REVIEW ARTICLE

Safety of selective IL-23p19 inhibitors for the treatment of psoriasis

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Abstract

Psoriasis is a chronic disease that requires long-term treatment. Consequently, understanding the safety and tolerability of any potential treatment over time is critical to effective prescribing. The biologic agents currently available for the treatment of psoriasis target a number of different inflammatory cytokines involved in psoriasis disease pathogenesis. The monoclonal antibodies tildrakizumab, guselkumab and risankizumab target the p19 subunit that is specific to interleukin (IL)-23. This article reviews published data on the safety of these IL-23p19 inhibitors in patients with psoriasis compared with other currently available biologic therapies. Data from randomized, placebo- and active-controlled phase 3 clinical trials show tildrakizumab, guselkumab and risankizumab to have a favourable risk–benefit profile in patients with moderate to severe psoriasis. No significant safety concerns have been observed for any of these IL-23p19 inhibitors in the data published to date. The most commonly reported adverse events (AEs) associated with these agents in phase 3 studies were upper respiratory tract infections. No increase was seen in rates of serious infections, malignancies or major adverse cardiovascular events, with no signals suggestive of an elevated risk of opportunistic infections, active tuberculosis or reactivation of latent tuberculosis infection, mucocutaneous *Candida* infections, triggering or worsening of inflammatory bowel disease, demyelinating disorders or suicidal ideation. Selectively targeting IL-23p19 may help avoid AEs that have been associated with biologic agents with other mechanisms of action. Data from long-term extension studies and patient registries will further establish the safety profile of IL-23p19 inhibitors for the treatment of moderate to severe psoriasis in routine practice.

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Conflicts of interest

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Introduction

Psoriasis is a chronic T-cell-mediated inflammatory skin disease, estimated to affect more than 100 million individuals worldwide, of whom approximately 20% have moderate to severe disease.[1,2] The pathogenesis of psoriasis is complex; however, there is robust evidence that the interleukin (IL)-23/IL-17 immune axis is a key driver of psoriatic inflammation.[3] Over the past 2 decades, biologic treatment of moderate to severe psoriasis has

changed the disease management paradigm. Multiple biologic therapies are now available or in late stages of development (Table 1), targeting different inflammatory cytokines (Fig. 1). These include tumour necrosis factor (TNF) antagonists, IL-17 inhibitors, an IL-12/23p40 inhibitor and monoclonal antibodies that target the p19 subunit that is specific to IL-23.

Psoriasis is a chronic disease that often requires ongoing treatment. Consequently, the long-term safety and tolerability of any treatment are critical to effective prescribing. Early biologic agents for the treatment of psoriasis typically induced non-specific immunosuppression, including agents targeting T-cell activation and migration (efalizumab and alefacept, both of which have now been withdrawn) and anti-TNF agents that target a key cytokine involved in most inflammatory and infectious processes in the body.[4] TNF antagonists have been associated with increased risk of serious bacterial, viral and fungal infections in patients with psoriasis, including active tuberculosis and reactivation of latent tuberculosis infection.[5–9] The data on malignancy risk with long-term exposure to TNF antagonists are conflicting, with some studies and recent registry data suggesting a potential increased risk.[5–8,10] Rare cases of new onset or exacerbation of demyelinating disorders have also been reported during treatment with TNF antagonists.[5–8]

As understanding of psoriasis disease mechanisms has advanced, more targeted therapies have become available with the potential for improved safety and tolerability. Three agents targeting the IL-17 cytokine pathway are available; secukinumab and ixekizumab are specific to IL-17A, whereas brodalumab is

Table 1 Biologics for the treatment of moderate to severe psoriasis in adults approved or filed for approval by the United States Food and Drug Administration as of June 2019

