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Tildrakizumab in the treatment of psoriasis: latest evidence and place in therapy

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Abstract: Psoriasis is a chronic inflammatory disorder that is clinically characterized by scaly cutaneous plaques. New evidence suggests that dysregulation of interleukin (IL)-23, a key cytokine in the T-helper-17 pathway, plays a vital role in the development of psoriatic systemic inflammation. The novel biologic medication tildrakizumab is among the first drugs with specific action against IL-23 that has recently been approved by the United States Food and Drug Administration and the European Medicines Agency for moderate-to-severe psoriasis. Tildrakizumab has been shown in large randomized controlled trials to be effective in improving skin manifestations as well as enhancing quality of life outcomes in patients with psoriasis. Its simple dosing, prolonged duration of action, and mild adverse event profile make it a practical option for patients; however, only a small number of trials have investigated the clinical effectiveness of tildrakizumab, and long-term data regarding the drug's efficacy and safety are currently limited. Hence, further research is needed to better understand the risks and benefits of tildrakizumab. This review summarizes and analyzes phase I, phase II, and phase III clinical trials that investigate the mechanism, pharmacokinetics, efficacy, and safety of tildrakizumab. It also identifies areas in which additional studies are warranted to further elucidate the advantages of tildrakizumab over other biologic therapies.

Keywords: biologics, IL-23 inhibitor, psoriasis, tildrakizumab

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Introduction

Psoriasis is a systemic inflammatory disorder with a prevalence ranging from 0.5% to as high as 11.4% in some countries.¹ It is characterized clinically by the presence of erythematous, scaly, and well-demarcated cutaneous plaques that classically occur on the extensor surfaces. On a microscopic and molecular level, the disorder is thought to be caused by dysregulated interaction between the immune system and keratinocytes. Although mild psoriasis is generally well-managed with localized treatments, some patients with more severe disease presentation may require systemic therapy with immunomodulatory drugs.

The newest therapies for psoriasis are monoclonal antibodies that target the inflammatory cytokines involved in the pathogenesis of psoriasis. These drugs, known as biologics, have generated

significantly improved outcomes for patients with moderate-to-severe psoriasis. Tildrakizumab, a specific inhibitor of interleukin (IL)-23, has recently gained approval by the United States Food and Drug Administration (US FDA) as well as the European Medicines Agency (EMA) for patients with moderate-to-severe plaque psoriasis. This discussion provides an overview of existing literature on the mechanism, efficacy, and safety of tildrakizumab. It also aims to analyze the utility of tildrakizumab in comparison with other biologics and define areas in which additional investigation is warranted to better understand its risks and benefits.

Mechanism of action

The earliest biologics for psoriasis introduced to the market were inhibitors of the acute phase

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cytokine tumor necrosis factor-alpha (TNF- α). Newer-generation biologics inhibit the cytokine components of the IL-12/T-helper-1 (Th1) pathway, which promotes a powerful inflammatory response through interferon gamma and IL-2,² or the IL-23/Th17 pathway, which is best known for generating an immune response against bacterial and fungal antigens.³ Structurally, IL-12 and IL-23 are heterodimers that share a p40 subunit. IL-12 additionally contains a p35 subunit and IL-23 contains a p19 subunit. It was initially believed that the efficacy of biologics inhibiting p40, such as ustekinumab, was due to inhibition of IL-12, which was considered the integral cytokine for the majority of inflammation in psoriasis since it initiates a strongly proinflammatory Th1 response. More recently, however, it has been found that dysregulated IL-23 production likely plays a more significant role than IL-12 overproduction in driving psoriatic cutaneous inflammation. In mouse models, direct intradermal administration of IL-23 into the skin caused psoriasis-like inflammation and epidermal thickening, an effect not observed following injection of IL-12.⁴ Furthermore, IL-23p19 and IL-12/23p40 mRNA levels have been found to be elevated in psoriatic skin lesions while IL-12p35 levels are normal.^{5,6} Genome-wide association studies have also demonstrated that single nucleotide polymorphisms in IL-23p19 and the IL-23 receptor are associated with psoriasis.⁷ Tildrakizumab, a humanized antibody, selectively inhibits IL-23p19, and it is among the first approved psoriasis therapies that is specific for IL-23. Other novel therapies that specifically target IL-23p19 include guselkumab, which gained EMA approval for psoriasis in November 2017,⁸ and risankizumab, which is actively undergoing phase III trials for efficacy and safety.³

