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Expert Opinion on Biological Therapy

ISSN: (Print) (Online) Journal homepage: www.tandfonline.com/journals/iebt20

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To cite this article: Marco Galluzzo, Andrea Chiricozzi, Elisa Cinotti, Giovanna Brunasso, Maurizio Congedo, Maria Esposito, Chiara Franchi, Giovanna Malara, Alessandra Narcisi, Stefano Piaserico, Rossana Tiberio, Giuseppe Argenziano, Gabriella Fabbrocini & Aurora Parodi (2022) Tildrakizumab for treatment of moderate to severe psoriasis: an expert opinion of efficacy, safety, and use in special populations, Expert Opinion on Biological Therapy, 22:3, 367-376, DOI: 10.1080/14712598.2022.1988566

To link to this article: https://doi.org/10.1080/14712598.2022.1988566

Published online: 12 Oct 2021.

EXPERT OPINION ON BIOLOGICAL THERAPY
2022, VOL. 22, NO. 3, 367–376
https://doi.org/10.1080/14712598.2022.1988566

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REVIEW

Tildrakizumab for treatment of moderate to severe psoriasis: an expert opinion of efficacy, safety, and use in special populations

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ABSTRACT

Introduction: Tildrakizumab is a monoclonal antibody that targets the p19 subunit of IL-23, a crucial cytokine for Th17 cells. Tildrakizumab has been assessed in several Phase I, II, and III clinical trials and is approved for treatment of adults with moderate to severe plaque psoriasis who are indicated for systemic therapy.

Areas covered: The available evidence on the efficacy, safety, and use of tildrakizumab in special populations was evaluated by 14 experts who critically reviewed the current literature.

Expert opinion: Tildrakizumab has good efficacy that lasts for at least 5 years in patients with moderate to severe psoriasis, and appears to be safe and well tolerated in the long-term with no apparent dose-related differences in adverse events, a low incidence of discontinuation due to adverse events, and no evidence of increased risk of malignancies. The safety and the efficacy of tildrakizumab has also been confirmed in special populations such as those with inflammatory bowel disease, cardiovascular disease, metabolic syndrome, and advanced age. Early intervention with IL-23-inhibitors, such as tildrakizumab, may help to control symptoms and change the long-term course of the disease in patients affected by plaque psoriasis, while improving the quality of life and potentially minimizing the risk of developing comorbidities.

ARTICLE HISTORY
Received 30 August 2021
Accepted 29 September 2021

KEYWORDS
Long-term; efficacy; psoriasis; real life; safety; special populations; tildrakizumab

1. Introduction

Psoriasis is a chronic inflammatory skin and/or joint disorder that has substantial negative impact on both physical and psychological parameters [1]. Psoriasis has a number of diverse clinical manifestations, although chronic plaque psoriasis is the most common form [1,2]. The condition is considered prevalent, affecting around 2% of the general population, and with an incidence that increases with age [2]. Even if the majority of patients can be adequately controlled by topical therapy, a proportion of patients with more severe forms will require treatment with systemic therapy [1].

In this regard, in recent years, advances in the understanding of immune-mediated mechanisms have identified cytokines such as IL-17 and IL-23 and related signaling pathways that are key players in the pathogenesis of psoriasis [3,4]. As a result, a number of new and effective targeted therapies have been developed and approved for moderate-to-severe psoriasis. These include biologic therapies, that are able to interfere with TNF-α, IL-17, IL-12/23p40, and IL-23p19, such as tildrakizumab, guselkumab, and risankizumab [5]. These agents have undoubtedly advanced therapeutic management of psoriasis, not only by increasing the number of available treatments, but also by establishing new and effective therapies for psoriasis.

Tildrakizumab is a highly selective, humanized monoclonal antibody that targets the p19 subunit of IL-23, a crucial cytokine for Th17 cells, and prevents IL-23 from docking to the IL-23 R receptor [6]. Tildrakizumab decreases downstream signaling of various immune cells, thereby preventing activation of IL-17 and the associated proinflammatory effects [6,7]. Tildrakizumab has been studied in a number of Phase I, II, and III clinical trials [6] and is approved by the FDA and EMA for treatment of adults with moderate to severe plaque psoriasis who are indicated for systemic therapy. In addition, recent literature reported the successful use of tildrakizumab in clinical practice in various other severe dermatological/inflammatory conditions, most notably hidradenitis suppurativa [8,9], in addition to PASH syndrome, pyoderma

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Article highlights

- Tildrakizumab is indicated for indicated for the treatment of adults with moderate to severe plaque psoriasis who are candidates for systemic therapy.
- The available literature on the efficacy, safety, and use of tildrakizumab in special populations was evaluated by 14 experts.
- Tildrakizumab has good efficacy that lasts for at least 5 years in patients with moderate to severe psoriasis.
- Tildrakizumab appears to be safe and well tolerated in the long-term.
- The safety and the efficacy of tildrakizumab have been confirmed in inflammatory bowel disease, cardiovascular disease, metabolic syndrome, and advanced age.
- Early intervention with IL-23-inhibitors, such as tildrakizumab, may help to control symptoms and improve the long-term course of plaque psoriasis.

This box summarizes key points contained in the article.

gangrenosum, polymyalgia rheumatica, lichen planus pemphigoides, SAPHO syndrome, and lichen planopilaris [10–14].