Biologic drug	Therapeutic target	Approval date	Other approved indications/notes
Etanercept	TNF	April 2004	Moderate to severe rheumatoid arthritis (November 1998) Moderate to severe polyarticular juvenile idiopathic arthritis (≥2 years) (May 1999) Psoriatic arthritis (January 2002) Ankylosing spondylitis (July 2003) Paediatric (4–17 years) chronic moderate to severe psoriasis (November 2016)
Infliximab	TNF	September 2006	Crohn's disease (August 1998) Rheumatoid arthritis (November 1999) Ankylosing spondylitis (December 2004) Psoriatic arthritis (May 2005)Ulcerative colitis (September 2005) Paediatric (≥6 years) Crohn's disease (May 2006) Paediatric (≥6 years) ulcerative colitis (September 2011)
Adalimumab	TNF	January 2008	Rheumatoid arthritis (December 2002) Psoriatic arthritis (October 2005) Ankylosing spondylitis (July 2006) Crohn's disease (February 2007) Polyarticular juvenile idiopathic arthritis (≥2 years) (February 2008) Ulcerative colitis (September 2012) Paediatric (≥6 years) Crohn's disease (September 2014) Moderate to severe hidradenitis suppurativa (≥12 years) (September 2015) Uveitis (≥2 years) (June 2016)
Ustekinumab	IL-12/IL-23p40	September 2009	Active psoriatic arthritis (September 2013) Moderately to severely active Crohn's disease (September 2016) Adolescent (≥12 years) moderate to severe psoriasis (October 2017)
Secukinumab	IL-17A	January 2015	Active psoriatic arthritis (January 2016) Active ankylosing spondylitis (January 2016)
Ixekizumab	IL-17A	March 2016	Active psoriatic arthritis (December 2017)
Brodalumab†	IL-17A receptor	February 2017	—
Guselkumab	IL-23p19	July 2017	—
Tildrakizumab	IL-23p19	March 2018	—
Certolizumab pegol	TNF	May 2018	Moderate to severe Crohn's disease (April 2008) Moderately to severely active rheumatoid arthritis (May 2009)Active psoriatic arthritis (September 2013) Active ankylosing spondylitis (October 2013)
Risankizumab	IL-23p19	Filed for approval April 2019	—

†Availability restricted through a Risk Evaluation and Mitigation Strategy (REMS) programme in the United States.
IL, interleukin; TNF, tumour necrosis factor.

