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ARTICLE

Five-year safety of tildrakizumab in patients with moderate-to-severe psoriasis from two phase 3 trials (reSURFACE 1 and reSURFACE 2): number needed to harm for occurrence of adverse events of special interest

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ABSTRACT

Background: Five-year tildrakizumab safety data have been reported as exposure-adjusted incidence rates (EAIRs) of patients with events per 100 patient-years (PYs) of exposure.

Objectives: To present 5-year safety data from reSURFACE 1/2 phase 3 trials as EAIRs of events per 100 PYs of exposure, and the number needed to harm (NNH) for one adverse event of special interest (AESI) to occur.

Methods: Pooled analysis from two randomized controlled trials in patients with moderate-to-severe plaque psoriasis ($n = 1800$). PSOLAR registry was used as safety reference data for NNH estimation.

Results: Rates of AESI with tildrakizumab were comparable with rates reported in PSOLAR. The NNH for one-year severe infection occurrence was 412 with tildrakizumab 200 mg, and negative for tildrakizumab 100 mg due to lower rates in reSURFACE trials; the NNH for malignancy was 990 for one year with tildrakizumab 100 mg (negative for tildrakizumab 200 mg); and the NNH for major adverse cardiovascular events was 355 for one year with tildrakizumab 200 mg (negative for tildrakizumab 100 mg).

Conclusion: Tildrakizumab demonstrated a favorable safety profile over 5 years with low rates of AESI, comparable to those of the PSOLAR. Consequently, the NNH for AESI with tildrakizumab were very high or negative due to lower event rates for tildrakizumab.

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KEYWORDS
Adverse event of special interest; number needed to harm; psoriasis; tildrakizumab

Introduction

Plaque psoriasis is a chronic systemic immune-mediated inflammatory disease characterized by skin lesions that requires long-term treatment (1). The monoclonal antibody tildrakizumab is an interleukin (IL)-23p19 inhibitor available for the treatment of moderate-to-severe plaque psoriasis that has shown to be effective and safe for up to 5 years (2). Following approval, rising data from real-world evidence is further establishing the effectiveness and safety profile of tildrakizumab for the treatment of psoriasis in routine clinical practice (3–5).

Long-term safety data of tildrakizumab have been previously reported as exposure-adjusted incidence rates (EAIRs) of number of patients with events per 100 patient-years (PYs) (2). In order to better allow indirect comparison of tildrakizumab safety data with other biologic therapies, this manuscript reports safety through 5 years of tildrakizumab treatment in reSURFACE 1 and reSURFACE 2 trials as number of events per 100 PYs of exposure.

The number needed to harm (NNH) informs us about how many patients need to be treated with a given drug for one extra patient to experience a particular adverse event. Thus, reporting safety data as NNH provides a clearer picture of the magnitude of risk and a basis for wiser medical decision making and patient education (6). Therefore, we aimed to evaluate the NNH for one adverse event of special interest (AESI) to occur through one year of treatment with tildrakizumab 100 mg and 200 mg in these two phase 3 trials.

Patients and methods

Study design

Both 64-week reSURFACE 1 (ClinicalTrials.gov NCT01722331) and 52-week reSURFACE 2 (ClinicalTrials.gov NCT01729754) were three-part, parallel-group, double-blinded, randomized, placebo-controlled phase 3 trials. The detailed methodology has been published previously (7,8). After completing the double-blinded base study, patients with ≥50% improvement from baseline Psoriasis Area and Severity Index (PASI) score entered an optional open-label 4-year extension period of up to week 256 (reSURFACE 1) or week 244 (reSURFACE 2) (Figure S1; see Supplementary Material).

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Inclusion/exclusion criteria

The detailed eligibility criteria for the trials have been published previously (7). Briefly, patients aged ≥18 years and with a diagnosis of moderate-to-severe plaque psoriasis (≥10% of body surface area affected, Physician's Global Assessment score ≥3, and PASI score ≥12).

