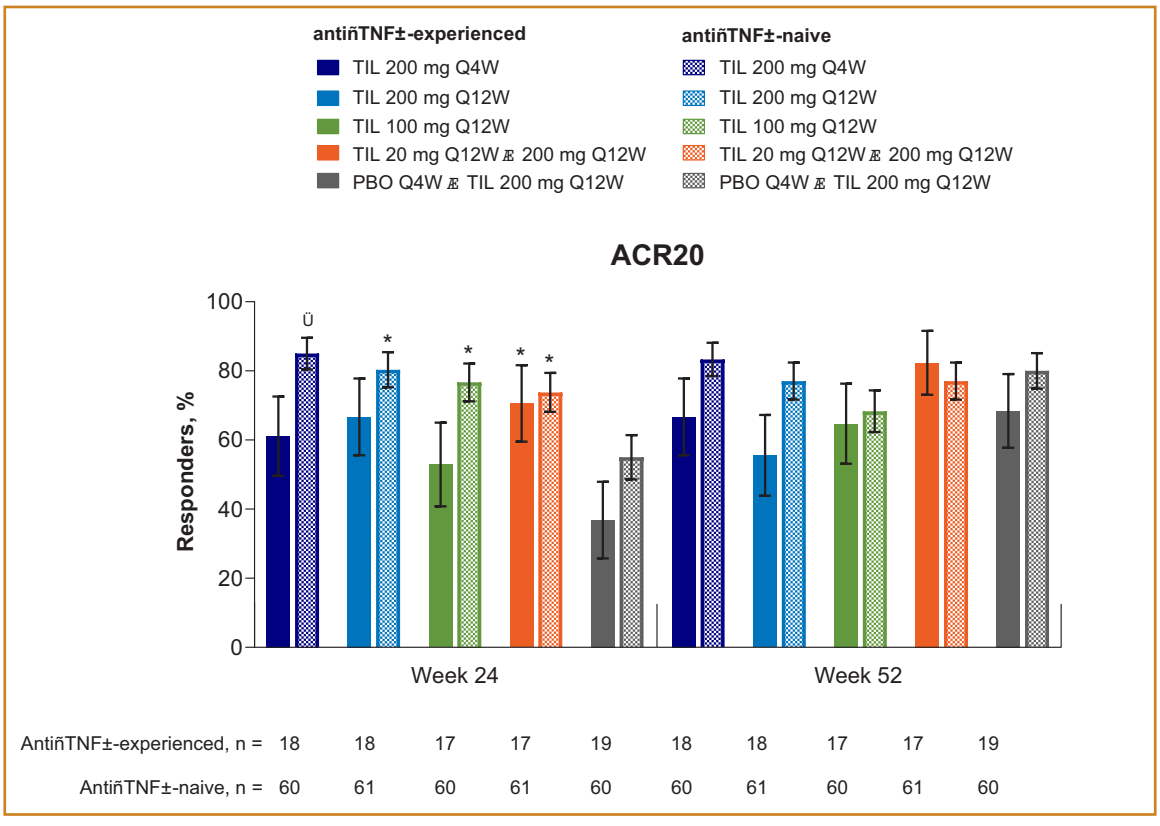


Figure 3: Efficacy – ACR20 at Weeks 24 and 52 by Prior Anti-TNF-α Experience

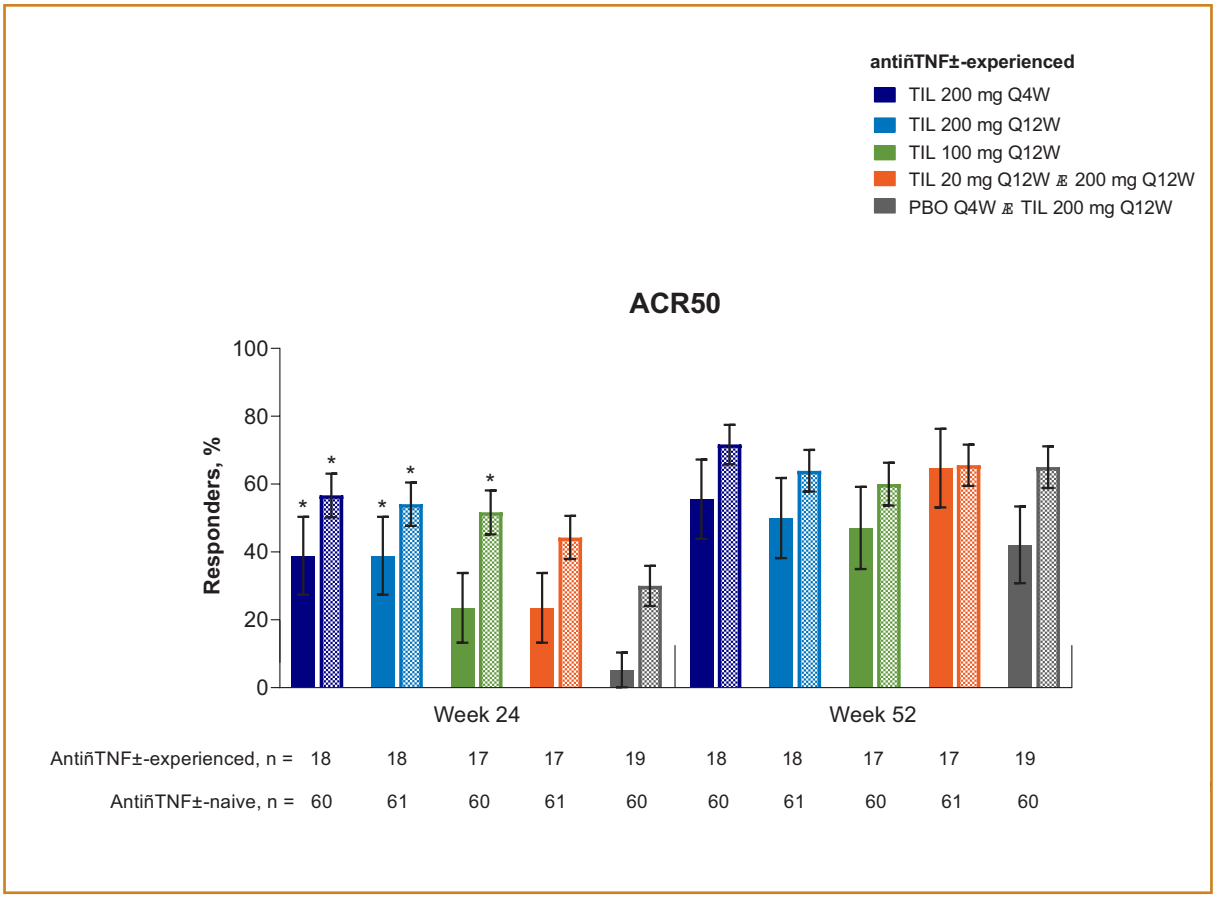


Figure 4a: Efficacy - ACR50 at Weeks 24 and 52 by Prior Anti-TNF-α Experience

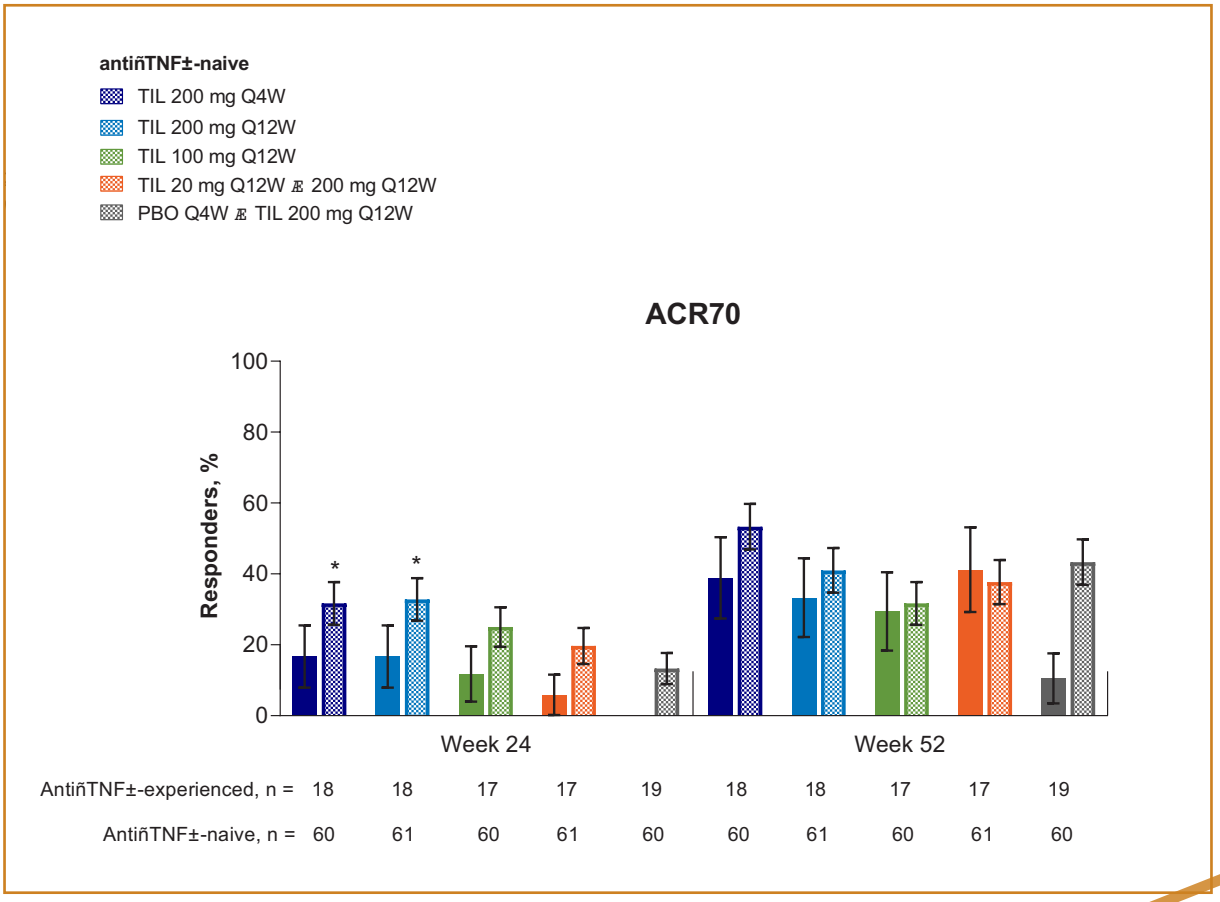