Pharmacokinetics and drug interactions

An open-label, phase I trial conducted by Zandvliet and colleagues (Table 1) was one of the earliest studies of the bioavailability of tildrakizumab. A total of 53 healthy patients without psoriasis were randomized to receive subcutaneous (SC) tildrakizumab at 50 mg, 200 mg, or 400 mg doses. Drug exposure over time was found to increase consistently with increased dosing. The maximum concentration of drug, total drug exposure over time, mean drug half-life, and median time to maximum drug concentration were comparable across Chinese, Japanese, and White

patients, which suggests that race may not significantly affect the metabolism of tildrakizumab. Both SC and intravenous (IV) dosing at 10 mg/kg were found to be well-tolerated by participants.⁹

There have been two randomized, placebo-controlled, phase I trials that tested the pharmacokinetic properties of IV tildrakizumab in healthy patients at doses ranging from 0.1 to 10 mg/kg and SC tildrakizumab at doses ranging from 50 to 200 mg (Table 1). These studies concluded that the maximum concentration and total drug exposure over time increased proportionally with both SC and IV dosing, corroborating the findings of Zandvliet and colleagues. It was also found that 50 mg SC dosing had a bioavailability of 80% (*versus* 0.5 mg/kg IV dosing) and 200 mg SC dosing had a bioavailability of 73% (*versus* 3 mg/kg IV dosing). Both of these bioavailabilities were deemed to result in adequate drug exposure for obtaining clinical efficacy.^{10,12}

Another trial has observed that tildrakizumab serum levels are generally higher in patients who demonstrated a 75% improvement in Psoriasis Area and Severity Index (PASI) scores (PASI-75) compared with those who did not show clinical improvement. However, in the group receiving the highest dose (200 mg SC), drug levels were similar in participants both with and without a favorable clinical response (Table 1).¹¹ The half-life of tildrakizumab is estimated to be between 3 and 4 weeks, such that it may be dosed infrequently as many weeks apart.^{9,12}

Currently, limited understanding exists regarding the interactions of tildrakizumab with other drugs. It is known that the reduction of systemic inflammation with biologic use may iatrogenically alter drug metabolism by cytochrome P450 (CYP) enzymes, as observed in patients with rheumatoid arthritis.¹³ Conversely, it has been hypothesized that biologics can normalize aberrant CYP activity in patients with psoriasis by blocking inflammatory cytokines that may alter the enzymes' action.¹⁴ A recent open-label, dual-period, fixed-sequence study found no significant changes in the pharmacokinetics or appearance of serum metabolites of CYP-metabolized drugs with the administration of tildrakizumab. Though this study was limited by a small sample size and a lack of blinding, it provides evidence that the incidence of drug-drug interactions in patients with psoriasis treated with tildrakizumab may be minimal.¹⁵

Table 1. Studies of the pharmacokinetics and clinical efficacy of tildrakizumab.