Assessments

Adverse events were evaluated at all study visits. Safety assessments consisted of overall adverse events and AESI. Pre-specified AESI included malignancies (excluding non-melanoma skin cancer), severe infections and confirmed extended major adverse cardiovascular events (MACEs) as previously defined (7,8). In reSURFACE 1 and reSURFACE 2 trials, 'severe infections' were either those infections meeting the regulatory definition of a serious adverse event (i.e., fatal, life-threatening, required or prolonged inpatient hospitalization, resulted in persistent or significant disability or incapacity, or required intervention to prevent one of these) or those requiring intravenous antibiotics. 'Extended MACEs' included non-fatal myocardial infarction, non-fatal stroke, unstable angina, coronary revascularization, resuscitated cardiac arrest, and cardiovascular deaths that were confirmed as 'cardiovascular' or 'sudden'. Deaths and serious cardiovascular events were adjudicated by an external clinical adjudication committee (7).

Safety was assessed from EAIRs of treatment-emergent adverse events and treatment-emergent AESI. Safety data are reported as EAIRs of events per 100 PYs of exposure. Both EAIRs and 95% confidence intervals were computed as previously reported (8).

Statistical analysis

Safety analyses were performed in the all-patients-as-treated population, defined as all randomized patients who received at least one dose of the study drug based on the treatment received. Data were pooled from patients treated with tildrakizumab 100 mg (i.e., patients who received tildrakizumab 100 mg in at least one part of the study) or tildrakizumab 200 mg (i.e., patients who received tildrakizumab 200 mg in at least one part of the study) between reSURFACE 1 (up to week 256) and reSURFACE 2 (up to week 244).

The NNH for AESI with tildrakizumab 100 mg or 200 mg is reported, i.e., the number of patients who would need to be treated with tildrakizumab 100 mg or 200 mg in order for one person to develop an AESI. The NNH was calculated by dividing 1 with the absolute risk for an AESI to occur over one year of treatment with tildrakizumab. Safety reference data was from Psoriasis Longitudinal Assessment and Registry (PSOLAR) (9,10). Accordingly, NNH for AESI with tildrakizumab 100 mg or 200 mg was corrected for the baseline risk (or risk in the unexposed) of AESI in general population with psoriasis as follows:

$$NNH = \frac{1}{(EAIR\ of\ events\ per\ PY\ in\ reSURFACE\ \ trials\ including\ extension - \text{EAIR in PSOLAR})}.$$

PSOLAR registry

PSOLAR is an ongoing intercontinental prospective registry designed to track the long-term safety experience of patients receiving, or eligible to receive, systemic non-biologic and biologic therapies for psoriasis (9,11). In PSOLAR, 'serious infections' were defined as those requiring hospitalization or considered medically important; non-melanoma skin cancer was also excluded from the event-class 'malignancies'; and 'MACEs' comprised cardiovascular death, non-fatal cerebrovascular accident, and non-fatal myocardial infarction. PSOLAR includes mainly patients who were exposed to etanercept, adalimumab, infliximab, and ustekinumab. Other treatments in the registry were efalizumab, alefacept, golimumab, and non-biologics such as methotrexate and cyclosporine (9).

Results

Overall, 872 patients on tildrakizumab 100 mg and 928 patients on tildrakizumab 200 mg were included in the analysis, with a total exposure to tildrakizumab 100 mg and 200 mg of 2688.4 and 2753.5 PYs, respectively. Baseline demographic and disease characteristics in the safety analysis set were similar among treatment groups (Table 1) and comparable to the total cohort in the PSOLAR (9).

