REVIEW

Anti-IL23 biologic therapies in the treatment of psoriasis: real-world experience versus clinical trials data

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Abstract

Nowadays, the biological equipment available for the treatment of moderate-to-severe psoriasis is plenty. Anti-interleukin-23 represents the latest class of biologic approved for the management of moderate-to-severe psoriasis. Their efficacy and safety have been assessed through two major sources: clinical trials (CTs) and real-world experiences data (RWE). Notably, the two sources differ from one another, but together, they complement information and current knowledge on both efficacy and safety of biological therapy. We carry out a review on CTs and RWE reports on the latest group of biological approved for moderate-to-severe psoriasis: anti-IL23 (guselkumab, risankizumab, and tildrakizumab).

Introduction

Psoriasis is an inflammatory skin disease with an estimated prevalence from 0.51 to 11.43% in adults, and 0 to 1.37% in children [1]. Epidemiological data hypothesize a current increase in the incidence of the disease [2]. Mild forms can be managed by topical therapies [3]; moderate-to-severe cases often require conventional systemic or biological therapies [4] Nowadays, the biological agents available are plenty: from the first approved anti-tumour necrosis factor (TNF)-alpha in 2006 [5] to the latest anti-interleukin (IL)-23 in 2019 [6]. Clinical safety and efficacy profiles of these new

Key points

- Anti-interleukin-23 represents the latest class of biologic approved for the management of moderate-to-severe psoriasis.
- Their efficacy and safety have been assessed through two major sources: clinical trials and real-world experiences data.
- Clinical trials and real-world evidence-related data differ one another, but together, they complement information and current knowledge on both efficacy and safety of biological therapy.

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drugs are assessed through pre- and post-marketing procedures: first of all, clinical trials (CTs) divided in different phases (I, II, and III) evaluate the agent under investigation in control and patient groups [7]. Then, regulatory entities analyse clinical trial data to approve the drug and thus, allowing the marketing phase [7]. In the post-marketing, phase IV trials continue the evaluation of the pharmaceutical agent, as well as pharmacovigilance reports by healthcare workers point out adverse events (AEs) occurring during the clinical practice [7]. Moreover, the authors can provide for real-world experience (RWE) data in the scientific literature.

Notably, clinical trials and RWE-related data differ one another, but together, they complement information and current knowledge on both efficacy and safety of biological therapy.

Herein, we carry out a review on clinical trials and RWE reports, comparing the two sources on the latest group of biological approved for moderate-to-severe psoriasis: anti-IL23 (guselkumab, risankizumab, and tildrakizumab). We decided to focus on anti-IL23 since they represent one of the last categories of approved biologics, but the clinical practice is not too recent to prevent from limited data on RWE.

Materials and methods

This review analyses the available English literature on efficacy and safety data of anti-IL23 currently approved for moderate-to-severe psoriasis: guselkumab, risankizumab,

and tildrakizumab. Clinical trials (CTs), real life studies, and case series along with metanalysis and pooled data analysis were included in our study, searching the following databases through to January 22, 2021: PubMed, Embase, The Cochrane Library, Google Scholar, and EBSCO. The keywords used for the research were the following: "anti-IL23 AND psoriasis", "guselkumab AND psoriasis", "risankizumab AND psoriasis", "tildrakizumab AND psoriasis". We excluded studies focusing on economical and healthcare management, work productivity, and life quality. Phase I clinical trials were excluded from this review.

Body

A total of 74 studies were included: 40 clinical trials and 34 RWE (Tables 1, 2, 3). The highest number of studies regarded guselkumab in both contexts, whereas tildrakizumab had the lowest. This finding is due to the different timing of approval (2017 for guselkumab (USA [8]) and 2019 for risankizumab (USA [9]). The majority of CTs were phase III, multicenter studies and the most frequent drug used as control was adalimumab for guselkumab [10, 20], ustekinumab for risankizumab [21], and etanercept for tildrakizumab [22, 23]. On the other hand, most of the RWEs was represented by case reports and single-centre study (Tables 1, 2, 3).

Guselkumab

The two main phase III trials, VOYAGE 1 and VOYAGE 2, as well as the phase II trial published in 2015 compared guselkumab not only with placebo but also with the first class of biologics approved for the treatment of moderate-to-severe psoriasis: anti-TNF-alfa (adalimumab) [10, 20]. Both in short- and long-term assessments, guselkumab showed higher efficacy rates according to the different endpoints used, such as mean Psoriasis Area Severity Index (PASI), PASI75, PASI90, and Investigator Global Assessment (IGA) [10, 20]. Moreover, a good maintenance of the clinical improvement achieved has been reported throughout years of therapy [16, 19]. In fact, as pointed out by the most recently published results from VOYAGE 1 and VOYAGE 2 trial, during the 4-year study extension, the authors reported high efficacy response rates with most of the patients experiencing a PASI90 and IGA 0/1 response (> 80%) and more than a half even PASI100 and IGA 0 [16, 19]. Further CTs have compared guselkumab with other biologics classes: ustekinumab in the NAVIGATE trial [24], secukinumab in the ECLIPSE trial [25], and ixekizumab in the IXORA-R study [26, 27]. In the NAVIGATE trial, the guselkumab group reported higher

rates of improvement, PASI90 and PASI100 responses [24]. The efficacy reflected also in a better DLQI assessment for the guselkumab than in the ustekinumab group [24]. Similar results were obtained in the comparison with secukinumab, as at week 48, a higher proportion of patients in the guselkumab group achieved a PASI90 response [25]. In the phase IV IXORA-R trial, Blauvelt et al. pointed out a faster response for the ixekizumab than for the guselkumab group at week 12 [26]. In 2020, Thaçi et al. have compared guselkumab with fumaric acid esters (FAEs) [28]: a huge difference in efficacy was outlined, as 82% of guselkumab-treated patients reached PASI90 versus 27% of FAEs-treated [28].

Studies of guselkumab efficacy in RWE are different from CTs mainly because of the lack of a comparison group treated with another biologic or conventional systemic therapy. Retrospective single- or multi-centre studies confirmed the efficacy of guselkumab in both short- and long-term periods also in RWE [29, 34]. PASI response rates were comparable to those from CTs: in fact, Ruiz-Villaverde et al. reported that 90.3% of patients reached PASI75, 71% PASI90 and 51.6% PASI100 at week 52 [34]. On the other hand, RWE added new insights in the use of guselkumab: some case reports pointed out the possibility of guselkumab efficacy and safety in patients with other comorbidities, as well as in cases of non-plaque psoriasis (e.g., erythrodermic psoriasis) otherwise excluded from clinical trials [35, 39]. Examples are represented by efficient and safe use of guselkumab in an HIV-positive patient [35], in a woman affected by psoriasis, hidradenitis suppurativa, and Crohn's disease [36], and in a patient with Cornelia De Lange syndrome [37]. Others are reported in Table 1. Moreover, RWE has widened the possibility of treating even severe forms (e.g., erythrodermic psoriasis) with guselkumab [38, 40]. Chiang et al. published a study on 13 erythrodermic psoriasis patients treated successfully and safely with guselkumab [38]: at week 28, a mean PASI improvement of 67.5% was experienced along with no common AEs reported at week 36 [38].