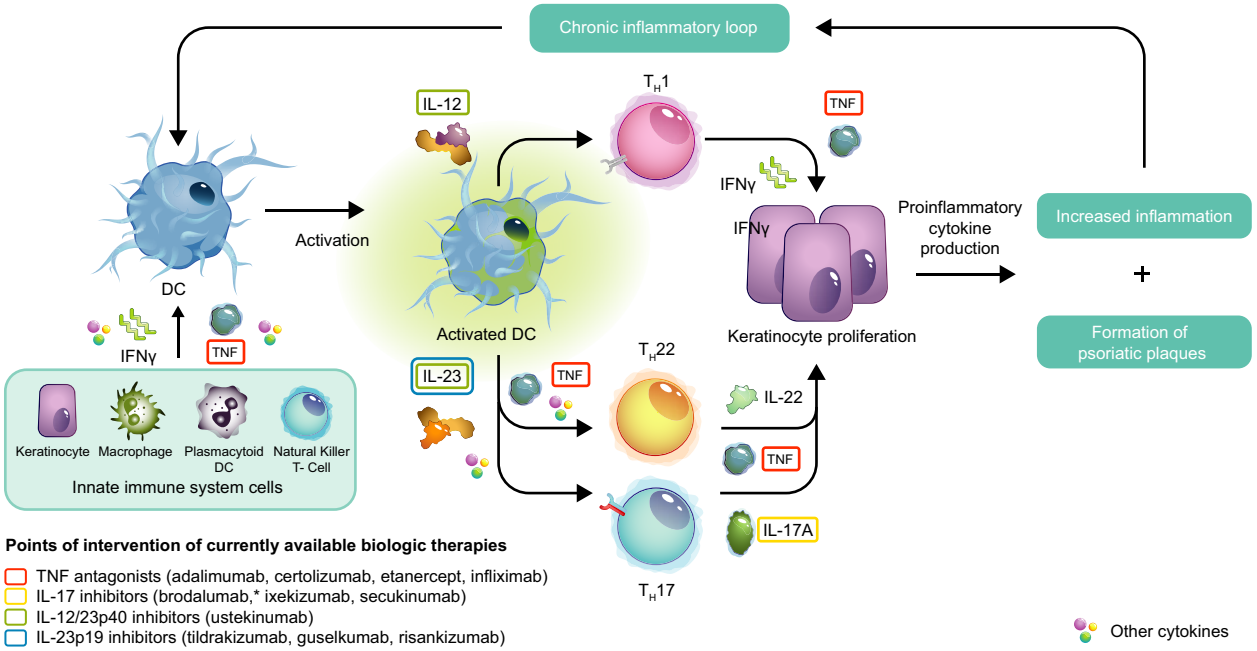

Figure 1 Schematic overview of psoriasis disease pathogenesis highlighting points of intervention of currently available biologic treatment options. *Brodalumab is directed against the IL-17 receptor, and not IL-17. DC, dendritic cell; IFN, interferon; IL, interleukin; T_H, T helper; TNF, tumour necrosis factor.

directed against the IL-17 receptor. IL-17 inhibitors have shown generally favourable safety profiles in patients with psoriasis.[11–13] However, increased risk of *Candida* infections, worsening of pre-existing inflammatory bowel disease and, rarely, new-onset ulcerative colitis and Crohn's disease have been reported during treatment.[11–16] The observed increase in *Candida* infections is not unexpected, as IL-17 is known to play a key role in the host defence against yeast and fungi.[17,18] In terms of inflammatory bowel disease, it is possible that blocking IL-17 signalling may interfere with a protective function of IL-17A in the intestine.[19] In addition, brodalumab has a warning for suicidal ideation and behaviour, although a causal relationship has not been established,[20] and availability is restricted through a Risk Evaluation and Mitigation Strategy (REMS) programme in the United States.[21]

Several agents targeting the IL-23 cytokine pathway are now available. IL-23 is a heterodimer composed of two subunits: p40, which is shared with IL-12, and p19.[3] Data from long-term clinical trials and a large safety registry (Psoriasis Longitudinal Assessment and Registry; PSOLAR) have shown the IL-12/23p40 inhibitor ustekinumab to be well tolerated in patients with psoriasis.[22–26] However, another anti-IL-12/23p40 agent, briakinumab, showed signs of a possible increased risk of major cardiovascular adverse events (MACE), infections and malignancies in clinical trials,[27,28] and development was stopped before approval. Additionally, there is evidence that blockade of IL-12 may be counterproductive in treating patients with psoriasis: mice lacking IL-12 signalling components develop worse psoriasis than wild-type animals[29] and IL-12 exhibits protective roles against malignancies[30] and infections.[31,32] However, clinical studies of IL-12/23 inhibitors have not detected signals for these safety events.[24,25] Differences in safety may exist among agents targeting the same cytokine(s), owing to dosing, pharmacokinetics, antibody-binding sites and affinities.

Selectively targeting IL-23p19 may avoid adverse events (AEs) that have been associated with biologic agents with other mechanisms of action. Here we review published data on the safety of the IL-23p19 inhibitors guselkumab, tildrakizumab and risankizumab in patients with psoriasis, focusing on the frequency of AEs that have been associated with other biologic therapies in pivotal randomized, controlled phase 3 clinical trials. An additional IL-23p19 inhibitor, mirikizumab, is in development, but clinical trial data have not yet been published.

Safety data from clinical trials

Results of phase 1 and 2 studies showed favourable safety and tolerability profiles in adult patients with moderate to severe psoriasis for guselkumab,[33–36] tildrakizumab[37,38] and risankizumab.[39,40] These findings were confirmed by results of randomized, controlled phase 3 clinical trials (Table 2), with no major

Table 2 Percentages of patients reporting AEs of special interest in pivotal phase 3 studies of biologics selectively targeting IL-23p19[41–46]