Exposure-adjusted incidence rates of adverse events

The EAIRs of adverse events per 100 PYs were 194.6 for tildrakizumab 100 mg and 202.5 for tildrakizumab 200 mg (Table 2); the majority were considered not to be related to tildrakizumab by the investigator. The most frequent adverse events were nasopharyngitis, with 24.0 and 23.4 events per 100 PYs of exposure to tildrakizumab 100 mg and 200 mg, respectively, and upper respiratory tract infection, with 6.7 and 7.7 events per 100 PYs of tildrakizumab 100 mg and 200 mg, respectively (Table 3). Among gastrointestinal disorders, the most common event was diarrhea, with 2.9 and 2.6 events per 100 PYs of exposure to tildrakizumab 100 mg and 200 mg, respectively (Table S1, see Supplementary Material). Few events led to treatment discontinuation (1.9 and 1.5 events per 100 PYs of tildrakizumab 100 mg and 200 mg) (Table 2).

Table 1. Baseline characteristics of the safety population.

	Tildrakizumab 100 mg ($N = 872$)	Tildrakizumab 200 mg ($N = 928$)
Male, *n* (%)	626 (71.8)	659 (71.0)
Age (years), mean (SD)	45.7 (13.3)	45.9 (13.3)
Weight (kg), mean (SD)	89.1 (23.2)	88.6 (22.8)
BMI (kg/m^2), mean (SD)	29.8 (7.1)	29.8 (7.4)
BSA (%), mean (SD)	31.8 (17.8)	31.2 (17.3)
PASI score, mean (SD)	20.0 (7.7)	20.2 (7.9)
PGA category, *n* (%)		
≤3	580 (66.7)	613 (66.5)
≥4	289 (33.3)	309 (33.5)
Psoriatic arthritis (yes), *n* (%)	136 (15.6)	143 (15.4)
Previously treated with biologics, *n* (%)	142 (16.3)	160 (17.2)

BMI: body mass index; BSA: body surface area; PASI: Psoriasis Area Severity Index; PGA: Physician's Global Assessment; SD: standard deviation.

Table 2. Exposure-adjusted incidence rates of adverse events through weeks 256/244 in reSURFACE 1 and reSURFACE 2 studies.

Preferred term	Tildrakizumab 100 mg (*N* = 872)	Tildrakizumab 200 mg (*N* = 928)
Total follow-up, PYs	2688.4	2753.5
Any TEAE	5232 (194.6 [189.2–200.0])	5577 (202.5 [197.1–208.0])
Drug-related TEAEs	793 (29.50 [27.40–31.59])	1040 (37.77 [35.43–40.11])
Any SAE	249 (9.26 [8.09–10.44])	245 (8.90 [7.76–10.03])
Drug-related SAEs	24 (0.89 [0.53–1.26])	16 (0.58 [0.29–0.87])
AEs leading to death	11 (0.41 [0.16–0.66])	5 (0.18 [0.02–0.34])
TEAEs leading to discontinuation	52 (1.93 [1.40–2.47])	40 (1.45 [0.99–1.91])
Drug-related AEs leading to discontinuation	19 (0.71 [0.38–1.03])	10 (0.36 [0.13–0.59])
SAEs leading to discontinuation	31 (1.15 [0.74–1.57])	23 (0.84 [0.49–1.18])
Drug-related SAEs leading to discontinuation	9 (0.33 [0.11–0.56])	5 (0.18 [0.02–0.34])

AE: adverse event; PYs: patient-years; SAE: serious adverse event; TEAE: treatment-emergent adverse event. Data shown as n (number of events per 100 patient-years of exposure [95% confidence interval]).

Table 3. Exposure-adjusted incidence rates of adverse events occurring in ≥5% of patients in one or more treatment groups through weeks 256/244 in reSURFACE 1 and reSURFACE 2 studies.