Another clinical aspect has been differently investigated in clinical trials and in RWE: psoriasis localization. Up until now, CTs focused on special areas and forms of psoriasis (e.g., palmoplantar pustulosis [41]) more than the RWE counterpart. This phenomenon is mainly due to the dissimilar assessment of patients in trials to the clinical practice: usually, clinical studies require a strict clinical evaluation most of the time carried out by specific scores (e.g., PSSI, Psoriasis Scalp Severity Index).

Regarding the safety profile, in CTs, the most frequent AEs were infectious diseases, particularly nasopharyngitis and upper respiratory tract infections [10, 20]. Safety and AEs were comparable to the other classes of biologics [10, 20] and in RWE [29, 34]. In 2020, a focus on

Table 1 Studies (clinical trials and RWEs) on guselkumab

Clinical trial

Authors, year	Study type	No. of prt	Study design (study groups)	Study period	Efficacy	Safety	Ref
Gordon et al., 2015	Phase II, dose-ranging, randomized, double-blind, placebo-controlled, active-comparator trial	293	1)Guselkumab 5 mg at weeks 0 and 4 and every 12 weeks thereafter 2)Guselkumab 15 mg every 8 weeks 3)Guselkumab 50 mg at weeks 0 and 4 and every 12 weeks thereafter 4)Guselkumab 100 mg every 8 weeks 5)Guselkumab 200 mg at weeks 0 and 4 and every 12 weeks thereafter 6)Placebo (at week 16: crossed over to receive guselkumab at a dose of 100 mg every 8 weeks) 7)Adalimumab (standard dosage for psoriasis)	40 weeks	Week 16: significantly higher proportion of patients with at least PASI75 score in each guselkumab group than in the placebo group ($p<0.001$ for all comparisons) Week 40: significantly higher proportion of patients with a PGA score of 0 or 1 in the 50-mg, 100-mg, and 200-mg guselkumab groups than in the adalimumab group (71%, 77%, and 81%, respectively, vs. 49%) ($p<0.05$ for all comparisons)	Infectious AEs (through week 16): guselkumab groups 20%, adalimumab, 12%, placebo 14%	10
Blauvelt et al., 2017	Phase III, multicenter, double-blinded, placebo- and active comparator-controlled VOYAGE 1	837	1)Guselkumab 100 mg at weeks 0, 4, 12, and every 8 weeks 2)Placebo at weeks 0, 4, and 12 followed by guselkumab 100 mg at weeks 16 and 20, and every 8 3)Adalimumab 80 mg at week 0, 40 mg at week 1, and 40 mg every 2 weeks	44 weeks (first and second groups) 47 weeks (third group)	Guselkumab superior to placebo at week 16 (85.1% vs. 6.9% [IGA 0/1] and 73.3% vs. 2.9% [PASI 90]) ($p<0.001$). Guselkumab superior to adalimumab for IGA 0/1 and PASI 90 at week 16 (85.1% vs. 65.9% and 73.3% vs. 49.7%), at week 24 (84.2% vs. 61.7% and 80.2% vs. 53.0%), at week 48 (80.5% vs. 55.4% and 76.3% vs. 47.9%) ($p<0.001$)	AEs rates and types (serious ones included), and abnormal laboratory results generally comparable between the 3 groups	11
Reich et al., 2017	Phase III, multicenter, double-blinded, placebo- and active comparator-controlled VOYAGE 2	992	1)Guselkumab 100 mg (weeks 0 and 4, then every 8 weeks) 2)Placebo → guselkumab (weeks 0, 4, and 12 then guselkumab at weeks 16 and 20) 3)Adalimumab (80 mg week 0, then 40 mg week 1, and every 2 weeks through week 23) Week 28: 1)Guselkumab PASI 90 or greater responders rerandomized to guselkumab or placebo with guselkumab after loss of response 2+3)Placebo → guselkumab responders and adalimumab responders received placebo, then guselkumab after loss of response. Nonresponders received guselkumab	72 weeks	Better persistence of response in guselkumab maintenance versus withdrawal groups ($p<0.001$)	No discontinuation because of AEs No additional malignancy, NMSC, or MACE No AEs reported among the 16 retreated patients 1 serious infection reported in the maintenance group	12

Table 1 (continued)

Clinical trial

Authors, year	Study type	No. of prt	Study design (study groups)	Study period	Efficacy	Safety	Ref
Foley et al., 2018	Post-hoc analysis of 2 phase III trials (VOYAGE 1 and 2)	1829	1) Guselkumab 100 mg (weeks 0 and 4, then every 8 weeks) 2) Placebo > guselkumab 100 mg (at week 16) 3) Adalimumab 80 mg (week 0) and 40 mg (week 1, then every 2 weeks)	24 weeks	Higher proportion of patients with a ss-IGA score of 0 or 1 in the guselkumab group vs. placebo (81.8% vs. 12.4%, week 16), and vs. adalimumab (85.0% vs. 68.5%, week 24) (both $p < 0.001$) Higher proportion of patients with hf-PGA score of 0 or 1 in the guselkumab vs. placebo group (75.5% vs. 14.2%, week 16), and vs. adalimumab group (80.4% vs. 60.3%, week 24) Higher proportion of patients with f-PGA score of 0 or 1 in the guselkumab group vs. placebo (46.7% vs. 15.2%, week 16; $p < 0.001$), and vs. adalimumab (60.0% vs. 64.3%, week 24, $p = 0.11$)	N/A	44
Griffiths et al., 2018	Phase III, multicentre, double-blinded, placebo- and active comparator-controlled and open-label beyond week 52 VOYAGE 1	992	1) Guselkumab 100 mg at weeks 0, 4, 12, and every 8 weeks 2) Placebo at weeks 0, 4, and 12 followed by guselkumab 100 mg at weeks 16 and 20, and every 8 3) Adalimumab 80 mg at week 0, 40 mg at week 1, and 40 mg every 2 weeks Placebo (at week 16) and adalimumab (at week 52) group patients crossed over to guselkumab Week 52: open-label guselkumab	100 weeks	Week 100: proportions of patients achieving PASI 75, PASI 90, PASI 100, IGA 0/1, and IGA 0 94.8%, 82.1%, 49.0%, 82.4%, and 53.8%, respectively (similar results for the placebo → guselkumab and adalimumab → guselkumab groups) Efficacy maintained during continuous treatment among guselkumab-treated patients Improved efficacy in adalimumab—> guselkumab group	AEs comparable among groups Higher proportion of ISRs in adalimumab versus guselkumab patients (6.9% vs. 2.6%)	13
Langley et al., 2018	Phase III, multicenter, randomized, double-blind trial NAVIGATE	871	Week 0 and week 4: open-label ustekinumab Week 16: if IGA ≥ 2 randomized 1) guselkumab 100 mg at weeks 16, 20 and every 8 weeks 2) ustekinumab continuation (at week 16 and every 12 weeks)	60 weeks	Significantly greater mean number of visits and proportion of patients with achievement of IGA 0/1 and at least a two-grade improvement ($p < 0.001$), and greater proportions of patients who achieved PASI 90, PASI100 and DLQI 0/1 (week 52) in the guselkumab group vs. the randomized ustekinumab group	Most frequent AE: infections After week 16, at least 1 AE in 64.4% of patients in the guselkumab group and 55.6% in the ustekinumab group At least 1 serious AE in 6.7% of patients in the guselkumab group and in 4.5% of the ustekinumab group	24