Study (year)	Study type	Participants	Objectives	Results
Zandvliet and colleagues ⁹	Open-label phase I	Part 1: 53 male and female Japanese, White and Chinese participants without psoriasis ages 18–55 years	<ul style="list-style-type: none"> Assess pharmacokinetics and tolerability of tildrakizumab 50–400 mg SC Evaluate differences in pharmacokinetics of tildrakizumab among ethnicities 	<ul style="list-style-type: none"> Drug exposure over time increased proportionally with increased SC dosing. Absolute bioavailability for tildrakizumab SC in Japanese patients was 92%. Dosing with 50–400 mg SC was well-tolerated. Maximum drug concentration, drug exposure over time, mean drug half-life, and median time to maximum was similar in Japanese, Chinese and White patients treated with tildrakizumab SC.
		Part 2: 6 male and female Japanese patients without psoriasis ages 18–55 years	<ul style="list-style-type: none"> Assess tolerability of tildrakizumab 10 mg/kg IV 	<ul style="list-style-type: none"> Dosing with 10 mg/kg IV was well-tolerated.
Khalilieh and colleagues ¹⁰	Randomized, placebo-controlled phase I	Study 1 (P05661): 29 participants without psoriasis ages 18–45 years at a single site in Melbourne, Australia	<ul style="list-style-type: none"> Assess pharmacokinetics and tolerability of ascending tildrakizumab IV doses (0.1–10 mg/kg) 	<ul style="list-style-type: none"> Drug exposure over time and maximum drug concentration increased proportionally with increased SC and IV dosing concentrations. Systemic clearance of drug following IV and SC dosing was slow, and half-life was long (ranging from 26.8 to 32.4 days). Half-life significantly decreased (to 10.1 and 13.5 days) in 2 of 6 patients who tested positive for ADAs to tildrakizumab. Bioavailability for 50 mg SC and 200 mg SC were 80% and 73%, respectively. All SC and IV doses tested were well-tolerated.
		Study 2 (P05776): 37 participants without psoriasis ages 18–45 years at a single site in Melbourne, Australia	<ul style="list-style-type: none"> Assess pharmacokinetics and tolerability of ascending tildrakizumab SC doses (50–200 mg) Determine the relative bioavailability of ascending tildrakizumab SC doses 	<ul style="list-style-type: none"> Half-life of IV dosing was long, ranging from 20.6 to 26.9 days. Dosing with 3 mg/kg and 10 mg/kg led to achievement of PASI-75 in the majority of patients between 16 and 28 weeks following initiation of treatment. Following drug discontinuation at 28 weeks, clinically meaningful PASI score reduction persisted through 36 weeks.
Kopp and colleagues ¹²	Randomized, placebo-controlled phase I proof-of-concept	77 male and female patients with moderate-to-severe plaque psoriasis ages 18–65 years at nine sites	<ul style="list-style-type: none"> Assess pharmacokinetics of tildrakizumab 0.05–10 mg/kg IV Evaluate clinical efficacy of tildrakizumab 0.05–10 mg/kg IV versus placebo through PASI reduction outcomes 	<ul style="list-style-type: none"> Half-life of IV dosing was long, ranging from 20.6 to 26.9 days. Dosing with 3 mg/kg and 10 mg/kg led to achievement of PASI-75 in the majority of patients between 16 and 28 weeks following initiation of treatment. Following drug discontinuation at 28 weeks, clinically meaningful PASI score reduction persisted through 36 weeks.

(Continued)

Table 1. (Continued)

Study (year)	Study type	Participants	Objectives	Results
Papp and colleagues ¹¹	Randomized, placebo-controlled, parallel group phase IIb	355 male and female patients with moderate-to-severe plaque psoriasis ages 18–82 years at 64 sites in USA, Canada, Japan, and Europe	<ul style="list-style-type: none"> Evaluate clinical efficacy of tildrakizumab 5–200 mg SC versus placebo through PASI reduction and PGA improvement outcomes 	<ul style="list-style-type: none"> Increasing SC dosing correlated with improvements in PASI scores and PGA scores versus placebo. The majority of patients treated with 100 mg or 200 mg for 52 weeks (dosing at week 0, week 4, and then every 12 weeks) showed maintained PASI–75 response at 16 weeks following drug discontinuation. Increased serum tildrakizumab levels correlated with a greater likelihood of achieving PASI–75. In patients receiving 200 mg dosing, serum levels were similar in clinically responsive and nonresponsive patients.
Reich and colleagues ¹⁶	Randomized, placebo-controlled, parallel group phase III	Study 1 (reSURFACE1): 772 male and female patients with moderate-to-severe plaque psoriasis ages 18 years and older at 118 sites in Australia, Canada, Japan, the UK, and USA	<ul style="list-style-type: none"> Evaluate clinical efficacy of tildrakizumab 100 mg and 200 mg SC versus placebo through PASI reduction, PGA improvement, and DLQI improvement outcomes 	<ul style="list-style-type: none"> Compared with patients treated with placebo, those treated with 100 mg and 200 mg tildrakizumab SC had significantly greater achievement of PASI–75 and dramatic decreases in PGA and DLQI scores after 12 weeks of treatment. Dosing with 100 mg and 200 mg tildrakizumab SC has similar clinical efficacy with respect to percent of patients who attain PASI–75 by 28 weeks. Compared with patients treated with etanercept 50 mg, those treated with 200 mg tildrakizumab SC had significantly higher rate of attainment of PASI–75 by week 12, PGA responses of 0 or 1 by week 12, and DLQI responses of 0 or 1 by week 28. This was not observed in patients treated with tildrakizumab 100 mg SC.
		Study 2 (reSURFACE2): 777 male and female patients with moderate-to-severe plaque psoriasis ages 18 years and older at 132 sites in Austria, Belgium, Canada, Czech Republic, Denmark, France, Germany, Hungary, Italy, Israel, Netherlands, Poland, and USA	<ul style="list-style-type: none"> Evaluate clinical efficacy of tildrakizumab 100 mg and 200 mg SC versus placebo and etanercept 50 mg through PASI reduction, PGA improvement, and DLQI improvement outcomes 	