Preferred term	Tildrakizumab 100 mg (*N* = 872)	Tildrakizumab 200 mg (*N* = 928)
Total follow-up, PYs	2688.4	2753.5
Arthralgia	104 (3.87 [3.11–4.63])	116 (4.21 [3.43–5.00])
Back pain	72 (2.68 [2.05–3.31])	88 (3.20 [2.51–3.88])
Bronchitis	62 (2.31 [1.72–2.89])	82 (2.98 [2.32–3.64])
Cough	67 (2.49 [1.88–3.10])	80 (2.91 [2.26–3.56])
Diarrhea	77 (2.86 [2.21–3.52])	71 (2.58 [1.97–3.19])
Gastroenteritis	54 (2.01 [1.46–2.56])	61 (2.22 [1.65–2.78])
Headache	99 (3.68 [2.94–4.42])	105 (3.81 [3.07–4.56])
Hypertension	92 (3.42 [2.71–4.14])	108 (3.92 [3.17–4.68])
Influenza	79 (2.94 [2.28–3.60])	104 (3.78 [3.04–4.52])
Injection site erythema	11 (0.41 [0.16–0.66])	35 (1.27 [0.84–1.70])
Injection site reaction	5 (0.19 [0.02–0.35])	9 (0.33 [0.11–0.54])
Nasopharyngitis	644 (23.95 [22.07–25.84])	643 (23.35 [21.51–25.19])
Nausea	29 (1.08 [0.68–1.48])	42 (1.53 [1.05–2.00])
Oropharyngeal pain	40 (1.49 [1.02–1.96])	47 (1.71 [1.21–2.20])
Pruritus	37 (1.38 [0.92–1.83])	39 (1.42 [0.96–1.87])
Psoriasis	31 (1.15 [0.74–1.57])	37 (1.34 [0.90–1.79])
Sinusitis	74 (2.75 [2.11–3.39])	67 (2.43 [1.84–3.03])
Upper respiratory tract infection	179 (6.66 [5.66–7.65])	213 (7.74 [6.68–8.80])
Urinary tract infection	69 (2.57 [1.95–3.18])	67 (2.43 [1.84–3.03])

PYs: patient-years. Data shown as n (number of events per 100 patient-years of exposure [95% confidence interval]).

Table 4. Exposure-adjusted incidence rates of adverse events of special interest through weeks 256/244 in reSURFACE 1 and reSURFACE 2 studies.

Preferred term	Tildrakizumab 100 mg (*N* = 872)	Tildrakizumab 200 mg (*N* = 928)
Total follow-up, PYs	2688.4	2753.5
Severe infection	38 (1.41 [0.95–1.87])	48 (1.74 [1.24–2.25])
Malignancy excluding NMSC	21 (0.78 [0.44–1.12])	17 (0.62 [0.32–0.92])
NMSC	14 (0.52 [0.24–0.80])	16 (0.58 [0.29–0.87])
Melanoma	3 (0.11 [0.00–0.24])	3 (0.11 [0.00–0.23])
Confirmed extended MACE	15 (0.56 [0.27–0.85])	24 (0.87 [0.52–1.23])
Injection-site reaction[a]	67 (2.49 [1.88–3.10])	86 (3.12 [2.45–3.80])
Drug-related hypersensitivity reaction	14 (0.52 [0.24–0.80])	5 (0.18 [0.02–0.34])

MACE: major adverse cardiovascular event; NMSC: non-melanoma skin cancer; PYs: patient-years. Data shown as n (number of events per 100 patient-years of exposure [95% confidence interval]). [a]Not recorded during the extension studies.

The EAIRs of serious adverse events were 9.3 and 8.9 (0.9 and 0.6 drug-related) events per 100 PYs of exposure to tildrakizumab 100 mg and 200 mg, respectively (Table 2). Fourteen deaths occurred during the trials: nine patients (corresponding to 11 events) in the tildrakizumab 100 mg group and five patients (corresponding to 5 events) in the tildrakizumab 200 mg group (Table 2). Details of adverse events leading to death through week 256 (reSURFACE 1) or week 244 (reSURFACE 2) have been reported previously (2,8,12).