Table 1 (continued)

Clinical trial

Authors, year	Study type	No. of prt	Study design (study groups)	Study period	Efficacy	Safety	Ref
Ohtsuki et al., 2018	Phase III, multicenter randomized, double-blind, placebo-controlled trial	192	1)Guselkumab 50 mg 2)Guselkumab 100 mg 3)Placebo at weeks 0, 4, and every 8 weeks thereafter Week 16: placebo group crossed over to receive guselkumab 50 mg or 100 mg	52 weeks	Week 16: higher proportion of patients achieved IGA 0/1 (92.3% and 88.9% vs. 7.8%), PASI-75 (89.2% and 84.1% vs. 6.3%), and PASI-90 (70.8% and 69.8% vs. 0%) in the guselkumab 50 mg and 100 mg group versus placebo ($p < 0.001$) Improvement maintained through week 52	AEs incidences comparable among the 3 groups through week 16 No new safety issues observed until the end of the study Most commonly reported AE: nasopharyngitis	45
Sano et al., 2018	Phase III, single-arm, open-label, multicenter trial	24 (GPP and EP)	Open-label: guselkumab 50 mg weeks 0, 4, and every 8 weeks thereafter until week 52 From week 20: dose escalation for patients with a CGI rating of "no change" or "worsened" at any scheduled study visit	52 weeks	Week 16, proportions of GPP and EP patients achieving treatment success: 77.8% and 90.9%, respectively	Most common AE: nasopharyngitis (28.6%)	46
Puig et al., 2019	Phase 3, randomized, double-blind, placebo- and active-comparator-controlled trials VOYAGE 1 and 2	1803	(See VOYAGE 1 and VOYAGE 2)	28 weeks	Week 16: guselkumab versus placebo, percentage points or IGA 0/1 (in the Hispanic and non-Hispanic populations) 67.4 and 77.2; percentage points PASI90 59.2 and 69.2, respectively. Guselkumab versus adalimumab percentage points for IGA 0/1 25.9 and 17.5, PASI90 21.4 and 23.5, respectively Similar results at week 24	Only through weeks 16 and 28 greater AEs frequency in adalimumab versus guselkumab group in the Hispanic population	14
Reich et al., 2019	Phase 3, randomized, double-blind, placebo- and active-comparator-controlled trials VOYAGE 1 and 2	1829	(See VOYAGE 1 and VOYAGE 2)	28 weeks	Week 16: guselkumab versus adalimumab (in the Asian and non-Asian populations) percentage points for IGA 0/1 31.1 and 16.1, PASI90 24.9 and 23.2, respectively. Similar results at week 24	Similar safety profiles	15
Reich et al., 2019	Phase III, multicentre, double-blind, randomized, comparator-controlled trial ECLIPSE	1048	1)Guselkumab 100 mg at weeks 0 and 4 then every 8 weeks 2)Secukinumab 300 mg at weeks 0, 1, 2, 3, and 4, and then every 4 weeks	56 weeks	Week 48: greater proportion of patients with a PASI 90 response in the guselkumab group than in the secukinumab group (84% vs. 70%; $p < 0.0001$)	Safety profiles similar between the 2 groups Most common AEs: infections (nasopharyngitis and upper respiratory tract)	25

Table 1 (continued)

Clinical trial

Authors, year	Study type	No. of prt	Study design (study groups)	Study period	Efficacy	Safety	Ref
Terui et al., 2019	Phase III, randomized, double-blind, multicenter, placebo-controlled trial	159 (PPP)	1) Guselkumab 100 mg weeks 0, 4, and 12, and every 8 weeks thereafter 2) Guselkumab 200 mg, weeks 0, 4, and 12, and every 8 weeks thereafter 3) Placebo at weeks 0, 4, and 12. rerandomization to guselkumab, 100 or 200 mg (weeks 16 and 20 and every 8 weeks thereafter)	52 weeks	Significant improvement in guselkumab groups in least-squares mean changes in PPPASI score versus placebo (−15.3 and −11.7 in the guselkumab 100-mg and 200-mg groups, respectively, and −7.6 in the placebo group; $p<0.001$ in the 100 mg group; $p<0.017$ in the 200 mg group) Significant least-squares mean changes in PPSI score in guselkumab groups (100 mg: −2.0; $p<0.001$; 200 mg: −1.0 $p=0.04$)	Serious AEs: 8 patients (3.8% in placebo group; 10.5% in combined guselkumab group) No serious infections	40
Blauvelt et al., 2020	Phase IV, multicentre, randomized, double-blinded, parallel-group study IXORA-R	1027	1) Ixekizumab (labelled dosage) 2) Guselkumab (labelled dosage, 100 mg at weeks 0, 4, and 12)	12 weeks	PASI 100 in 41% of patients treated with ixekizumab and 25% in the guselkumab (25%) ($p<0.001$) All major secondary end points measured up to week 12 were met, including PASI 50 at week 1 and PASI 75 at week 2	No new safety issues	26
Blauvelt et al., 2020	Phase IV, multicentre, randomized, double-blinded, parallel-group study IXORA-R	924	1) Ixekizumab (labelled dosage) 2) Guselkumab (labelled dosage, 100 mg at weeks 0, 4, and 12)	24 weeks	Ixekizumab noninferior to guselkumab in skin clearance at week 24	Serious AEs: 3% (each group) No new safety issues	27
Ferris et al., 2020	Phase III, multicentre, double-blind, placebo-controlled novel patient-controlled injector ORION	78	1) Guselkumab 100 mg at Weeks 0/4/12/20/28 2) Placebo at weeks 0/4/12 with crossover to guselkumab 100 mg at weeks 16/20/28	40 weeks	Week 16: significantly greater proportions of IGA 0/1 and PASI 90 achievement in the guselkumab group than placebo ($p<0.001$) Self-Injection Assessment Questionnaire (SIAQ) and Patient-Controlled Injection Device Questionnaire showed that 99% of patients were satisfied/very satisfied with the new device (week 28)	Safety profiles comparable between the 2 groups	47
Griffiths et al., 2020	Phase III, multicenter, double-blinded, placebo- and active comparator-controlled and open-label beyond week 52 4-years treatment VOYAGE 1	646	1) Guselkumab 100 mg at weeks 0, 4, 12, and every 8 weeks 2) Placebo at weeks 0, 4, and 12 followed by guselkumab 100 mg at weeks 16 and 20, and every 8 3) Adalimumab 80 mg at week 0, 40 mg at week 1, and 40 mg every 2 weeks Placebo (at week 16) and adalimumab (at week 52) group patients crossed over to guselkumab Week 52: open-label guselkumab	204 weeks	High efficacy response rates (>80% with PASI 90 and IGA 0/1 and >50% with PASI 100 and IGA 0)	Favourable safety profile No new AEs reported	16