IL-23p19 inhibitor	Guselkumab					Tildrakizumab				Risankizumab		
Study	**VOYAGE 1 & 2**			**NAVIGATE†**		**reSURFACE 1 & 2**				**UltIMMa-1 & UltIMMa-2**		
Intervention	GUS 100 mg	ADA 40 mg	PBO	GUS 100 mg	UST 45/90 mg	TIL 200 mg	TIL 100 mg	ETN‡ 50 mg	PBO	RIS 150 mg	UST 45/90 mg	PBO
Dosing schedule												
Initial	Wk 0, 4	Wk 0,§ 1	Wk 0, 4	Wk 16, 20	Wk 0, 4	Wk 0, 4	Wk 0, 4	biw	Wk 0, 4	Wk 0, 4	Wk 0, 4	Wk 0, 4
Maintenance	q8w	q2w	q8w	q8w	q12w	q12w	q12w	qw	q12w	q12w	q12w	q12w
N	823	581	422			622	616	313	310	598	199	200
Safety, %	Wk 0–16	Wk 0–16	Wk 0–16			Wk 0–12	Wk 0–12	Wk 0–12	Wk 0–12	Wk 0–16	Wk 0–16	Wk 0–16
AE	48–52	48–51	45–49			42–49	44–47	54	48–55	46–50	50–54	46–51
Discontinued owing to AE	1	1–2	1			1–2	0–1	2	1	0.3–0.7	0–2	1–4
SAE	2	2	1–2			2–3	1–2	2	1–3	2	3–8	1–3
Infection	22–26	23–26	19–25			NR	NR	NR	NR	19–25	20	9–17
Serious infection	0–0.2	0.6–0.8	0–0.4			0.3	0–0.3	0	0-0.6	0.3–1	1–3	0
Malignancies	0	0	0			0–0.3	0–0.3	0.3	0	0.3	0	0–1
MACE	0–0.3	0.3–0.4	0			0	0–0.3	0	0	0	0	0
N	823	581		135	133	597	594	289		588	193	
Long-term safety, %	Wk 0–48¶	Wk 0–48¶		Wk 16–60	Wk 16–60	Wk 12–28	Wk 12–28	Wk 12–28		Wk 16–52	Wk 16–52	
AE	58–74	63–75		64	56	40–45	44–46	57		56–61	67–75	
Discontinued owing to AE	2–3	2–4		2	2	0.3–1	0.3	1		0–0.7	0–2	
SAE	4–5	4–5		7	5	2	2–3	5		5	4	
Infection	31–52	35–50		42	35	NR	NR	NR		35–38	41–49	
Serious infection	0.6	0.9–1		0.7	0	0.3–0.7	0.3–0.7	1		0.7	0–1	
Malignancies	0.2–0.6	0		1	0	0–0.7	0–0.3	1		0–0.3	0–1	
MACE	0.2–0.3	0.3–0.4		1	0.8	0	0	0		0–0.7	0	

†Randomized patients only. ‡reSURFACE 2 only. §Initial dose of 80 mg at Wk 0. ¶Weeks 0–28 in VOYAGE 2.
ADA, adalimumab; AE, adverse event; biw, twice per week; ETN, etanercept; GUS, guselkumab; IL, interleukin; MACE, major cardiovascular adverse event; *N*, number of patients included; NR, not reported; PBO, placebo; RIS, risankizumab; SAE, serious adverse event; TIL, tildrakizumab; UST ustekinumab; q2w, every 2 weeks; q8w, every 8 weeks; q12w, every 12 weeks; qw, every week; Wk, week.

safety concerns identified for any available IL-23p19 inhibitor.[41–45] Key exclusion criteria for these studies typically included any malignancy within the past 5 years (except non-melanoma skin cancer), active or untreated latent tuberculosis and testing positive for human immunodeficiency, hepatitis B virus or hepatitis C virus infection. Women could not be pregnant, and those of child-bearing potential had to practice abstinence or use medically accepted contraception methods.

No head-to-head studies have compared the different IL-23p19 inhibitors, and care must be taken when comparing data among studies because of differing study designs, patient populations and study lengths.