Overall, in treatment of moderate to severe plaque psoriasis, tildrakizumab has been shown to be effective with a favorable safety profile [6]. Herein, the available evidence on the efficacy and safety of tildrakizumab is reviewed as well as its use in special populations. For this purpose, 14 experts, divided into three groups, focused, respectively, on efficacy, safety, and special populations, met to assess and critically review the available literature and develop expert opinion using an interactive process of individual feedback. This narrative review represents the synthesis of their opinions on the value of tildrakizumab for the treatment of moderate to severe psoriasis patients, focusing on its position in clinical practice.

2. Efficacy

2.1. Phase I trials

The Phase 1 study by Kopp et al. was a three-part, randomized, placebo-controlled, sequential, rising multiple-dose trial in patients with moderate-to-severe psoriasis [7]. In part 1, patients were randomized to placebo or 0.1 mg/kg, 0.5 mg/kg, 3 mg/kg, or 10 mg/kg tildrakizumab on days 0, 56, and 84. In part 2, subjects were randomized to placebo or 3 mg/kg or 10 mg kg tildrakizumab on days 1, 28,and 56. In part 3, subjects received placebo or 0.05 mg/kg or 0.1 mg/kg tildrakizumab on days 1, 56, and 84. In parts 1 and 3 (pooled analysis; n = 32) in the 3 and 10 mg/k groups, all patients achieved a 75% reduction in the psoriasis area and severity index (PASI) score (PASI 75). In part 2, 10 of 15 patients in the 3 mg kg group and 13 of 14 subjects in the 10 mg/kg group achieved PASI 75 within day 112. The study concluded that tildrakizumab was associated with clinically significant improvement and was well tolerated overall.

2.2. Phase II trials

The Phase 2b dose-finding, randomized, double-blind trial by Papp et al. enrolled 355 adult patients with moderate-to-severe psoriasis [15]. In the first part, patients were randomized to tildrakizumab (5, 25, 100, 200 mg) or placebo at weeks 0 and 4 (part I) and every 12 weeks thereafter until week 52 (part 2). Tildrakizumab was discontinued at week 52 and follow-up continued up to week 72 (part 3). Considering the primary endpoint of PASI 75 responses at week 16, this was seen in 33.3%, 64.4%, 66.3%, and 74.4%, in the 5-, 25-, 100-, and 200-mg tildrakizumab groups, respectively, and 4·4% for placebo ($P \leq 0.001$ for each dose vs. placebo). Moreover, PASI 75 responses were generally maintained up to week 52. The overall incidence of adverse events for the active treatment arms did not differ substantially from placebo.

2.3. Phase III trials

The reSURFACE trials were parallel group, double-blind, randomized controlled studies with optional long-term extensions [16–18]. The reSURFACE 1 trial enrolled 772 patients (308 to tildrakizumab 200 mg, 309 to tildrakizumab 100 mg, and 155 to placebo), and the reSURFACE2 trial enrolled 1090 patients (314 to tildrakizumab 200 mg, 307 to tildrakizumab 100 mg, 313 to etanercept, and 156 to placebo [16]. The proportions of patients achieving improvement from baseline PASI score were evaluated through week 244 in tildrakizumab responders (PASI 75 response) at week 28.

Tildrakizumab is the first anti-IL-23p19 agent reporting data on efficacy and safety for up to 5 years from two phase III studies [18]. The analysis included 329 patients who responded to tildrakizumab 100 mg and 227 who responded to tildrakizumab 200 mg at week 28, in addition to 121 partial/non-responders to etanercept who were switched to tildrakizumab. Among patients entering the long-term extension, nearly 8 of 10 patients achieved and maintained PASI <3 response during 5 years of continued treatment with both tildrakizumab 100 mg (85.1% at week 28 and 78.8% at week 244), and tildrakizumab 200 mg (86.8% at week 28 and 82.6% at week 244), indicating that more than 90% of week 28 responders maintained the response for up to 5 years (Figure 1). Thus, tildrakizumab is associated with sustained control of disease in the long-term among patients responding at week 28.

Kimball et al. used data from Part 3 of the reSURFACE 1 study to evaluate relapse (50% reduction in maximum PASI response) after interruption of treatment and retreatment effect upon relapse [19]. In the subgroup of patients withdrawn from tildrakizumab treatment (both 100 or 200 mg) and rerandomized to placebo at week 28, the median time to relapse was 24 weeks, which means 36 weeks after the last administration. The vast majority of patients (86%) retreated with tildrakizumab for at least 12 weeks, reached PASI 75 again by week 64 and no patients experienced rebound. These data indicate that the effect of IL-23 inhibition by tildrakizumab is sustained in the long-term even after withdrawal of treatment, and outcomes were favorable during maintenance, reinitiation, dose adjustment, or initiation of tildrakizumab.