Table 1 (continued)

Clinical trial

Authors, year	Study type	No. of prt	Study design (study groups)	Study period	Efficacy	Safety	Ref
Puig et al., 2020	Pooled safety data from VOYAGE 1 and VOYAGE 2 trials	1721	1)Guselkumab-treated LTBI+ 2)Guselkumab-treated LTBI − patients	N/A	100 weeks	Week 100: -no active TB in the guselkumab-treated LTBI-group -2 cases of active TB in adalimumab-treated LTBI-patients Week 16: higher proportions of ALT and AST elevations in LTBI+ patients vs. LTBI-patients Comparable AEs	17
Reich et al., 2020	Phase III, multicenter, double-blinded, placebo- and active comparator-controlled open-label beyond week 76 VOYAGE 1 and 2	1483	VOYAGE 1: 1)Guselkumab 100 mg at weeks 0, 4, 12, and every 8 weeks 2)Placebo at weeks 0, 4, and 12 followed by guselkumab 100 mg at weeks 16 and 20, and every 8 3)Adalimumab 80 mg at week 0, 40 mg at week 1, and 40 mg every 2 weeks Placebo (at week 16) and adalimumab (at week 52) group patients crossed over to guselkumab Week 52: open-label guselkumab VOYAGE 2: 1)Guselkumab 100 mg (weeks 0 and 4, then every 8 weeks) 2)Placebo → guselkumab (weeks 0, 4, and 12 then guselkumab at weeks 16 and 20) 3)Adalimumab (80 mg week 0, then 40 mg week 1, and every 2 weeks through week 23) Week 28: 1)Guselkumab PASI 90 or greater responders rerandomized to guselkumab or placebo with guselkumab after loss of response 2+3)Placebo → guselkumab responders and adalimumab responders received placebo, then guselkumab after loss of response. Nonresponders received guselkumab Week 76: open-label guselkumab	156 weeks	Guselkumab groups, VOYAGE 1 and VOYAGE 2, respectively: PASI 90 82.8% and 77.2%, PASI100 50.8% and 48.8%, IGA 0/1 82.1% and 83.0%, IGA 0 53.1% and 52.9%	Serious adverse events: 5.68/100 PY; serious infections: 1.15/100 PY; nonmelanoma skin cancers: 0.28/100 PY; other malignancies: 0.47/100 PY; major adverse cardiovascular events: 0.28/100 PY	18

Table 1 (continued)

Clinical trial

Authors, year	Study type	No. of prt	Study design (study groups)	Study period	Efficacy	Safety	Ref
Reich et al., 2020	Phase III, multicenter, double-blinded, placebo- and active comparator-controlled open-label beyond week 76 VOYAGE 2	766	1)Guselkumab 100 mg (weeks 0 and 4, then every 8 weeks) 2)Placebo→guselkumab (weeks 0, 4, and 12 then guselkumab at weeks 16 and 20) 3)Adalimumab (80 mg week 0, then 40 mg week 1, and every 2 weeks through week 23) Week 28: 1)Guselkumab PASI 90 or greater responders rerandomized to guselkumab or placebo with guselkumab after loss of response 2+3)Placebo→guselkumab responders and adalimumab responders received placebo, then guselkumab after loss of response. Nonresponders received guselkumab Week 76: open-label guselkumab	204 weeks	Maintenance of efficacy responses in the guselkumab group (from week 100 through to week 204) Comparable rates in the adalimumab→guselkumab group	Maintenance of favourable safety profile	19
Thaçi et al., 2020	Phase III, multicentre, randomized, open-label, assessor-blinded, active-comparator-controlled trial POLARIS	119	1)Guselkumab 100 mg week 0 and 4, then every 8 weeks 2)Fumaric acid esters tablets (self-administration according to the local label)	24 weeks	Higher PASI90 response in the guselkumab vs. fumaric acid esters group (82% vs. 14%, $p<0.001$), and PASI 75 response (90% vs. 27%, $p<0.001$), DLQI 0 or 1 (62% vs. 17%, $p<0.001$), and PASI100 (32% vs. 3%, $p<0.001$)	Lower AEs with guselkumab than with FAE (73% vs. 98%)	28
Youn et al., 2020	Post-hoc analysis VOYAGE 1 and VOYAGE 2 trials	126 (Korean patients)	VOYAGE 1: 1)Guselkumab 100 mg at weeks 0, 4, 12, and every 8 weeks 2)Placebo at weeks 0, 4, and 12 followed by guselkumab 100 mg at weeks 16 and 20, and every 8 3)Adalimumab 80 mg at week 0, 40 mg at week 1, and 40 mg every 2 weeks Placebo (at week 16) patients crossed over to guselkumab VOYAGE 2: 1)Guselkumab 100 mg (weeks 0 and 4, then every 8 weeks) 2)Placebo→guselkumab (weeks 0, 4, and 12 then guselkumab at weeks 16 and 20) 3)Adalimumab (80 mg week 0, then 40 mg week 1, and every 2 weeks through week 23)	28 weeks	Week 16: guselkumab superior to placebo in achieving IGA score of 0 or 1 (90.5 vs. 20.0%, $p<0.001$), and PASI90 response (71.4 vs. 3.3%, $p<0.001$) Week 24: greater proportion of guselkumab-treated patients with PASI 75 (93.7 vs. 66.7%, $p<0.001$) and IGA 0 (52.4 vs. 21.2%, $p=0.004$) versus adalimumab-treated patients	Comparable efficacy profile in guselkumab and adalimumab groups	20
Real world experience							
Authors, year	Study type	No. of prt	Study design	Study period	Efficacy	Safety	Ref

Table 1 (continued)