Exposure-adjusted incidence rates of AESI

Incidence rates of severe infections, malignancies and MACEs across tildrakizumab groups were low and comparable with the rates reported in PSOLAR (Tables 4 and 5) (9,10). The EAIRs of severe infections were 1.4 and 1.7 events per 100 PYs of tildrakizumab 100 mg and 200 mg, respectively (Table 4); the most common were diverticulitis and pneumonia (Table S2, see Supplementary Material). The EAIRs of malignancies (excluding non-melanoma skin cancer) were 0.8 and 0.6 events per 100 PYs of exposure to tildrakizumab 100 mg and 200 mg, respectively (Table 4); the most common were malignant melanoma *in situ* and rectal adenocarcinoma (Table S3, see Supplementary Material). The EAIRs of confirmed extended MACEs were 0.6 and 0.9 events per 100 PYs of tildrakizumab 100 mg and 200 mg, respectively (Table 4); the most common were acute myocardial infarction and coronary artery disease (Table S4, see Supplementary Material).

Candida infections were uncommon; the most frequent was skin candidiasis with EAIRs of 0.2 and 0.3 events per 100 PYs of

Table 5. Number needed to harm for occurrence of adverse events of special interest with tildrakizumab 100 mg and 200 mg corrected for the baseline risk in reference population with psoriasis.

			Tildrakizumab 100 mg ($N = 872$)			Tildrakizumab 200 mg ($N = 928$)		
		Total follow-up, PYs	2688.4			2753.5		
		Exposure-adjusted incidence rate[a] in the PSOLAR [9,10]	Number of events	Exposure-adjusted incidence rate[a]	NNH	Number of events	Exposure-adjusted incidence rate[a]	NNH
AESI	Severe/Serious infection	0.0150[b]	38	0.01413	−1149.4	48	0.01743	**411.5**
	Malignancy	0.0068[b]	21	0.00781	**990.1**	17	0.00617	−1587.3
	Extended MACE/MACE	0.0059[b]	15	0.00558	−3125.0	24	0.00872	**354.6**

AESI, adverse event of special interest; MACE, major adverse cardiovascular event; NNH, number needed to harm; PSOLAR, Psoriasis Longitudinal Assessment and Registry; PYs, patient-years. [a]Number of events per patient-year of exposure. [b]Total cumulative incidence rate. In reSURFACE trials, 'severe infections' were either those infections meeting the regulatory definition of a serious adverse event or those requiring intravenous antibiotics; non-melanoma skin cancer was excluded from 'malignancies'; and 'extended MACEs' included non-fatal myocardial infarction, non-fatal stroke, unstable angina, coronary revascularization, resuscitated cardiac arrest, and cardiovascular deaths that were confirmed as 'cardiovascular' or 'sudden'. In PSOLAR, 'serious infections' were either those requiring hospitalization or considered medically important; non-melanoma skin cancer was also excluded from 'malignancies'; and 'MACE' comprised cardiovascular death, non-fatal cerebrovascular accident and non-fatal myocardial infarction.
Positive NNH values are marked in bold.

tildrakizumab 100 mg and 200 mg, respectively (Table S5, see Supplementary Material). One case of suspected new-onset Crohn disease occurring in the tildrakizumab 100 mg group (0.04 events per 100 PYs) was previously reported (2).

Number needed to harm for AESI occurrence with tildrakizumab 100 mg or 200 mg per year

For one severe infection to occur, 412 patients needed to be treated with tildrakizumab 200 mg for one year, whereas the NNH value was not possible to calculate (i.e., negative value) for tildrakizumab 100 mg due to lower event rate in the reSURFACE trials versus the PSOLAR. For one malignancy to occur, 990 patients needed to be treated with tildrakizumab 100 mg for one year, while the event rate for tildrakizumab 200 mg was lower in the reSURFACE trials than in the PSOLAR registry. For one MACE to occur, 355 patients needed to be treated with tildrakizumab 200 mg for one year, while the NNH value was negative for tildrakizumab 100 mg (Table 5).