To study the possibility that the efficacy outcomes in the reSURFACE trials could be better represented by residual disease during therapy, Gordon et al. recently carried out a post-hoc analysis by supplementing relative PASI evaluation with

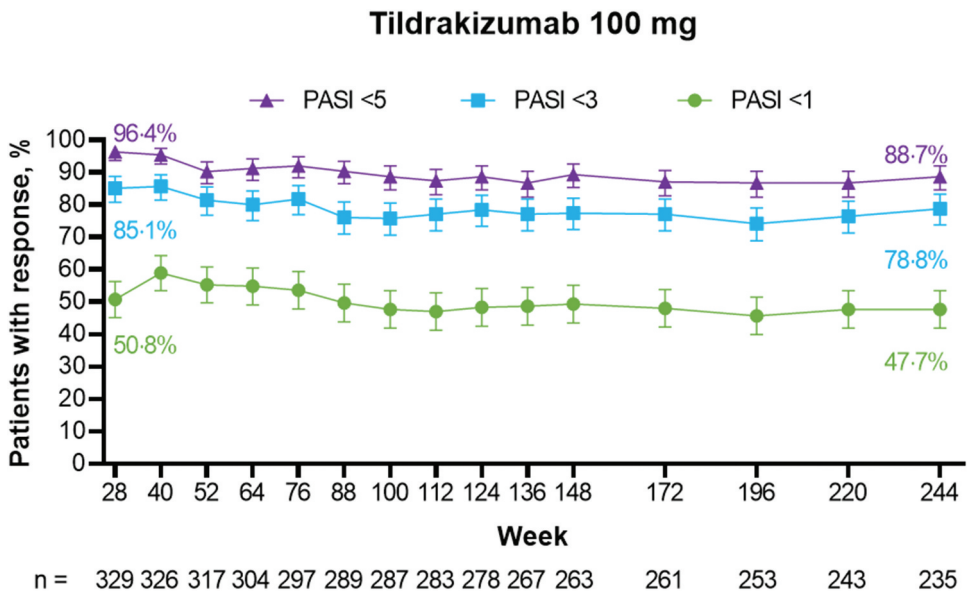


Figure 1. PASI responses to tildrakizumab 100 mg for up to 244 weeks. Adapted from [18] with permission.

residual disease activity [20]. The investigation used pooled data on treatment with tildrakizumab 100 mg (n = 616) or placebo (n = 309) from the reSURFACE 1/2 trials. Median baseline PASI was 17.9 for patients given tildrakizumab 100 mg; after 12 weeks, median PASI was 2.9 with a PASI 90 response rate of 36.9%. After 28 weeks, median PASI was 1.7 with a PASI 90 response rate of 51.9%. In this study, post-treatment PASI scores were found to provide more reliable information on residual disease compared to percentage PASI improvement, which gives only limited clinical information on residual disease following treatment, mainly because at baseline patients may start from different levels of PASI scores. Indeed, at week 12, half of the patients receiving tildrakizumab 100 mg achieved a PASI score <3.0 [20].

Blauvelt et al. evaluated 1156 patients, from reSURFACE 1 and 2 (575 in the 100-mg and 578 in the 200-mg cohorts) in a post-hoc analysis [21]. At week 28, 8.3%, 14.3%, 23.8%, 30.4%, and 23.1% in the 100-mg cohort achieved PASI <50, 50–74, 75–89, 90–99, and 100 (Figure 2). In addition, those achieving PASI <50 at week 28 could be recognized at week 8, and patients with PASI ≥90 at week 28 showed 50% improvement in PASI within week 4. In those with PASI >50 at week 28 who continued on the equivalent dose of tildrakizumab to week 52, mean improvement in PASI was either preserved or further improved over time, with comparable results for both the 100 mg and 200 mg doses. These data indicate that patients that will achieve PASI response ≥90 can be detected as early as week 4, very important in terms of predictivity of response [21].

Quality of life was also evaluated in the same post-hoc analysis using the Dermatology Life Quality Index (DLQI) 0/1 [21]. Greater proportions of patients receiving tildrakizumab achieved DLQI 0/1 in groups with higher PASI scores at week 28. Moreover, DLQI 0/1 was seen to be continued or even improved up to week 52. Although not every patient with PASI 100 had DLQI 0/1, it was noted that 100% skin clearance is not always associated with no impairment in quality of life. However, PASI scores and quality of life improvement generally showed similar trends, and higher PASI improvement correlated with amelioration in quality of life.