Figure 4b: Efficacy - ACR70 at Weeks 24 and 52 by Prior Anti-TNF-α Experience

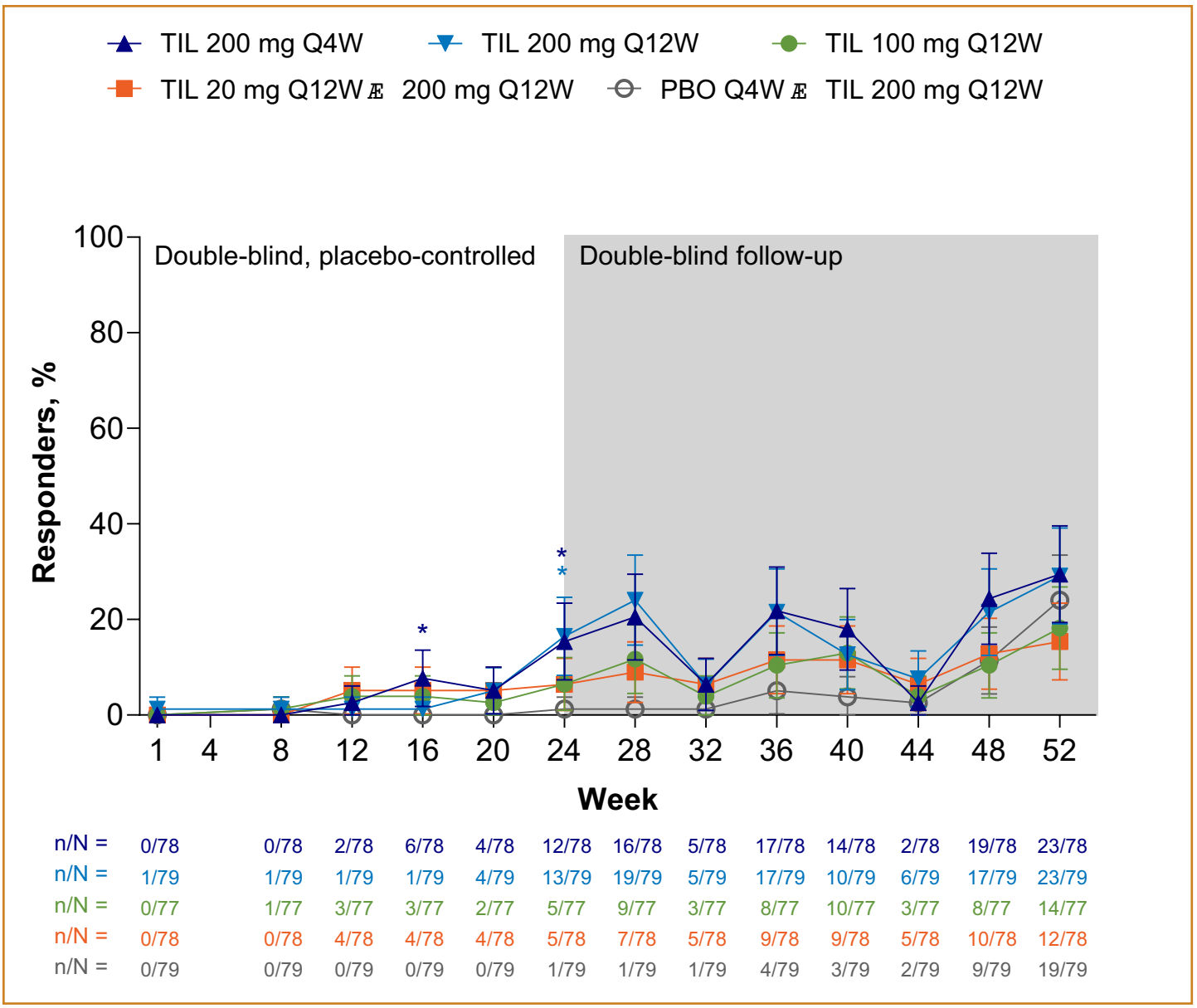


Figure 5: Proportion of patients achieving very low disease activity by treatment and time point.

	TIL 200 mg Q4W (N = 78)	TIL 200 mg Q12W (N = 79)	TIL 100 mg Q12W (N = 77)	TIL 20 → 200 mg Q12W (N = 78)	PBO → 200 mg (N = 79)
Any TEAE	51 (65.4)	50 (63.3)	53 (68.8)	51 (65.4)	47 (59.5)
Any serious TEAEs	2 (2.6)	2 (2.5)	2 (2.6)	4 (5.1)	3 (3.8)
Discontinuation due to TEAEs	0	1 (1.3)	0	0	0
Deaths due to TEAEs	0	0	0	0	0
TEAEs of special interest	0	0	1 (1.3)	1 (1.3)	
TEAEs of clinical interest			1 (1.3)	2 (2.6)	1 (1.3)

Shown as n (%) for patients who received ≥ 1 dose of study medication. [a]Reported on day 51 of the trial.
AE, adverse events; PBO, placebo; TEAE, treatment-emergent AE; Q4W, every 4 weeks; Q12W, every 12 weeks; TIL, tildrakizumab.