Clinical trial

Authors, year	Study type	No. of prt	Study design (study groups)	Study period	Efficacy	Safety	Ref
Bartos et al., 2018	Case report	1, 51-year old man	Guselkumab at labelled dosage	6 months	Complete clearance of psoriatic lesions in a HIV-positive patient	Stable CD4 count	35
Berman et al., 2019	Case report	1, 28-year old woman	Guselkumab at labelled dosage	N/A	good response in a patient with HS, psoriasis, and CD, multifailure to other previous biological therapies	No AEs reported	36
Grossberg et al., 2019	Case report	1, 66-year old woman	Guselkumab at labelled dosage and methotrexate 15 mg weekly	Months (unspecified number)	deep remission of Crohn's disease	No AEs reported	53
Hall et al., 2019	Case report	1, 20-year old woman	Guselkumab at labelled dosage	6 months	Resolution of guttate psoriasis after 10 weeks of therapy, maintained at 6 months	No AEs reported	54
Hosokawa et al., 2019	Case report	1, 67-year old man	Guselkumab at labelled dosage	N/A	Efficacy on paradoxical psoriatic alopecia	No AE reported	55
Kim et al., 2019	Case report	1, 12-year old girl	Guselkumab at labelled dosage and methotrexate 20 mg weekly 8decreased at 10 mg weekly from week 8)	5 months	Week 4: beginning of improvement Month 5: clinical resolution, PASI 1	No AEs reported	56
Lee et al., 2019	Case report	1, 41-year old man	Guselkumab at labelled dosage	1 year	Complete clearance of psoriatic lesions	Lentigines in areas of resolving psoriatic plaques	43
Rathod et al., 2019	Case report	1, 46-year-old woman	Guselkumab and adalimumab combination therapy	6 months	Baseline PASI 42; 2-month PASI 2 and improvement of psoriatic arthritis symptoms	No serious AEs reported	57
Reyn et al., 2019	Case report	1, 47-year old man	Guselkumab at labelled dosage	N/A	Week 7: PASI100, maintained for several weeks	Week 10: eczematous eruption Interruption of treatment	41
Truong et al., 2019	Case report	1, 40-year-old man (palmoplantar psoriasis)	Guselkumab at labelled dosage	3 months	N/A	Nummular dermatitis	42
Benhadou et al., 2020	Multicenter retrospective study	112	Guselkumab at labelled dosage	16 weeks	Mean PASI: baseline 14.8±6.5, week 16 2.03±2.5 32.1% achieved PASI-100, 55.4% PASI-90 and 82.1% PASI-75, respectively	AEs: 2 patients (1.8%) infection of upper respiratory tract and 1 patient (0.9%) asthenia	48
Galluzzo et al., 2020	Single centre retrospective study	52	Guselkumab at labelled dosage	1 year	12 weeks: PASI 75, 90, and 100 response achieved in 68%, 36%, and 18%, respectively 20 weeks: 79.1%, 62.8%, and 46.5%, respectively 1 year: 84.2%, 78.9%, and 63.2%, respectively	Well-tolerated No cases of discontinuation due to AEs	49
Kamiya et al., 2020	Case report	1, 58-year old man	Guselkumab at labelled dosage	N/A	Successful treatment of psoriasis in a patient treated with carboplatin plus nanoparticle albumin-bound paclitaxel therapy for advanced non-small cell lung cancer	No AE reported	58
Kromer et al., 2020	Case series	2/39 treated with guselkumab	Guselkumab at labelled dosage	10 months	Excellent response in both patients	No AE reported for patients treated with guselkumab	52

Table 1 (continued)

Clinical trial

Authors, year	Study type	No. of prt	Study design (study groups)	Study period	Efficacy	Safety	Ref
Lee et al., 2020	Single-centre retrospective chart review		Guselkumab at labelled dosage	16 months	The overall drug survival rate of in patients on guselkumab was higher compared to patients on ixekizumab at the end of the study period	No AE reported	50
Maliyar et al., 2020	Single centre retrospective chart review	71 patients ongoing treatment	Guselkumab at labelled dosage	Median treatment duration 1.2 years	Clinically significant clearance of psoriasis with a global assessment of clear or almost clear (BSA < 1%) in 73.3% of patients	Well-tolerated, no new AEs reported	29
Megna et al., 2020	Case report (erythrodermic psoriasis)	1, 38-year old man	Guselkumab at labelled dosage	48 weeks	Achievement of PASI 100 after 20 weeks of therapy	No AEs reported	59
Megna et al., 2020	Prospective, single-centre	23	Guselkumab at labelled dosage	44 week	Mean PASI score: baseline 15.1 ± 6.1, week 12 3.2 ± 1.9 ($p < 0.001$), week 44 0.8 ± 0.7 ($p < 0.001$) Mean BSA: baseline 36.4 ± 13.6, week 12 8.3 ± 7.4 ($p < 0.001$), week 44 2.2 ± 1.4 ($p < 0.001$)	AEs: 4 patients (17.4%) mild blood tests alterations and 6 subjects (26%) potential AEs One treatment discontinuation due to increase in liver enzymes	51
Mufti et al., 2020	Multicenter, retrospective case series	27	Guselkumab dosing interval optimization: -22.2% patients increased dosing frequency to 100 mg every 6 weeks -77.8% increased to 100 mg every 4 weeks	Mean follow-up time: 19.0 weeks	Efficacy reached when PASI75 response at 3 to 6 months after dose optimization or PGA 0 or 1: 74.1% after they switched to a shortened dosing interval	11.1% reported AEs: common cold, gastrointestinal-related symptoms (nausea, vomiting), headache, and dizziness	30
Mugheddu et al., 2020	Case report	1, 58-year-old woman affected by Cornelia De Lange syndrome	Guselkumab at labelled dosage	6 months	At 3 months: PASI100 achieved At 6 months: maintenance of complete remission	No AEs reported	37
Ruggiero et al., 2020	Single-centre, retrospective study	13	Guselkumab at labelled dosage	52 weeks	mean PASI score: baseline 13.2 ± 6.8, week 4 5.9 ± 2.8 ($p < 0.01$), week 12 2.4 ± 1.9 ($p < 0.001$), week 52 0.5 ± 0.7 ($p < 0.001$) mean BSA score: baseline 22.3 ± 10.5, week 4 14.2 ± 7.5 ($p < 0.01$), week 12 6.3 ± 5.4 ($p < 0.001$), week 52 0.8 ± 1.1 ($p < 0.001$)	AEs: pharyngitis (15.4%, $n = 2$) and flu (7.7%, $n = 1$). No AE required guselkumab discontinuation	31

Table 1 (continued)