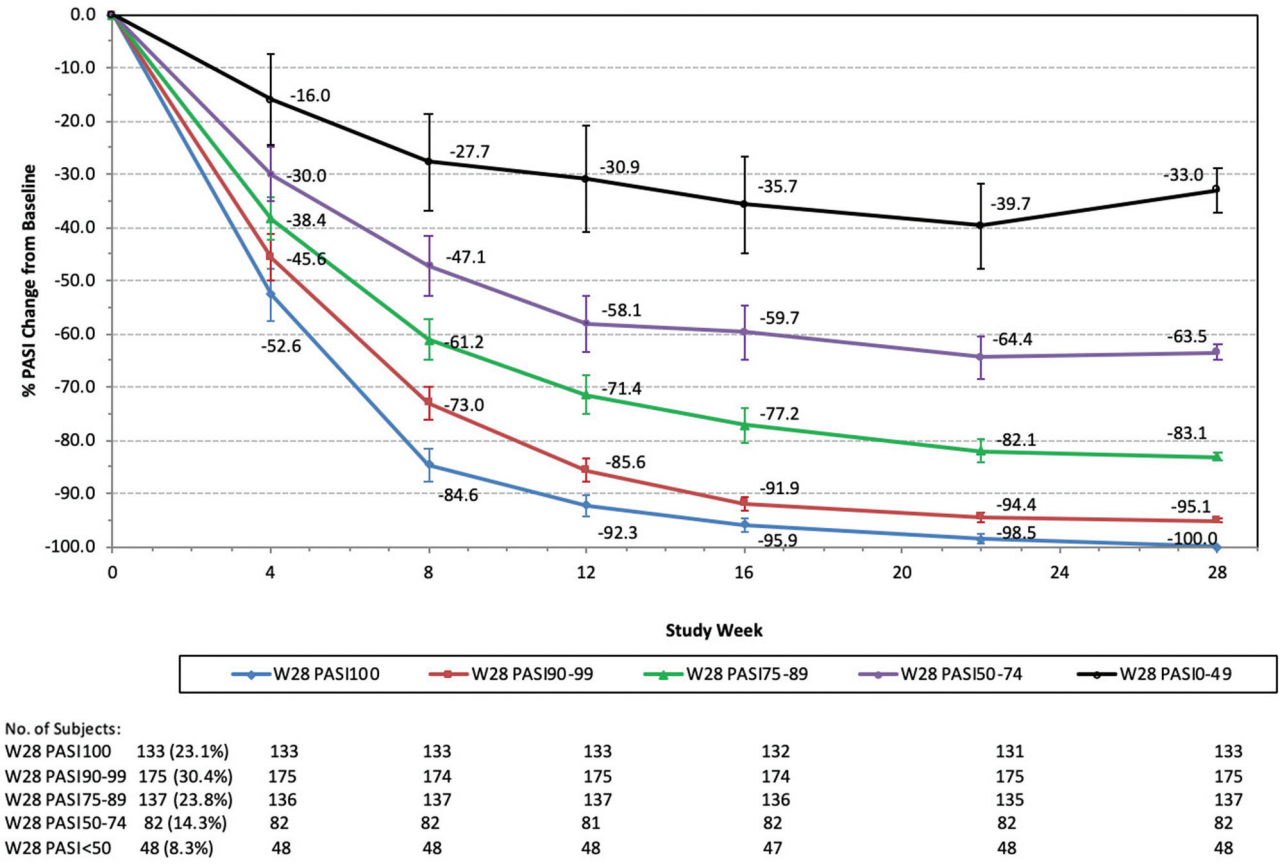
2.4. Difficult-to-treat areas

Data from the reSURFACE 1 trial has also been analyzed in terms of efficacy on difficult-to-treat areas of psoriasis. In a post hoc analysis, efficacy of tildrakizumab on the head, including the face, neck, and scalp, was investigated using PASI head (PASIh) (range 0.0–7.2) in 309 patients administered tildrakizumab 100 mg and 154 administered placebo were evaluated [22]. Significant decreases in PASIh were observed at weeks 4 and 12 that were maintained at week 28, with decreases seen across all PASIh scores at the start of the study, even in those with severe disease at baseline, which further improved at week 28. To date, tildrakizumab is the first anti-IL-23 effective on neck and face as well as scalp. A phase 3b study of tildrakizumab 100 mg for scalp psoriasis is ongoing and will provide additional evidence (NCT03897088).

A case report also documented clinical improvement in a male patient with psoriatic nail dystrophy associated with psoriatic arthritis and psoriasis treated with tildrakizumab 100 mg at weeks 0 and 4 [23]. Twelve weeks later significant improvement in both nail dystrophy and arthritis was observed. In another report of two cases of treatment-resistant nail psoriasis with tildrakizumab 100 mg baseline and Week 4, followed by 100 mg every 12 weeks, clinically significant improvement was seen in the Nail Psoriasis Severity Index at both 6 and 12 months [24]. The efficacy of tildrakizumab on nail psoriasis is being further studied in a dedicated Phase 3b clinical trial (NCT03897075).

2.5. Real-world evidence

There is limited evidence for the efficacy of tildrakizumab in real-world settings, and the TILOT study is the first to provide real-world data on tildrakizumab [25]. TILOT study is



No. of Subjects:

W28 PASI100	133 (23.1%)	133	133	133	132	131	133
W28 PASI90-99	175 (30.4%)	175	174	175	174	175	175
W28 PASI75-89	137 (23.8%)	136	137	137	136	135	137
W28 PASI50-74	82 (14.3%)	82	82	81	82	82	82
W28 PASI<50	48 (8.3%)	48	48	48	47	48	48

Figure 2. Percentage PASI responses to tildrakizumab 100 mg by week-28 PASI response groups from a post hoc analysis of reSurface 1 and 2 (575 in the 100-mg and 578 in the 200-mg cohorts). Adapted from [21] with permission.

a prospective, multicenter, non-interventional study evaluating the effectiveness of tildrakizumab in moderate to severe plaque psoriasis over 3 years in clinical practice, and has enrolled 133 patients in Germany, the first country that approved the use of tildrakizumab in 2018. In an interim analysis, at week 28 after 3 doses of tildrakizumab, mean PASI improved by 86%, from 18.0 to 2.6. An absolute PASI <3 and <5 was achieved by 65.1% and 83.3% of patients at week 28. In patients with scalp psoriasis (n = 131), the Scalp-physician global assessment 0/1 improved being reported by 26.7% at baseline to 76.8% at week 16 to 85.8% at week 28. In those with nail psoriasis (n = 60), nail-physician global assessment improved from 1.8 as baseline to 0.7 at week 28.