Discussion

Long-term safety of tildrakizumab through 5 years has been previously reported as EAIRs of patients with events per 100 PYs (2). This pooled analysis from the reSURFACE 1 and reSURFACE 2 trials presents safety data of tildrakizumab as events per 100 PYs from 1800 patients with moderate-to-severe psoriasis treated for up to 5 years, with 5442 PYs of total exposure. As some events might happen more than once for one patient, reporting safety data as number of events per 100 PYs in addition to previously reported number of patients with events per 100 PYs, may provide additional clinical value and allow statistical indirect comparison with other datasets.

Incidence rates of either adverse events leading to treatment discontinuation or drug-related serious adverse events were low for tildrakizumab 100 mg and 200 mg. Similarly, few severe infections, malignancies, and MACEs were reported, indicating low risk of these events with tildrakizumab treatment. There was no dose-dependent effect on the safety outcomes. Overall, similar rates of adverse events have been reported for other IL-23p19 inhibitors (13,14).

The NNH for pre-specified AESI is reported for tildrakizumab. Reporting risk of adverse events as NNH is a valuable tool for physicians by providing them with the best information available to improve patient management and treatment decisions (6), and allows the clinician to describe the risk-benefit profile of tildrakizumab to the patient in a way that is easy to understand. In addition to perhaps providing a more clinically tangible value, NNH also allows for correction of an inherent risk in the study population. For example, psoriasis patients may have higher risk of cardiovascular events or malignancies than the general population (15,16). Rates of AESI with tildrakizumab were consistent with those captured in the PSOLAR (total exposure of 31,818 PYs) (9,10). Therefore, the NNH for AESI with tildrakizumab, corrected for the risk in a general population of moderate-to-severe psoriasis patients treated with systemic therapies, were very high or even negative due to lower events rates for tildrakizumab. Treatments with 'negative' NNH have a reduced risk of an adverse event in relation to the comparator, and treatments with higher NNH are associated with a more favorable safety profile (17). It should be noted, however, that PSOLAR did not include non-serious infections that required intravenous antibiotics or extended MACEs (9).

Limitations of this analysis include the above already mentioned slightly different definitions of severe (or serious) infections, malignancies, or MACEs (extended or not) between reSURFACE trials and PSOLAR (9) registry. However, definitions of AESI in the reSURFACE trials were overall more extensive and thus, included a greater number of events. In addition, registries collect safety as part of normal routine care with fewer study visits and less structured safety reporting compared to randomized controlled trials. Thus, PSOLAR, as an observational study, may have been subject to selection bias and less stringent follow-up, which in turn would bias our results against treatment with tildrakizumab. For instance, in the PSOLAR the true rates of AESI may have been expectedly higher (and consequently the NNH would have been at lower values) in comparison to the current analyses. Lastly, an ideal comparator group as a reference would be an untreated cohort of patients with moderate-to-severe psoriasis. However, it would be very difficult to find such a group.

In conclusion, tildrakizumab demonstrated a favorable safety profile over 5 years with low event rates of severe infections, malignancies, and MACEs, comparable with those from the psoriasis reference registries. Consequently, the NNH for AESI with tildrakizumab were very high or even negative due to lower event rates for tildrakizumab.

These results further support the favorable safety profile of IL-23p19 inhibitors for patients with moderate-to-severe psoriasis.

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Ethics statement

The original reSURFACE 1 and reSURFACE 2 trials were conducted following the ethical principles of the Helsinki Declaration and were approved by local institutional review boards or ethics committees at each study site (7). All patients provided written informed consent before their inclusion in the trials.

Author contributions

AE, DJ and KGdJ substantially contributed to the conception and design of the work, analysis and interpretation of data, and drafted the work and revised it critically for important intellectual content. DT substantially contributed to the conception and design of the work, acquisition, analysis and interpretation of data, and drafted the work and revised it critically for important intellectual content. All authors approved the final version of the manuscript.

Disclosure statement

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Data availability statement

The datasets generated or analyzed during this study are available from the corresponding author on reasonable request.

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