Guselkumab

Results of three pivotal phase 3 trials of guselkumab in adult patients with moderate to severe psoriasis have been reported: VOYAGE 1 (NCT02207231), VOYAGE 2 (NCT02207244) and NAVIGATE (NCT02203032).[41–43] In VOYAGE 1 (n = 837) and VOYAGE 2 (n = 922), patients were randomized to guselkumab (100 mg at Weeks 0 and 4, then every 8 weeks), adalimumab (80 mg at Week 0, 40 mg at Week 1, then 40 mg every 2 weeks) or placebo (Weeks 0, 4 and 12, then guselkumab at Weeks 16 and 20, then every 8 weeks).[41,42] Rates of AEs, serious AEs (SAEs) and infections were comparable across groups in both studies over the 48 weeks of follow-up (Table 2). The most common AEs in all groups were nasopharyngitis, headache and upper respiratory infection, and few patients (≤4%) discontinued treatment owing to AEs. Incidence rates of serious infections and candidiasis were low and comparable between groups in both studies, and no AEs of inflammatory bowel disease were reported. Rates of malignancies and MACE were low in all groups (<1% over the study period). A single suicide attempt was reported in a patient taking adalimumab in VOYAGE 1.[41] In VOYAGE 2, greater improvements in anxiety and depression scores were seen in patients treated with guselkumab than in those who received adalimumab or placebo.[46]

The NAVIGATE trial assessed guselkumab in adult patients with an inadequate response to ustekinumab.[43] All patients (n = 871) initially received open-label ustekinumab (45 or 90 mg at Weeks 0 and 4). At Week 16, 268 patients with an inadequate response were randomized to guselkumab (100 mg at Weeks 16 and 20, then every 8 weeks) or remain on ustekinumab. No safety concerns were identified in patients transitioning from ustekinumab to guselkumab, despite use of a guselkumab loading dose. The overall incidence of AEs was slightly higher in the guselkumab group than the ustekinumab group (64.4% vs. 55.6%) owing to a higher incidence of musculoskeletal and connective tissue disorders (e.g. back pain and psoriatic arthropathy), general disorders and mild injection-site reactions. Overall, infections were the most common AE, occurring at a similar rate in both groups (41.5% for guselkumab and 35.3% for ustekinumab). Few patients discontinued treatment owing to AEs [3 (2.2%) in the guselkumab group and 2 (1.5%) in the ustekinumab group]. Rates of serious infection, malignancies and MACE were low (all ≤1.5% in both groups). No opportunistic infections, cases of active tuberculosis or AEs of Crohn's disease were reported.

Guselkumab was also well tolerated in a 52-week, phase 3, placebo-controlled study in 192 adult Japanese patients with moderate to severe plaque psoriasis (NCT02325219), with no safety concerns identified in this population.[47] Again, nasopharyngitis was the most commonly reported AE in all groups.

Tildrakizumab

Week 28 data from two phase 3 trials of tildrakizumab have been reported: reSURFACE 1 (NCT01722331) and reSURFACE 2 (NCT01729754).[44] A total of 772 adult patients were randomized (2 : 2 : 1) to tildrakizumab 200 mg, tildrakizumab 100 mg or placebo in reSURFACE 1; in reSURFACE 2, 1090 patients were randomized (2 : 2 : 2 : 1) to tildrakizumab 200 mg, tildrakizumab 100 mg, etanercept or placebo. In both studies, AEs and SAEs were reported at similar rates across all treatment groups, and discontinuations due to AEs were infrequent (Table 2). Nasopharyngitis was the most common AE in both studies. *Candida* skin infections and oral candidiasis were infrequent, and no cases of new onset or worsening of inflammatory bowel disease were reported. Incidences of serious infections, malignancies and MACE were low and similar across groups (≤1% in any group). One patient died in reSURFACE 2 in the tildrakizumab 100-mg group; the patient had alcoholic cardiomyopathy and steatohepatitis, and adjudication was unable to determine the cause of death.