ADA, antidrug antibody; DLQI, Dermatology Quality of Life Index; IV, intravenous; PASI, Psoriasis Area and Severity Index; PGA, Physician's Global Assessment; SC, subcutaneous.

Laboratory studies of efficacy

Kopp and colleagues performed microscopic, immunohistochemical, and gene expression testing of the lesional skin of patients at baseline and following 63 or 84 days of initiating treatment with various doses of tildrakizumab.¹² Cutaneous expression of IL-23p19, the target of tildrakizumab, was successfully reduced following tildrakizumab treatment. On microscopic examination, treated skin showed a resolution of epidermal thickening but had not fully reverted to the nonlesional state. A histopathological psoriasis severity score was found to be significantly reduced in skin of patients treated with tildrakizumab, with an average reduction of 67%. This effect was particularly prominent in patients treated with 3 mg/kg and 10 mg/kg tildrakizumab, who showed especially significant reductions in epidermal, vascular, and inflammatory parameters. Furthermore, expression of the proliferation markers Ki67 and epithelial antigen keratin 16 in the skin were normalized following tildrakizumab treatment, correlating with mitosis reduction in the suprabasal epidermal layer. Finally, tildrakizumab dosing also decreased the levels of inflammatory cells that are generally elevated in psoriasis, including that of epidermal and dermal CD4⁺ and CD8⁺ T-cells, dermal myeloid dendritic cells, CD11c⁺ myeloid dendritic cells, and CD15⁺ neutrophils.¹²

Clinical efficacy and dosing

Kopp and colleagues conducted one of the first randomized, double-blinded, placebo-controlled trials that investigated the clinical efficacy of tildrakizumab.¹² A total of 77 patients aged 18–65 years old with moderate-to-severe plaque psoriasis were administered IV injections of three doses of 0.05, 0.1, 0.5, 3, or 10 mg/kg tildrakizumab, with treatment intervals ranging from 4 to 8 weeks. Nearly all patients treated with 3 mg/kg and 10 mg/kg regimens reached PASI-75 between 16 and 28 weeks following initiation of treatment, and a significant portion of two groups also achieved PASI-90 by 28 weeks. Mean improvement in PASI scores were up to 80% for all groups by 28 weeks. A clinically meaningful response, defined as a PASI score reduction of 50% from baseline, persisted through 36 weeks of monitoring after administration of the final dose in both of these treatment groups.¹² These results were limited by a small sample size preventing appropriate dose–response correlation. Nonetheless, they provided preliminary evidence

that specifically targeting IL-23p19 with tildrakizumab results in the symptomatic improvement of psoriasis.