Clinical trial

Authors, year	Study type	No. of prt	Study design (study groups)	Study period	Efficacy	Safety	Ref
Snast et al., 2020	Retrospective cohort study	33	Guselkumab at labelled dosage	Overall mean duration of treatment: 9.5 ± 3.7 months	Week 24 (n=29): 22 (76%) achieved> =PASI 75, 18 (62%) > =PASI 90, 5 (17%) PASI 100. Week 36 and at the end of the study period: PASI 75/90/100 achieved by a similar proportion of patient. Subgroup analysis (PASI 90 response at week 24): -a higher proportion of obese patients failed to achieve PASI 90 response (56% vs. 23%; no statistically significant difference, p=0.07) -no association between age, sex, baseline PASI, psoriatic arthritis, or duration of psoriasis	No AEs reported	32
Schwensen et al., 2020	Retrospective, real-world evidence study	50	Guselkumab at labelled dosage	Overall mean time of treatment: 80.6 weeks	Three months: -63.6% and 36.4% experienced ≥ PASI 50 and ≥ PASI 90, respectively from baseline -31.4% and 68.6% PASI <1 and 3, respectively. No statistically significant difference between subgroups if stratifying drug survival rate of guselkumab for sex, psoriatic arthritis, previous treatment with TNF inhibitors or anti-IL–17or anti-IL–23, or number of previous biologic treatments before initiating treatment with guselkumab	No new AEs reported	33
Song et al., 2020	Case report	1, 13-year-old girl with active hepatitis B infection	Guselkumab at labelled dosage	12 weeks	At 4 weeks: BSA decreased to 3%, IGA 3; complete clearance of forehead plaques. Week 12: BSA 1%. IGA 2. Stable liver enzymes, viral load undetectable	No AEs reported	60
Chiang et al., 2021	Retrospective study	13 (erythrodermic psoriasis)	Guselkumab at labelled dosage	Week 28 (at least)	Week 4, 12, 20, and 28, respectively: -mean PASI improvement: 37.5%, 60.9%, 67.5%, and 64.7%. -PASI 75: 15.4%, 38.4%, 53.8%, and 46.2% -PASI 90: 0%, 7.7%, 23.1%, and 30.8%	Week 36: no nasopharyngitis, headache, upper respiratory tract infection, or injection-site reaction reported	38
Kromer et al., 2021	Multicenter, retrospective study	5/201 with generalized pustular psoriasis treated with guselkumab	Guselkumab at labelled dosage	Mean treatment time until last observation: 5.2 months	1 /5 partial response, 4 /5 response non reported	1 AE reported	39

Table 1 (continued)

Clinical trial

Authors, year	Study type	Study design (study groups)	No. of prt	Study period	Efficacy	Safety	Ref
Ruiz-Villaverde et al., 2021	Observational, longitudinal, retrospective study	Guselkumab at labelled dosage	87	52 weeks (3 patients at 76 weeks, maximum exposition 93.4 weeks)	Week 52: PASI 75 in 90.3%, PASI90 in 71%, and PASI100 in 51.6% After 93.4 weeks (1 year, 9 months, and 14 days), the overall survival rate was 94% (4 events were reported)	4.6% discontinued (average follow-up of 48 weeks): 1 patient for primary failure, 2 patients for secondary failure, 1 patient due to AE (headache)	34

Abbreviations: *AEs*, adverse events; *FAEs*, fumaric acid esters; *IGA*, Investigator Global Assessment; *ISRs*, injection site reactions; *LTBI*, latent tuberculosis infection; *MACE*, major adverse cardiac event; *NMSC*, non melanoma skin cancer; *PASI*, Psoriasis Area Severity Index; *PGA*, Physician Global Assessment; *PPP*, palmo-plantar pustulosis; *prt*, participants; *PY*, patient-years; *ref.*, reference

latent tuberculosis infection (LTBI) was carried out in the VOYAGE 1 and VOYAGE 2 pooled data: Puig et al. have assessed the onset of active tuberculosis infection (TB) in patients with LTBI and without LTBI (LTBI-) treated with guselkumab [17]. At week 100, no active TB case was found in the guselkumab group, whereas 2 cases were reported in the adalimumab group [17]. Besides, RWE counterpart has signalled new AEs not previously pointed out, such as eczematous eruption, nummular dermatitis, and lentigines in areas of resolving psoriasis [42, 45]. Also, RWE did not report TB reactivation cases so far.

Other studies include post hoc analysis from CTs (44), additional phase III trials [46, 47], and CT on novel patient-controlled injector [47]. On the other hand, RWE includes further retrospective studies [49, 52], case series [53], and case reports [54, 61].

Risankizumab

The two main phase III trials, UltIMMa-1 and UltIMMa-2 (replicate studies), as well as a phase II CT compared risankizumab with ustekinumab [21, 62]. In these two replicate studies, higher efficacy regarding PASI90 and static Physician Global Assessment (sPGA) at week 16 compared to ustekinumab was found (UltIMMa-1: PASI90 75.3% vs. 42%, sPGA 0/1 87.7% vs. 63%; UltIMMa-2: PASI90 74.8% vs. 47.5, sPGA 0/1 83.7% vs. 61.6, with risankizumab and ustekinumab respectively) [21]. In 2020, Blauvelt et al. [63] in the IMMhance placebo-controlled trial confirmed the long-term efficacy of risankizumab [63]. At week 104, the sPGA 0/1 score was achieved by 81.1% of patients receiving risankizumab versus 7.1% receiving placebo [62]. Other studies have compared risankizumab with different biologics, such as adalimumab (IMMvent) [63], secukinumab (IMMerge) [65], and FAEs [66]. In all of these studies, risankizumab has shown a higher efficacy, achieving > 72% of patients PASI90 and > 83% sPGA of 0/1 at week 16 [64–66]. In the IMMerge study, which compared risankizumab to secukinumab, risankizumab was found non inferior to secukinumab regarding PASI90 at week 16 (73.8% versus 65.6%), and superior to secukinumab at week 52 (86.6% versus 57.1%, $p < 0.001$). Also, secondary end points (sPGA 0/1, PASI75, and PASI100) demonstrated superiority for risankizumab at week 52 ($p < 0.001$) [64]. A wide difference between risankizumab and FAEs at week 24 was found in the study by Thaçi et al. [65]; PASI90 of 83.3% with risankizumab versus 10% with FAEs [66].