These results were confirmed by a pooled analysis of data from three randomized controlled trials [a phase 2b study (NCT01225731) and reSURFACE 1 and 2], which showed that long-term treatment (>64 weeks) with tildrakizumab was well tolerated in patients with moderate to severe psoriasis.[48] Data were included for 2081 adult patients treated with tildrakizumab 200 mg, tildrakizumab 100 mg, etanercept or placebo. Over the full-trial period, exposure-adjusted rates of AEs and SAEs with tildrakizumab were lower than or comparable with etanercept and placebo (Table 3). Rates of discontinuation due to AEs were lower in the tildrakizumab groups {both 2.2 per 100 patient-years [95% confidence interval (CI) 1.3–3.3]} than etanercept [5.9 per 100 patient-years (95% CI 2.7–11.0)] and were comparable with the placebo group [2.3 per 100 patient-years (95% CI 0.7–5.3)]. No AEs of new onset or exacerbation of pre-existing inflammatory bowel disease were reported. *Candida* skin infections and oral candidiasis were infrequent, with exposure-adjusted rates per 100 patient-years of 0.7, 0.2, 0 and 0 in the tildrakizumab 200-mg, tildrakizumab 100-mg, placebo and etanercept groups, respectively. Rates of severe infections, malignancies and MACE were low and similar across groups and compared favourably with those reported in similar pooled

Table 3 Incidence of AEs of special interest from long-term follow-up studies, pooled analyses and patient registries. Data are presented as rates per 100 PY[11,12,24,48,49]

Biologic therapy	*N*	PY	AE	SAE	Infections	Severe/serious infections	Malignancies	NMSC	MACE	Ref.
Tildrakizumab 200 mg	1041	929	79.3	7.2	52.6	1.6	1.2	0.9	0.3	[48]
Tildrakizumab 100 mg	1083	998	77.0	5.8	48.9	1.1	1.7	1.1	0.4	
Etanercept 50 mg	313	153	148.6	13.0	86.0	2.0	2.6	1.3	0	
Placebo	588	219	153.5	6.4	79.5	0.9	0.9	0.9	0.5	
Ustekinumab 45 mg	1319	3766	242.6	7.0	89.8	1.0	1.2	0.6	0.6	[24]
Ustekinumab 90 mg	2001	5232	225.3	7.2	84.1	1.2	1.1	0.4	0.4	
Secukinumab pooled	3430	2725	252.9	7.8	91.4	1.5	1.0	0.5	0.4	[11]
Secukinumab 300 mg	1410	1178	236.1	7.4	91.1	1.4	0.8	0.4	0.4	
Secukinumab 150 mg	1395	1142	239.9	6.8	85.3	1.1	1.0	0.6	0.4	
Etanercept	323	294	243.4	7.0	93.7	1.4	0.7	0	0.3	
Ixekizumab 80 mg†	4209	6480	NR	NR	39.2	1.3	0.9	0.4	0.6	[12]
Ixekizumab 80 mg‡	1463	337	250.5	8.3	113.2	2.1	0.9	0.6	0.3	
Etanercept‡	739	169	235.8	8.3	93.9	1.8	0.6	0	0.6	
Placebo‡	360	83	192.3	8.4	89.0	2.4	0	0	1.2	
Adalimumab	6051	23 660	21.8	4.4	NR	1.0	1.0	NR	<0.1§	[49]

†All treatment periods. ‡Placebo-controlled treatment period (Weeks 0–12). §Congestive heart failure only.
AE, adverse event; MACE, major cardiovascular adverse event; *N*, number of patients included; NMSC, non-melanoma skin cancer; NR, not reported; PY, patient-years; SAE, serious adverse event.

analyses of safety data for other classes of biologic agents.[11,12,24,49] No AEs of multiple sclerosis or suicides were reported. One suicide attempt was reported in a patient receiving tildrakizumab 200 mg and antipsychotic therapy for a known history of schizophrenia; this was considered unrelated to treatment by the investigator.