Burlando et al. recently published the first Italian case series on the real-life use of tildrakizumab in moderate-to-severe plaque psoriasis [26]. Altogether, the results of 26 patients treated with tildrakizumab 100 mg and followed for up to 24 weeks were presented. In particular, there were no adverse events and no patient discontinued tildrakizumab. While no patient had a PASI score of <5 at study initiation, by week 4, 8 (32%) subjects had a PASI score of <3; of these, 6 had a PASI score of 0. At week 24, 22 (96%) patients had a PASI score of <3 and 20 (87%) had a PASI score of 0. Thus, the results in this small cohort of patients in a real-life setting confirm the efficacy and safety of tildrakizumab seen in controlled clinical trials. In addition, a recent case report suggested tildrakizumab may be a new therapeutic option for erythrodermic psoriasis, reporting the case of a 61-year-old man with erythrodermic psoriasis (PASI 35, BSA 90%) who reached PASI 100 after 16 weeks of tildrakizumab [27].

3. Safety

3.1. Safety in reSURFACE1 and reSURFACE2

In reSURFACE1 and reSURFACE2, discontinuations because of adverse events were infrequent in the short term, over 28 weeks (about 2%) [16]. The most common adverse event in reSURFACE1 and reSURFACE2 was nasopharyngitis (8–14%) and with a frequency similar to placebo. The rates of major adverse cardiovascular events, severe infections, and malignancies and were all low (about 1%). The safety profile was considered encouraging.

In the long-term, rates of discontinuations due to adverse events were low at 148 weeks (1.7 and 1.2 per 100 patient years (PY) for tildrakizumab 100 mg and 200 mg, respectively) [17], as were the rates of serious adverse events (5.9 and 5.5 per 100 PY, respectively). Thus, tildrakizumab was held to have a favorable safety profile for up to 3 years. Considering 5-year data, exposure-adjusted rates of serious adverse events were 6.3 and 6.0 per 100 PY for tildrakizumab 100 mg and 200 mg, respectively, broadly confirming the 3-year data [18]. All pre-specified adverse events were reported at rates ≤1.6 events per 100 PY and were similar for both doses of tildrakizumab, suggesting

Table 1. Summary of safety profile of tildrakizumab at 5 years. Adapted from [18] with permission.

	Tildrakizumab 100 mg (N = 872)	Tildrakizumab 200 mg (N = 928)
Total follow-up, patient-years	2668.4	2753.5
Severe infection	33	37
	1.2 (0.8–1.7)	1.3 (0.9–1.9)
Malignancy excluding NMSC	20	17
	0.7 (0.5–1.1)	0.6 (0.4–1.0)
NMSC	12	11
	0.4 (0.2–0.8)	0.4 (0.2–0.7)
Melanoma	2	3
	0.1 (0–0.3)	0.1 (0–0.3)
Confirmed extended MACE	14	20
	0.5 (0.3–0.9)	0.7 (0.4–1.1)
Injection site reaction[a]	33	41
	1.2 (0.8–1.7)	1.5 (1.1–2.0)
Drug-related hypersensitivity reaction	7	4
	0.3 (0.1–0.5)	0.1 (0–0.4)

Data shown as N followed by events per 100 patient-years of exposure (95% CI).
[a]Not recorded during the extension studies.
TIL, tildrakizumab; NMSC, non-melanoma skin cancer; MACE, major adverse cardiovascular events; CI, confidence interval.

a lack of dose effect on safety events. Drug-related hypersensitivity reactions were rare, with 0.2 events per 100 PY in each dose group.

3.2. Events of special interest

Events of special interest are summarized in Table 1. Overall, the data at 5 years confirmed the favorable safety profile of tildrakizumab, and no new or unexpected adverse events were observed during 5 years of continuous treatment. Few patients discontinued due to adverse events in tildrakizumab 100 or 200 mg groups. Candida infections were uncommon in the tildrakizumab groups and none was rated as severe.

4. Special populations

4.1. Psoriatic arthritis

Tildrakizumab is indicated for the treatment of adults with moderate to severe plaque psoriasis who are candidates for systemic therapy [28]. Tildrakizumab has been studied in patients with psoriatic arthritis (PsA) in a randomized, double-blind, placebo-controlled phase IIB study [29]. A total of 391 patients were randomized 1:1:1:1:1 to tildrakizumab 200 mg every 4 weeks to week 52, tildrakizumab 200 mg Q12W to week 52, tildrakizumab 100 mg Q12W to week 52, tildrakizumab 20 mg every 12 weeks (Q12W) until week 24 then tildrakizumab 200 mg Q12W to week 52, or placebo every 4 weeks until week 24 then tildrakizumab 200 mg Q12W to week 52. The proportions of ACR20/50/70 responders were higher with tildrakizumab vs placebo up to week 24; after week 24, responses continued to increase for tildrakizumab 20→200 mg Q12W and placebo→200 mg Q12W up to week 52. Tildrakizumab was considered to be well tolerated [29]. This suggests that tildrakizumab might be effective in patients with psoriasis and comorbid PsA.

4.2. Inflammatory bowel disease

Inflammatory bowel disease (IBD) is not uncommon in patients with psoriasis and therefore of special interest when considering treatment [30]. In a dedicated analysis of data from the Phase 2 and Phase 3 reSURFACE1 and reSURFACE2 trials (n = 1911), six patients had a history of IBD receiving tildrakizumab, none experienced an exacerbation [31]. Among all patients, no new cases of IBD were reported. A single case of new-onset Crohn's disease was suspected in a patient being administered tildrakizumab at a dose of 100 mg. The patient had prior history of diverticulitis. The event was rated as mild and it was not necessary to discontinue treatment. The rates per 100 PY of patients with serious gastrointestinal adverse events in the pooled dataset were 0.80 for tildrakizumab 100 mg and 0.43 for tildrakizumab 200 mg, and thus infrequent. Recent expert recommendations have suggested that tildrakizumab can be considered effective and well tolerated in patients with inactive and active IBD, even if the evidence level is low [32].