Table 3: Safety profile of tildrakizumab including treatment emergent adverse effects, including those of special and clinical interest.

References

1. *Rachakonda TD, Schupp CW, Armstrong AW. Psoriasis prevalence among adults in the United States. J Am Acad Dermatol. 2014;70(3):512-516. doi:10.1016/j.jaad.2013.11.013*
2. *Brezinski EA, Dhillon JS, Armstrong AW. Economic Burden of Psoriasis in the United States: A Systematic Review. JAMA Dermatol. 2015;151(6):651. doi:10.1001/jamadermatol.2014.3593*
3. *Ritchlin CT, Colbert RA, Gladman DD. Psoriatic Arthritis. Longo DL, ed. N Engl J Med. 2017;376(10):957-970. doi:10.1056/NEJMra1505557*
4. *Hawkes JE, Yan BY, Chan TC, Krueger JG. Discovery of the IL-23/IL-17 Signaling Pathway and the Treatment of Psoriasis. J Immunol. 2018;201(6):1605-1613. doi:10.4049/jimmunol.1800013*
5. *Veale DJ, Fearon U. The pathogenesis of psoriatic arthritis. The Lancet. 2018;391(10136):2273-2284. doi:10.1016/S0140-6736(18)30830-4*
6. *Singh JA, Guyatt G, Ogdie A, et al. 2018 American College of Rheumatology/National Psoriasis Foundation Guideline for the Treatment of Psoriatic Arthritis. Arthritis Care Res. 2019;71(1):2-29. doi:10.1002/acr.23789*
7. *Coates LC, Corp N, van der Windt DA, Soriano ER, Kavanaugh A. GRAPPA Treatment Recommendations: An Update From the 2020 GRAPPA Annual Meeting. J Rheumatol. Published online February 15, 2021:jrheum.201681. doi:10.3899/jrheum.201681*
8. *Reich K, Warren RB, Iversen L, et al. Long-term efficacy and safety of tildrakizumab for moderate-to-severe psoriasis: pooled analyses of two randomized phase III clinical trials (re SURFACE 1 and re SURFACE 2) through 148 weeks. Br J Dermatol. 2020;182(3):605-617. doi:10.1111/bjd.18232*
9. *Mease PJ, Chohan S, Fructuoso FJG, et al. Efficacy and safety of tildrakizumab in patients with active psoriatic arthritis: results of a randomised, double-blind, placebo-controlled, multiple-dose, 52-week phase IIb study. Ann Rheum Dis. Published online May 13, 2021:annrheumdis-2020-219014. doi:10.1136/annrheumdis-2020-219014*
10. *Deodhar A, Gottlieb AB, Boehncke W-H, et al. Efficacy and safety of guselkumab in patients with active psoriatic arthritis: a randomised, double-blind, placebo-controlled, phase 2 study. The Lancet. 2018;391(10136):2213-2224. doi:10.1016/S0140-6736(18)30952-8*
11. *Nash P, Luggen ME, Ferran JGF. Proportions of patients achieving a minimal disease activity state upon treatment with tildrakizumab in a psoriatic arthritis phase 2b study. Poster Presentation presented at the: American College of Rheumatology Convergence; November 5, 2020; Virtual Presentation.*
12. *Chohan S, Kavanaugh A, Strand V. Efficacy of Tildrakizumab in PsA: DAPSA Remission and Low Disease Activity in PASDAS Through Week 52. Poster Presentation presented at the: American College of Rheumatology Convergence; November 5-9; Virtual Presentation.*
13. *Yang K, Oak ASW, Elewski BE. Use of IL-23 Inhibitors for the Treatment of Plaque Psoriasis and Psoriatic Arthritis: A Comprehensive Review. Am J Clin Dermatol. 2021;22(2):173-192. doi:10.1007/s40257-020-00578-0*

PERSPECTIVES AND INSIGHTS ON TILDRAKIZUMAB

TILDRAKIZUMAB IN PSA: A DATA REVIEW

Juthika Thakur, MD