A multicenter, placebo-controlled, phase IIb trial affirmed the above results and provided a dose–response correlation for treatment. It included 64 clinic study sites in North America, Japan, and Europe, and it followed a total of 355 adult patients for 52 weeks. Patients were administered 5 mg, 25 mg, 100 mg, or 200 mg tildrakizumab SC at week 0, week 4, and then every 12 weeks until week 52. The percentages of patients that reported that their skin manifestations were ‘cleared’ or ‘minimal’, corresponding to a Physician’s Global Assessment (PGA) score of 0 or 1, were 33%, 58%, 62% and 74% for the 5 mg, 25 mg, 100 mg, and 200 mg groups, respectively. At the primary endpoint at week 16, PASI-75 responses were found to be 33%, 64%, 66%, and 74% for the 5 mg, 25 mg, 100 mg, and 200 mg groups, respectively. From 16 to 52 weeks, the dose of tildrakizumab was increased in nonresponders and decreased to 25 mg or kept constant in those with a favorable clinical response. Over 90% of those who received a constant dose attained PASI-75, compared with just 70% of those whose doses were reduced. In the group receiving a higher dose, the percentage of patients who attained PASI-75 increased with time. After 1 year of treatment, more than 90% of patients receiving doses of 100 mg or 200 mg of tildrakizumab from initiation of the study maintained PASI-75 6 months after treatment cessation, compared with just 68% of those who underwent dose reduction at week 16. This suggests that maintaining 100 mg to 200 mg dosing may provide a lasting clinical benefit even after discontinuation.¹¹

The phase III, parallel group, double-blinded, randomized, controlled reSURFACE1 and reSURFACE2 trials randomly assigned 1549 patients with moderate-to-severe psoriasis in North America, Europe, Australia, Israel, and Japan into groups based on the region of origin, body weight, and previous exposure to biologic therapy (Table 1). Each group was treated with placebo, 100 mg tildrakizumab or 200 mg tildrakizumab at week 0, week 4, and then every 12 weeks subsequently, and data were reported through 28 weeks from initiation of the studies. In reSURFACE1, at week 12, 64% and 62% of patients in the 100 mg and 200 mg groups, respectively, attained PASI-75, compared with only 6% in the placebo group. Similar trends

were observed in Dermatology Quality of Life Index (DLQI) and PGA scores of these patient groups as well as in analogous reSURFACE2 experiments. At 28 weeks, 90% and 84% of patients who initially responded to treatment with 200 mg tildrakizumab maintained PASI-75 in reSURFACE1 and reSURFACE2, respectively. In reSURFACE1, a group of patients received therapy with placebo for 12 weeks and were then randomized to receive tildrakizumab 100 mg or 200 mg; by week 28, their clinical responses were comparable with those treated with the analogous doses of tildrakizumab from the initiation of the study.¹⁶

The results of a 3-year follow up of a pooled analysis of individuals enrolled in reSURFACE1 and reSURFACE2 who had at least 75% improvement from baseline in PASI-75 at week 20 were recently publicized. It was found that PASI-75 or greater was maintained in 91% of individuals who continued the 100-mg dosing and in 92% of those continuing the 200-mg dosing. A subset of PASI-75 responders within reSURFACE1 were switched to placebo at week 28. A total of 54% and 47% of individuals relapsed in the groups formerly on the 100-mg and 200-mg dosing, respectively. The median time to relapse was very long, at 226 days in the 100 mg group and 258 days in the 200 mg group.¹⁷

The current US FDA-approved and EMA-approved dosing of tildrakizumab consists of 100 mg injected SC at weeks 0 and 4, followed by 100 mg SC every 12 weeks thereafter,^{18,19} a regimen that aims to optimize cost-effectiveness while maintaining appropriate skin relief and quality of life improvement. The EMA label additionally states that patients with a high disease burden and body weight may benefit from 200 mg dosing,¹⁹ although this has not been formally validated by any randomized controlled trials. Future prospective studies may focus on delineating the ideal time of treatment and frequency of dosing for the quickest response and longest maintenance following discontinuation of treatment. Furthermore, studies that evaluate the efficacy of tildrakizumab in different variants of psoriasis and patients with psoriatic arthritis and other systemic symptoms are merited.