4.3. Cardiovascular disease

Cardiovascular disease is common in patients with psoriasis [33]. The risk of MACE associated has been investigated in a specific post hoc analysis of data from the Phase 2 and Phase 3 reSURFACE1 and reSURFACE2 trials [34]. At study initiation, the majority of patients had at least 1 CV or metabolic medical condition, with similar rates in the different treatment arms. During the trial, 84% of patients had received ≥1 concomitant medication related to CV and metabolic disorders. During the base study period the rates of confirmed adverse CV events were low, similar to placebo, and similar in the different treatment groups and (exposure adjusted incidence rates: placebo, 0.46; tildrakizumab 100 mg, 0.40; tildrakizumab 200 mg, 0.86; etanercept, 0.65). During the extension period, the exposure adjusted incidence rates were similarly low (tildrakizumab 100 mg, 0.60; tildrakizumab 200 mg, 0.4).

Tildrakizumab also has a favorable safety profile in the long term as seen by the low rate of MACE throughout 5 years in patients with moderate to severe plaque psoriasis [35]. Overall, exposure adjusted incidence rates of confirmed extended MACE were 0.7 for tildrakizumab 200 and 0.5 for tildrakizumab 100 mg. The most common MACE for tildrakizumab 200 and 100 groups was acute myocardial infarction (exposure adjusted incidence rates: 0.15 and 0.07, respectively). Other MACE confirmed comprised coronary artery disease (exposure adjusted incidence rates: 0.15 and 0.04), angina pectoris (exposure adjusted incidence rates 0.07 and 0.04), cerebrovascular accident (exposure adjusted incidence rates: 0.04 and 0.07), and coronary artery stenosis (tildrakizumab 200 only: exposure adjusted incidence rates: 0.11). No dose-related increase in the rate of MACE was observed.

4.4. Metabolic syndrome

Observational studies have reported an increased prevalence of metabolic syndrome in patients with psoriasis compared with the general population [36]. In reSURFACE1 and reSURFACE2, PASI scores reduced to similar levels across

body weight deciles [37]. A modest relationship with weight-efficacy with tildrakizumab 100 mg was seen up to week 12, and the efficacy of tildrakizumab was more rapid in those with lower weight. However, efficacy improved across all weight categories through week 28. The efficacy in PASI 75 responders at week 28 was preserved, with >90% median PASI increases in all weight categories at week 52.

Moreover, neither the efficacy nor safety of tildrakizumab were altered by the presence of metabolic syndrome in a post hoc analysis of reSURFACE 1 and 2 through 52 weeks [38] and confirmed at 148 weeks [39]. Percentages of patients with PASI 75, 90 and 100 improvements at weeks 12, 52, and 148 were similar in patients with and without metabolic syndrome for both tildrakizumab doses and median absolute PASI values decreased to comparable low levels over 148 weeks (Figure 3). The safety profile in patients with and without metabolic syndrome was confirmed over 5 years [39,40].

In a recent analysis evaluating the correlation of the efficacy of tildrakizumab with glucose levels, it was demonstrated that there was also no clinically meaningful relationship between baseline glucose-level category and the efficacy in patients with or without metabolic syndrome, with similar efficacy across dose groups [41]. Notably, regardless of glucose levels, no malignancies or worsening of diabetes were observed in any patient with metabolic syndrome [41].

4.5. Women of childbearing potential

Haycraft et al. analyzed pregnancies occurring in the Phase 1–3 trials with tildrakizumab [42]. In these trials, contraception was compulsory for all individuals of both genders when one partner was a female of childbearing age. In this post hoc study, there were 528 female patients, in whom 14 pregnancies were reported (contraception failed in 6 patients and 8 patients did not use contraception). All patients discontinued tildrakizumab when pregnancy was diagnosed. The exposure time varied form 29 days (1 dose) to 1196 days. Data was available for all 14 pregnancies. There were six cases of loss of the fetus consisting of four elective abortions and two spontaneous abortions, with an incidence similar to that seen in the general population. Among the eight live births, one was born premature at 36 weeks, while seven were carried to full term. There were no identifiable congenital anomalies in any of the infants. Similar findings were seen in preclinical investigations in pregnant cynomolgus monkeys, wherein there was no evidence of adverse outcomes related to treatment with tildrakizumab. Nonetheless, additional data are needed on the use of tildrakizumab during pregnancy, and all women of childbearing potential should use contraception while on treatment with tildrakizumab and continue for a minimum of 17 weeks after its discontinuation [28]. Very recently, Russo et al., reviewed the available data on the use of anti-IL-23 agents in pregnant women as some studies have hypothesized a role of IL-23 in spontaneous abortions. In fact, increased levels of IL-23, IL-17, IL-17 R, and p-STAT3 were found in peripheral blood and in decidua of women with recurrent early spontaneous abortions [43]. From this analysis it was concluded that anti-IL-23 agents are not likely to affect pregnancy outcomes provided that they are discontinued as soon as a pregnancy is discovered. Nonetheless, it should be mentioned that a dedicated perspective observational safety study is being carried out within the OTIS registry to assess pregnancy outcomes in women treated with tildrakizumab (NCT03992729).