Risankizumab

Two 52-week, phase 3 trials of risankizumab vs. ustekinumab have been reported, with no unexpected safety findings: UltIMMa-1 (NCT02684370) and UltIMMa-2 (NCT02684357).[45] In both studies, adult patients were randomized (3 : 1 : 1) to receive risankizumab 150 mg, ustekinumab 45 mg or 90 mg or placebo (506 in UltIMMa-1 and 491 in UltIMMa-2). Rates of AEs were similar across all groups during both the placebo-controlled period (Weeks 0–16) and long-term follow-up (Weeks 16–52) (Table 2). Rates of discontinuation due to AEs were low and similar across all groups during both study periods. In both studies, infections were more frequently reported in patients receiving risankizumab or ustekinumab compared with placebo, and the most common AE was upper respiratory tract infection. Rates of serious infections were low (≤1% for risankizumab and placebo, ≤3% for ustekinumab). No clinically relevant opportunistic infections were reported, and there were no reports of *Candida* infections or new onset/worsening of inflammatory bowel disease. Incidences of malignancies and MACE were low (all ≤1%). No demyelinating disorders or suicide were reported. In UltIMMa-2, one patient died in the risankizumab group of an unknown cause.

Other safety data

Data from head-to-head comparator trials of IL-23p19 inhibitors vs. IL-17 or IL-12/23p40 inhibitors are starting to emerge. Risankizumab was compared with ustekinumab in a 48-week phase 2 trial (NCT02054481)[40] and in the phase 3 UltIMMAa-1 and UltIMMAa-2 studies, in which broadly similar safety profiles were reported for both treatments.[45] Ustekinumab was compared with guselkumab in the NAVIGATE trial (described above),[43] in which more AEs occurred in the guselkumab group (64%) than the ustekinumab group (56%). Further studies comparing treatments are ongoing or awaiting publication, including guselkumab vs. secukinumab (phase 2, NCT03553823; phase 3, NCT03090100) and vs. ixekizumab (phase 4, NCT03573323) and risankizumab vs. secukinumab (phase 3, NCT03478787). In addition, three recent meta-analyses have assessed the safety of IL-23p19 inhibitors compared with other classes of biologic agents used for the treatment of psoriasis.[50–52] To avoid risk of confounding, these meta-analyses exclusively used data from the placebo-controlled treatment periods of randomized controlled trials (typically 12–16 weeks). Sbidian and colleagues[50] conducted a network meta-analysis of 109 studies to compare the efficacy and safety of conventional systemic agents, small molecules and biologic agents in 39 882 patients with moderate to severe psoriasis. They found no significant differences between tildrakizumab, guselkumab, ustekinumab, etanercept, infliximab, adalimumab and certolizumab verses placebo in terms of the risk of SAEs, serious infections, malignancies or MACE.[50]

The second meta-analysis assessed the efficacy and safety of IL-23p19, IL-12/23p40 and IL-17 inhibitors in moderate to

severe plaque psoriasis and included data from 24 trials involving 15 388 patients.[51] Safety outcomes included the number of patients with at least one AE, with at least one SAE and withdrawing from therapy because of an AE at 12–16 weeks. No differences in any safety outcomes were reported for tildrakizumab 100 mg or 200 mg compared with placebo. A slight, but statistically significant, increased risk in the number of AEs compared with placebo was seen for ustekinumab 45 mg, secukinumab 150 mg or 300 mg and brodalumab 140 or 210 mg. The number of withdrawals due to AEs was significantly higher for ixekizumab 80 mg vs. placebo irrespective of dosing frequency (every 2 or 4 weeks). Analysis of the other safety endpoints (number of SAEs and AEs) was not performed for ixekizumab owing to lack of available data. An increased frequency of *Candida* infections was seen with the IL-17 inhibitors secukinumab, ixekizumab and brodalumab, consistent with previous reports.[11–13]

The third meta-analysis was undertaken to compare the safety of biologics targeting IL-17 and IL-23 in the treatment of moderate to severe plaque psoriasis and found anti-IL-23 agents were associated with a lower risk of AEs.[52] Data from the placebo-controlled periods of 21 randomized clinical trials of secukinumab, brodalumab, ixekizumab, ustekinumab, guselkumab and tildrakizumab were included, involving 14 935 patients (11 100 of whom were treated with a biologic and 3835 with placebo). Tildrakizumab 200 mg was associated with the lowest risk of AEs [relative risk (RR) 0.88 (95% CI 0.78–0.99); $P = 0.04$ vs. placebo], and ixekizumab (160 mg at Week 0, then 80 mg every 4 weeks) was associated with the highest risk [RR 1.27 (95% CI 1.16–1.39); $P < 0.00001$ vs. placebo]. No statistically significant differences in SAEs were seen for any agent vs. placebo. The risk of AEs was significantly higher for biologics targeting IL-17 [RR 1.18 (95% CI 1.12–1.24); $P < 0.00001$ vs. placebo] compared with IL-23 [RR 0.97 (95% CI 0.91–1.04); $P = 0.44$ vs. placebo]. However, the risk of SAEs was similar in the IL-17 and IL-23 groups [RR 0.98 (95% CI 0.66–1.47); $P = 0.94$, and RR 1.13 (95% CI 0.69–1.86); $P = 0.63$, respectively, vs. placebo].