The main difference found between CTs and RWE was the absence of a control group. Moreover, endpoints for RWE were different from the typical endpoints found in CTs (PASI50, PASI75, PASI90, PASI100, or sPGA) and vary from one to another. The biggest RWE multicentre

Table 2 Studies (clinical trials and RWEs) on risankizumab

Clinical trial

Authors, year	Study type	No. of prt	Study design (study groups)	Study period	Efficacy	Safety	Ref
Papp et al., 2017	Phase II, multicentre, randomized, dose-ranging trial. Double-blind within risankizumab dose groups and single-blind (patients) with regard to drug	116	1) Single 18-mg SC dose of risankizumab at week 0 2) 90-mg dose of risankizumab at weeks 0, 4, and 16 3) 180-mg dose of risankizumab at weeks 0, 4, and 16 4) Ustekinumab 45 mg or 90 mg depending on body weight at weeks 0, 4, and 16	48 weeks	Week 12: PASI90 73% in 90-mg risankizumab, 81% in the 180-mg risankizumab versus 40% in ustekinumab. At least PASI75 was achieved in 63% in the 18-mg risankizumab, 98% in the 90-mg, and 88% in the 180-mg, as compared to 72% in ustekinumab. Week 24: At least PASI75 was achieved in 53% of 18-mg risankizumab, 90% in the 90-mg, 88% in the 180-mg, compared to 70% in the ustekinumab	In the 18-mg and 90-mg risankizumab and the ustekinumab group 12%, 15%, and 8%, respectively had serious AEs, including 2 BCCs and 1 major cardiovascular adverse event. No serious AEs in the 180-mg risankizumab group were found	61
Gordon et al., 2018	Replicate phase III, randomized, placebo-controlled, and active comparator-controlled trial UltIMMa-1 and UltIMMa-2	997	1) 150 mg risankizumab at weeks 0, 4, 16, 28, and 40 2) Ustekinumab based on weight (45 mg or 90 mg) at weeks 0, 4, 16, 28, and 40 3) Placebo at weeks 0 and 4 → 150 mg risankizumab at weeks 16, 28, and 40	52 weeks	Week 16: UltIMMa-1: PASI90 was achieved by 75.3% risankizumab group, 4.9% placebo group, and 42% of the ustekinumab group UltIMMa-2: PASI90 was achieved by 74.8% risankizumab group, 2% placebo group, and 47.5% of the ustekinumab group UltIMMa-1: sPGA 0 or 1 was achieved by 87.7% risankizumab group, 7.8% placebo, and 63% ustekinumab group UltIMMa-2: sPGA 0 or 1 was achieved by 83.7% risankizumab group, 5.1% placebo, and 61.6% ustekinumab group	Treatment-related AEs in UltIMMa-1 and UltIMMa-2 in risankizumab group were found in 49.7% and in 45.6%. Serious AEs were reported in 2.3% of patients on risankizumab in UltIMMa-1 and in 2% in UltIMMa-2	21

Table 2 (continued)

Clinical trial

Authors, year	Study type	No. of prt	Study design (study groups)	Study period	Efficacy	Safety	Ref
Ohtsuki et al., 2019	Phase II / III, randomized, double-blinded, placebo-controlled trial SustaIMM	171 Japanese	1) 75 mg risankizumab weeks 0, 4, 16, 28, and 40 2) 150 mg risankizumab weeks 0, 4, 16, 28, and 40 3) Placebo weeks 0 and 4 → 75 mg risankizumab weeks 16, 28, and 40 4) Placebo weeks 0 and 4 → 150 mg risankizumab weeks 16, 28, and 40	52 weeks	Week 16: Risankizumab 75 and 150 mg versus placebo were superior versus placebo for PASI90 (75.9%, 74.5%, and 1.7%, respectively) (p<0.001). PASI75 for risankizumab 75 and 150 mg were significantly higher than placebo (89.7%, 94.5%, and 8.6%, respectively) sPGA score of 0 or 1 was achieved by 86.2% and 92.7% versus 10.3% for risankizumab 75, 150 mg versus placebo Week 52: PASI90 and PASI100 were achieved by 86.2% and 43.1% in risankizumab 75 mg; 92.7% and 41.8% in the risankizumab 150 mg	The safety profile was consistent with previous trials, no new or unexpected safety events were found	72

Table 2 (continued)

Clinical trial

Authors, year	Study type	No. of prt	Study design (study groups)	Study period	Efficacy	Safety	Ref
Reich et al., 2019	Phase III, randomized, double-blind, active-comparator-controlled trial IMMvent	605	1) Risankizumab 150 mg week 0 and 4 2) Adalimumab 80 mg at randomization, then 40 every 2 weeks until week 15 Week 16: 1) Patients remained in risankizumab group (150 mg at week 16 and 28) 2) Adalimumab intermediate responders → re-randomized to continue 40 mg adalimumab every other week or switch to risankizumab 150 mg (week 16, 20, and 32). Responders to adalimumab (PASI90) remained on adalimumab every other week	44 weeks	Week 16: A significantly higher proportion of patients who were assigned to risankizumab achieved PASI90 and sPGA scores of clear or almost clear compared to adalimumab (72% versus 47% and 84% versus 60%, respectively) Week 44: Among adalimumab intermediate responders a larger proportion of patients that were rerandomized to risankizumab achieved PASI90, and PASI 100	In part A AEs occurred in 56% on risankizumab and 57% on adalimumab, with serious AE in 3% of risankizumab and 3% of adalimumab. The most frequently reported were viral upper respiratory tract infection, upper respiratory tract infection, and headache	63

Table 2 (continued)

Clinical trial

Authors, year	Study type	No. of prt	Study design (study groups)	Study period	Efficacy	Safety	Ref
Blauvelt et al., 2020	Phase III, randomized, double-blind, placebo-controlled trial IMMhance	507	1) Risankizumab 150 mg at weeks 0 and 4 2) Placebo at weeks 0 and 4 Week 16: All patients received risankizumab 150 mg Week 28: 1) Patients with risankizumab that achieved an sPGA of 0/1 were rerandomized to risankizumab or placebo every 12 weeks 2) Patients with an inadequate response to initial therapy received open-label risankizumab 150 mg every 12 weeks	104 weeks	Week 16: 73.2% patients in the risankizumab group achieved PASI90 versus 2% in placebo. 83.5% receiving risankizumab versus 7% receiving placebo achieved sPGA 0/1 scores Week 52: sPGA score of 0/1 was achieved by 87.4% of risankizumab versus 61.3% receiving placebo Week 104: the sPGA score of 0/1 was achieved by 81.1% receiving risankizumab versus 7.1% receiving placebo	Rates of treatment-related AEs were similar between risankizumab and placebo group (45.7% and 49%) in part A and remained stable over time	62
Warren et al., 2020	Phase III, multicentre, open-label, efficacy assessor-blinded, active-comparator trial IMMerge	327	1) Risankizumab 150 mg at week 0, 4, and every 12 weeks 2) Secukinumab 300 mg at weeks 0, 1, 2, 3, 4, and every 4 weeks	52 weeks	Week 16: Risankizumab was noninferior to secukinumab in proportion of patients achieving PASI90 (73.8% versus 65.6%) Week 52: PASI90 Risankizumab was superior to secukinumab (86.6% versus 57.1%, $p<0.001$) PASI 100, sPGA 0/1, and PASI75 demonstrated superiority for risankizumab ($p<0.001$)	AEs were reported in 71.3% of patients treated with risankizumab vs. 71.2% with secukinumab. Serious AEs were found in 5.5% and 3.7% with risankizumab and secukinumab, respectively Most common AEs with risankizumab were nasopharynhitis, upper respiratory tract infection, headache, arthralgia, diarrhoea, and bronchitis	64