4.6. Elderly

Post hoc analyses from reSURFACE 1 and reSURFACE 2 in the elderly have shown that tildrakizumab is well tolerated [35]. In particular, safety data at 256 weeks of patients aged ≥65 years were analyzed, which included 82 patients treated with tildrakizumab 200 mg and 79 with the 100 mg dose. The overall exposure adjusted incidence rates for severe infections in the tildrakizumab 200 and tildrakizumab 100 arms were 2.70 and 2.99, respectively (6 events each). Considering malignancies (excluding non-melanoma skin cancer), the exposure adjusted incidence rates were somewhat greater vs. the entire study population, but still low overall. The exposure adjusted incidence rates were 2.70 (six events) for tildrakizumab 200 mg, and 1.99 (four events) for tildrakizumab 100; the rates for non-melanoma skin cancer were 2.70 (six events) and 2.99 (six events), respectively. Considering specific tumor types, rectal adenocarcinoma and bladder cell carcinoma and was seen in both tildrakizumab-dose groups (exposure adjusted incidence rates of 0.45 and 0.50 for tildrakizumab 200 mg and 100 mg, respectively). Considering this data, there appear to be no new safety signals in elderly patients treated with tildrakizumab compared to younger patients.

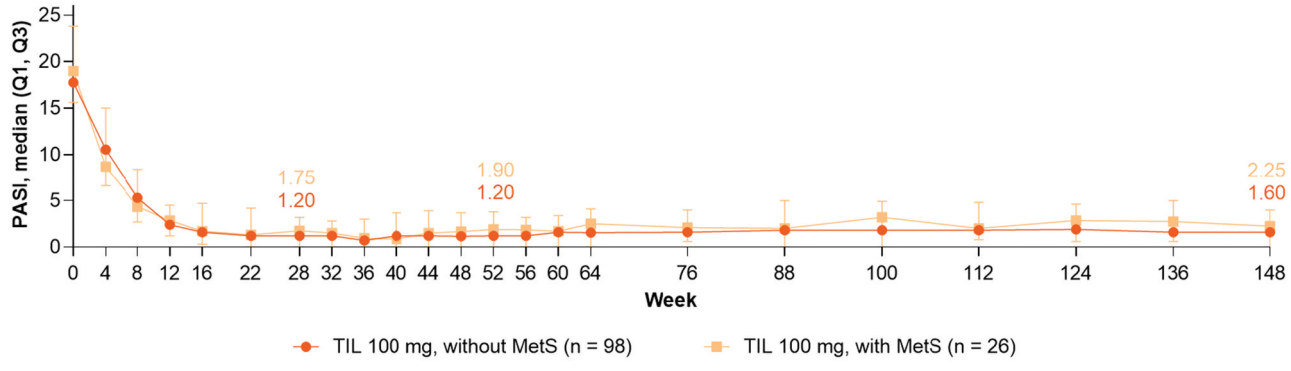


Figure 3. Efficacy and durability of tildrakizumab by metabolic syndrome status over 148 weeks. Adapted from [39] with permission.

5. Conclusions

This updated overview of the efficacy and safety of tildrakizumab highlights that overall the efficacy appears to be good, with a rapid response in the majority of patients that is maintained for up to 5 years among responders. Good responses have also been noted in difficult-to-treat areas such as the scalp and nails and in special populations like in patients with concomitant IBD, cardiovascular disease, metabolic syndrome, or advanced age. Overall, tildrakizumab appears to have a favorable safety profile and in the reSURFACE trials the rates of adverse events are low and similar to placebo, with few discontinuations due to adverse events. Moreover, long-term safety data for up to 5 years has shown that there is a low rate of discontinuations due to adverse events and no unexpected adverse events. The rate of severe infections is low, and there does not appear to be any increased risk for malignancies. MACEs are also uncommon.

6. Expert opinion

The review of the available data on tildrakizumab led to conclude that tildrakizumab has a favorable efficacy and safety profile in moderate to severe psoriasis patients that lasts for at least 5 years. This represents the longest follow-up for an IL-23 inhibitor. Interestingly, it is important to point out that residual PASI <3.0, a more reliable outcome than percentage PASI improvement [20], in about half of patients receiving tildrakizumab 100 mg, highlighting its short-term efficacy. One of the most interesting findings from all clinical studies is PASI <1 or <3 is maintained in a large proportion of patients in the long-term, which renders tildrakizumab distinctive. Moreover, according to preliminary data from clinical practice, tildrakizumab is a highly effective biologic for the treatment of moderate-severe plaque psoriasis, confirming data from clinical trials. From a safety point of view, the available evidence suggests that tildrakizumab is safe and well tolerated for up to 5 years of treatment with no apparent dose-related differences in adverse events, with very low incidence rate of discontinuation due to adverse events, particularly low rate of severe infections and MACEs, no apparent increased risk of malignancies including non-melanoma skin cancer (NMSC), even if additional data is needed to confirm the lack of relationship. Furthermore, since some medication adjustments in routine clinical practice include interruption and reinitiation of treatment, part 3 of the reSURFACE 1 study also assessed this possibility. Among those who relapsed and reinitiated tildrakizumab for at least 12 weeks, the vast majority of patients achieved PASI 75 again, thus indicating that the drug can be discontinued and reinitiated without major concerns in terms of efficacy [19].