Studies of IL-23p19 inhibitors in other indications, including ankylosing spondylitis, psoriatic arthritis and Crohn's disease, have also not identified any new or unexpected safety concerns.[53–57]

Unmet needs

Real-world data concerning the safety of IL-23p19 inhibitors in routine practice settings are not yet available. Registry data are important for identifying safety signals arising during wider and longer term clinical use, which may not have been recognized during clinical trials. Registry data may also provide reassurance regarding real-world safety and tolerability by failing to confirm spurious signals occasionally seen in trials. For example, although three possible MACE were recorded in a phase 2 ustekinumab study,[58] no further signal was identified in long-term follow-up or registry data.[24–26]

Although a significant proportion of patients with psoriasis are women of child-bearing potential, only limited data are available concerning the safety of biologic agents during pregnancy. No reports of pregnancies during treatment with an IL-23p19 inhibitor in clinical trials have been published, although preliminary data from 13 pregnancies during treatment with tildrakizumab reported no anomalies.[59] Similarly, data from pregnant women with psoriasis treated with ustekinumab have not identified any safety concerns.[60,61] It is generally recommended that live vaccines should not be given to infants exposed to biologic agents in utero for at least 6 months after birth, because of a theoretical concern about the response to vaccination. Although there are no published data following exposure to IL-23p19 inhibitors, the Pregnancy in Inflammatory Bowel Disease and Neonatal Outcomes (PIANO) registry found use of other biologic therapies by pregnant women with inflammatory bowel disease did not affect infant response to *Haemophilus influenzae B* or tetanus vaccines.[62] In adult patients, long-term (≥3 years) treatment with ustekinumab was not found to compromise immune response to pneumococcal or tetanus vaccines, but there are no data on vaccine response during treatment with IL-23p19 inhibitors.[63] However, it is recommended that patients receive all age-appropriate immunizations prior to initiating treatment, and patients should not receive live vaccines while on therapy with ustekinumab, guselkumab or tildrakizumab.[64–66]

Biologic therapies are increasingly used for the treatment of moderate to severe psoriasis in children.[67] Data on the safety of IL-23p19 inhibitors in paediatric patients are not yet available, although a study of guselkumab in adolescents is ongoing (PROTOSTAR; NCT03451851). Ustekinumab has been approved for the treatment of moderate to severe plaque psoriasis in adolescents aged 12 years or older; the safety profile is similar to that in adults, with nasopharyngitis the most common AE and no unexpected AEs.[68]

Conclusions

Available data show anti-IL-23p19 agents have an acceptable safety profile in adults with moderate to severe psoriasis. The most commonly reported AEs during treatment with IL-23p19 inhibitors in phase 3 studies were upper respiratory tract infections. Rates of serious infections, malignancies or MACE were extremely low and comparable to those seen with placebo or active comparators. Importantly, few patients discontinued treatment with IL-23p19 inhibitors owing to AEs during clinical trials. Selectively targeting IL-23p19 appears to avoid AEs that have been associated with biologic agents with other mechanisms of action, with no signals for elevated risk of opportunistic infections, tuberculosis, mucocutaneous *Candida* infections, de novo onset or potential exacerbation of inflammatory bowel disease or demyelinating disorders observed to date. Data from long-term extension studies and patient registries are needed to

fully establish the safety profile of these agents for the treatment of moderate to severe psoriasis in routine practice.

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