Immunogenicity

With the use of biologics, patients occasionally develop antidrug antibodies (ADAs) against the biologic that prevent or diminish drug efficacy.^{20,21}

Many of the aforementioned trials evaluated the development and effects of ADAs against tildrakizumab. Of those who were pretreatment negative for ADAs, between 8% and 18% of patients developed ADAs.^{9,11,12} Overall, two studies found decreased tildrakizumab levels in a small fraction of the patients with positive ADA measurements,^{9,12} and one noted a significantly decreased tildrakizumab half-life in one-third of patients with positive ADAs.¹⁰ Most studies did not specifically comment on the relationship between clinical response and immunogenicity, although Kopp and colleagues reported that none of the ADA-positive patients had a diminished PASI response compared with those who did not have decreased drug levels.¹² While Zandvliet and colleagues outlined the lower limit of quantification of both the ADA and drug level measurement assays¹⁰ and Papp and colleagues described the use of an electrochemiluminescence-based immunoassay to screen patients for ADA presence,¹¹ the remainder of the studies failed to comment on a specific method of measuring ADA levels. Other limitations of many of these trials include a small cohort size and a lack of differentiation between primary and secondary nonresponse. Additionally, each of the studies varied in the time frames of ADA measurement following the initiation of treatment, making head-to-head comparisons among studies challenging. Future research may focus on determining the efficacy of antibody suppressants used for the management of ADAs against other biologics, such as methotrexate, in preventing a lack of response and treating loss of response to tildrakizumab.

Safety and adverse events

The majority of the aforementioned randomized trials found that approximately half of patients treated with tildrakizumab experienced at least one adverse event.^{9,11,12,16} The most consistently reported of these across the trials were headache (24–27%) and nasopharyngitis (8–39%).^{10,11,12,16} Injection site-associated complications, including hematomas, pain, and erythema were also commonly reported (1–15%).^{9,10,16} Dysmenorrhea was experienced by 2 of 29 patients in one of the studies.¹⁰ One trial observed that 9 of 307 patients treated with tildrakizumab *versus* none of the 45 patients receiving placebo experienced hypertension. However, six out of these nine patients were found to be hypertensive or pre-hypertensive at baseline.¹¹ A patient in another trial experienced

convulsions, but it was discovered that the patient had a history of sleep deprivation, alcohol consumption, and a recent reduction in benzodiazepine use.¹²

In spite of the aforementioned findings, tildrakizumab has been found to be, overall, well-tolerated. Most adverse events were mild and did not require treatment cessation and there was no dose-related increase in adverse events observed. Tildrakizumab did not cause any significant changes in vital signs and electrocardiogram results,^{10,11,12} and the risk of cardiovascular events was not significantly increased compared with that of untreated patients with moderate-to-severe psoriasis.¹¹ In the reSURFACE trials, inflammatory bowel disease, which has been reported to worsen with therapeutic inhibition of IL-17,²² was not observed in patients treated with tildrakizumab over 28 weeks of treatment.¹⁶ Furthermore, a recent pooled analysis of reSURFACE1 and reSURFACE2 reported that the 3-year safety profile of tildrakizumab is comparable with placebo, particularly with regards to the rates of serious infection and major cardiovascular events.¹⁷

There is a theoretical increased risk of infection and malignancy with the use of any immunosuppressant medications, including biologics.^{11,16} Isolated cases of bacterial arthritis, epiglottitis, malignant melanoma and other unspecified malignancies have been reported in patients treated with tildrakizumab.¹¹ Interestingly, however, compared with the inhibition of other inflammatory cytokines, inhibition of IL-23 may only minimally impair the ability to generate immune response. It has been observed in animal models that targeting IL-23p19 is associated with a lower risk of *Salmonella*, *Candida*, and *Mycobacterium* infections compared with the targeting of IL-12/23p40.¹¹ Furthermore, *Candida* infections, which are slightly more common in patients on IL-17 inhibitors, were considered ‘infrequent’ in one trial, though the particular frequency was not noted.¹¹

A major limitation of our knowledge regarding the side-effect profile of tildrakizumab is that much of the evidence available has been pooled from different studies with various endpoints.²³ More data regarding long-term safety outcomes of individuals formerly enrolled in various tildrakizumab trials would be of utility to further our understanding of the real-world scope and

severity of adverse effects related to therapy. In particular, follow-up studies investigating the incidence of infection and cancer in patients treated with tildrakizumab compared with those treated with other biologics may be warranted.