A number of post hoc analyses have examined the efficacy and safety of tildrakizumab in special populations for which there may be some concern in patients with psoriasis. These include patients with IBD, cardiovascular disease, metabolic syndrome, advanced age, and history of malignancy. For each of these conditions, analysis of data from Phase 2 and 3 trials has shown no overt cause for concern, with exposure adjusted incidence rates being similar across all treatment groups with no clear-dose response relationship. In the absence of additional data, and especially from real-world data, at present prescribers will have to use best judgment when administering tildrakizumab to patients with such comorbidities or conditions with the knowledge that there is no evidence that hints at a safety signal in these groups of patients. Thus, tildrakizumab may be a valid choice of therapy in these subgroups of patients. At present, however, real-world evidence for the efficacy of tildrakizumab is limited and thus further study is needed to validate its efficacy outside the more rigid confines of randomized controlled trials. Lastly, while additional data is needed on pregnancy, prescribers should nonetheless carefully counsel women patients of child-bearing age about the need for continued contraception.

The pathological relevance of the IL-23/Th17 axis in psoriasis has been hypothesized and the key role of IL-23 has been documented by genetic studies with alleles of IL-23 and IL-23 R with susceptibility to psoriasis [44,45]; initial clinical trials demonstrated that inhibiting IL-23p19 leads to rapid clinical benefits of psoriasis, as well as improvement in histological characteristics that appears to be at least similar, and possibly even better, to that seen with blockade of IL-17 [46],while blockade of IL-12 is apparently not needed to obtain clinical efficacy.

Moreover, there is evidence to suggest that many processes involved in host defense are still viable if IL-12 remains functional, even when IL-23 is targeted [47,48]. At present, the differences between the clinical benefits of inhibition of IL-17 and IL-23 remain unclear, although inhibition of IL-23 might have a broader range of effects compared to IL-17 inhibition, such as the potential clinical impact of inhibition of the production of IL-22. Regarding sustained response over time, it is tempting to speculate that the favorable long-term results with tildrakizumab may possibly be related to its inhibition of IL-23, which acts upstream in the IL-23/Th17 pathway, and as a consequence may be less prone to the triggering of collateral pathways which could favor the loss of response over time [49]. The possibility that anti-IL-23 agents are associated with more durable responses compared to agents acting on other more downstream pathways is interesting and warrants further investigation. While antibodies against IL-17 or its receptor suppress levels of IL-17, deactivation of IL-23 has the possibility to reduce the activity of pathogenic Th17 cells [50,51]. Targeting IL-23 has the potential to explain the good efficacy and lasting responses of tildrakizumab by impairing the function of pathogenic T17 cells, restoring function of Treg cells, and inhibiting the production of IL-22, all of which are dependent on IL-23 [50,51]. Tissue resident memory cells can also be downregulated by anti-IL-23 inhibition [52].

Minimizing the clonal expansion of Th17 cells through targeting IL-23 has some potential benefits, such as a low frequency of dosing and prolonged drug effects. Indeed,

following induction, adalimumab remains effective for 2 weeks, and inhibitors of IL-17 remain effective when administered every 4 weeks; in contrast, blockers of IL-23 remain effective when administered every 8–12 weeks [46,51]. In contrast, the median time to loss of PASI 75 response among tildrakizumab responders is at 5–7 months after interruption of treatment [53]. This may be related to the fact that Th17 cells are long-lived and continue to be metabolically active, even after healing of skin lesions [54,55]. Therefore, inhibiting the production of Th17 cells by blocking IL-23 may be beneficial. This gives rise to the concept of lesional memory, which has been receiving increasing attention in recent years. In this regard, in biopsies of clinically healed lesions Clark et al. reported upregulation of IL-17, IL-22, and IFN-γ [56]. Park et al. later focused on the role of memory T-cells in tissue, which are likely to have a key role in the chronic course of the disease [57]. It has been proposed that a continuum, called 'the psoriatic march,' starts at an early stage and continues indefinitely [57]. It is thus possible that the adaptive immunity seen in stable disease, together with innate immunity that prevails in active disease, gives rise to systemic inflammation and augments the risk of the multitude of comorbidities linked with psoriasis. In this respect, it is interesting to note that the efficacy and safety of tildrakizumab is maintained in patients with severe comorbid conditions, such as metabolic syndrome compared to patients without comorbidities. In this regard, in an animal model, IL-23, by maintaining an intestinal T-helper type 17 response, appears to protect against development of obesity and metabolic disease [58]. In other immune-mediated inflammatory pathologies like rheumatoid arthritis and Crohn's disease, targeted therapy – when administered early in the course of the disease – has been hypothesized to improve long-term outcomes [59]. Therefore, early intervention in patients with plaque psoriasis with an IL-23 inhibitor such as tildrakizumab may help to improve control of symptoms, also in special populations, and may have the potential to change the long-term course of the disease, while improving the quality of life and minimizing the risk of developing comorbidities. Lastly, as noted by other authors, it is clear that a personalized approach should be taken when choosing the most appropriate therapy for the individual patients considering comorbidities, age, and expectations of treatment [60,61].

Funding

This paper is not funded.

Declaration of interests

A. Chiricozzi served as advisory board member and consultant, he has received speaker's honoraria or has participated in clinical trials for AbbVie, Almirall, Biogen, Fresenius Kabi, Leo Pharma, Lilly, Janssen, Novartis, Sanofi Genzyme and UCB Pharma. The author(s) have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

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