Comparisons to other biologics

The reSURFACE2 trial also directly compared the efficacy of tildrakizumab with that of etanercept. In this study, 310 patients were dosed with tildrakizumab 100 mg and 314 with tildrakizumab 200 mg. A total of 313 patients were treated with etanercept 50 mg twice weekly, which is the maximum approved dose for psoriasis. Compared with patients treated with etanercept, a significantly greater proportion of patients in the tildrakizumab 200 mg group achieved PASI-75 and PGA responses of 0 or 1 by week 12 as well as DLQI responses of 0 or 1 by week 28; however, tildrakizumab 100 mg did not have significantly more clinical efficacy than etanercept at week 12. Etanercept and tildrakizumab had similar rates and profiles of adverse events, though injection site erythema was more common in etanercept. This study also noted that suicidal ideation, observed in patients treated with the IL-17RA inhibitor brodalumab,²⁴ was not reported in the cohort treated with tildrakizumab.¹¹

The remainder of studies that compare the efficacy of tildrakizumab with that of other biologics synthesize data from independently performed randomized controlled trials. A study that reviewed phase II data available for tildrakizumab and guselkumab, which share the IL-23p19 target, found that the percentage of patients reaching PGA of 0 or 1 and PASI-75 was greater than 70% following 16 weeks of treatment with each agent at doses closest to those utilized in phase III clinical trials (200 mg tildrakizumab at weeks 0, 4, and then every 12 weeks; 100 mg guselkumab every 8 weeks).²⁵ Another study pooled PASI reduction scores and percentage of patients achieving a PGA of 0 or 1 from reSURFACE1 and reSURFACE2 as well as the phase III VOYAGE 1 and VOYAGE 2 trials analyzing the efficacy of guselkumab. Comparison of results found that tildrakizumab may be less clinically effective than guselkumab; however, this is not entirely reliable since the reSURFACE trials initially evaluated patients at 12 weeks and the VOYAGE trials at 16 weeks.²⁶ A recent meta-analysis synthesized data from 24 randomized

placebo-controlled trials to compare the efficacy and safety of IL-12/23 inhibitor ustekinumab, IL-17 inhibitors secukinumab, ixekizumab and brodalumab, and the selective IL-23 inhibitors guselkumab and tildrakizumab. The results of the study suggested that compared with placebo, 100mg tildrakizumab incurs a lower risk of adverse events related to achieving PASI-75, PASI-90, and PGA 0/1 compared with standard doses²⁷ of nearly every other biologic; the only exception was a slightly lower risk of adverse events related to achieving PGA 0/1 when using ustekinumab 45mg.²⁸ These results indicate that tildrakizumab may be safer than other approved biologics. At present, further meta-analyses, particularly studies that include data from trials of TNF- α inhibitors, would be useful to better elucidate the efficacy and tolerability of tildrakizumab compared with other biologics.

Conclusion

Tildrakizumab, an inhibitor of IL-23p19, has been demonstrated to significantly improve both cutaneous manifestations and quality of life in patients with moderate-to-severe psoriasis. Given the additional advantages of the simplicity of dosing, long period of action and mild adverse effects, it is a feasible therapeutic option for patients with moderate-to-severe psoriasis. However, since these claims are based on the findings of a limited number of clinical trials with shortcomings such as small cohort sizes and early endpoints, further study of the long-term efficacy and safety of tildrakizumab in direct comparison with other biologics on the market is still warranted. Investigations of the utility of tildrakizumab in patients who experience less common forms of psoriasis, systemic comorbidities, and failure of response to multiple biologic agents, as well as further meta-analyses comparing tildrakizumab with other biologics may help to better elucidate the complete spectrum of therapeutic potential for this novel drug and to better define its place in therapy.

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