Table 2 (continued)

Clinical trial

Authors, year	Study type	No. of prt	Study design (study groups)	Study period	Efficacy	Safety	Ref
Papp et al., 2021	Phase II, multicenter OLE trial. Patients already treated in the 48-week, phase 2, double-blind, active comparator trial were included (Papp et al. 2017)	110	1)Risankizumab 90 mg every 12 weeks for at least 48 weeks. If at week 12 <PASI90 was found→Risankizumab 150 mg every 12 weeks	48 weeks	74.1% achieved PASI90, whereas 98.1%, 91.7%, 53.7%, and 67.6% achieved PASI50, PASI75, PASI100, and sPGA 0/1, respectively	77.3% patients reported AEs. The most frequent were naso-pharyngitis (17.3%), upper respiratory tract infection (13.6%), and arthralgia (10%)	71
Thaçi et al., 2021	Phase III, randomized, active-controlled, open-label study	120	1)Risankizumab 150 mg at weeks 0, 4, and 16 2)FAEs 30 QD from week 0 to week 2, then up to 240 mg, TID from week 3 to week 24 if PASI90 was not achieved	24	Week 24: PASI90 achieved by 83.3% of risankizumab group vs. 10% receiving FAEs PASI50 was achieved by 100% of risankizumab vs. 53.3% of FAEs	Serious AEs were reported by 3.51% of FAEs group and 1.67 of risankizumab group	65

Real world experience

Authors, year	Study type	No. of prt	Study design	Study period	Efficacy	Safety	Ref
Megna et al., 2020	Single-centre, retrospective study	8	Risankizumab at labelled dosage	16 weeks	Baseline mean PASI and BSA were 11.9±5.5, and 22.9±13.1, respectively. Week 16: 3.3±1.7 and 7.5±5 ($p<0.001$ and $p<0.01$), respectively. Mean baseline NAPSI reduced from 18.0±8.5 to 7±1.4. Palmo-plantar and scalp area showed a reduction of 67.5% and 99.9%	No AEs were reported	68
Bonifati et al., 2020	Prospective, real-world study	12 (9 guselkumab and 3 risankizumab)	1)Risankizumab at labelled dosage 2)Guselkumab at labelled dosage	24 weeks	PASI and PGA decreased significantly through the 24 weeks of treatment Week 12: all sites involved at baseline were free from psoriasis in 6 patients	No AEs were reported	73

Table 2 (continued)

Clinical trial

Authors, year	Study type	No. of prt	Study design (study groups)	Study period	Efficacy	Safety	Ref
Reddy et al., 2020	Observational, single-centre, retrospective study	41	1)Risankizumab at labelled dosage after failing guselkumab 2)Risankizumab+apremilast at labelled dosage after failing guselkumab 3)Risankizumab at labelled dosage without prior switch from guselkumab	Risankizumab after failing guselkumab 21.6±10.4 weeks Risankizumab without guselkumab 18±15.2 weeks	In the guselkumab failures BSA decreased from 28.5 to 5.9 with a 79.3% average decrease In the group without guselkumab treatment BSA decreased from 49.8 to 7.8 for an 84.3% decrease	NR	67
Hansel et al., 2020	Real-life multicenter study	57	Risankizumab at labelled dosage	16 weeks	49.1% reached PASI100, PASI90 was achieved by 63.2%, and PASI75 by 86%	1 patient experienced an upper respiratory tract infection	66
Kromer et al., 2020	Case report	1, 45-year-old woman	Risankizumab at labelled dosage	28 weeks	PASI at week 0: 12.8, week 11: 4.8, week 16: 3.8, and week 28:2.2	NR	74
Ruiz-Villaverde et al. 2020	Case report	1, 47-year-old male	Risankizumab at labelled dosage	56 weeks	Week 8: PASI 0, BSA 0, and sPGA 8	None	75
Tsuchida et al. 2021	Case report	1, 37-year-old man with recurrent colonic diverticulitis	Risankizumab at labelled dosage	48 weeks	PASI100 after a year of treatment	NR	69

Abbreviations: *AEs*, adverse events; *BCC*, basal cell carcinomas; *FAEs*, fumaric acid esters; *PASI*, Psoriasis Area Severity Index; *prt*, participants; *QD*, once a day; *ref*, reference; *SC*, subcutaneous; *sPGA*, static Physician Global Assessment; *TID*, three times a day (TID)

Table 3 Studies (clinical trials and RWEs) on tildrakizumab

Clinical trial

Authors, year	Study type	No. of prt	Study design (study groups)	Study period	Efficacy	Safety	Ref
Papp et al., 2015	Phase IIb, randomized, double-blind, placebo-controlled trial P05495	355	1) Tildrakizumab 5 mg at week 0, 4, and every 12 weeks until week 52 2) Tildrakizumab 25 mg at week 0, 4, and every 12 weeks until week 52 3) Tildrakizumab 100 mg at week 0, 4, and every 12 weeks until week 52 4) Tildrakizumab 200 mg at week 0, 4, and every 12 weeks until week 52 5) Placebo at week 0, 4, and every 12 weeks	72 weeks	Week 16: PASI75 33.3%, 64.4%, 66.3%, 74.4%, and 4.4% in the 5, 25, 100, 200 mg, and placebo respectively PGA1/0 33% 58%, 62%, 74%, and 2.2% for tildrakizumab 5, 25, 100, 200 mg, and placebo respectively	Most common AEs were nasopharyngitis and headache. 23 patients treated with tildrakizumab reported serious AEs: bacterial arthritis, lymphoedema, melanoma, stroke, epiglottitis, and knee infection	22
Reich et al., 2017	Phase III, three-part, double-blind, randomized, placebo-controlled, parallel-group studies reSURFACE 1 and 2	1,862	reSURFACE 1 1) Tildrakizumab 200 mg weeks 0, 4, and every 12 weeks 2) Tildrakizumab 100 mg weeks 0, 4, and every 12 weeks 3) Placebo → re-randomized at tildrakizumab 100 or 200 mg reSURFACE 2 1) Tildrakizumab 200 mg weeks 0, 4, and every 12 weeks 2) Tildrakizumab 100 mg weeks 0, 4, and every 12 weeks 3) Placebo → re-randomized at tildrakizumab 100 or 200 mg 4) Etanercept 50 mg twice weekly for 12 weeks, then once weekly At week 28 of both studies, >PASI75 and >PASI50 but <PASI75 were re-randomized to continue same treatment, different dose tildrakizumab, or placebo	reSURFACE 1 64 weeks reSURFACE 1 52 weeks	reSURFACE 1 Week 12: PASI75 was achieved by 62% and 64% in 200 mg and 100 mg tildrakizumab respectively compared to 6% in placebo group PGA 0/1 was achieved by 59% in the 200 mg group and 58% in the 100 mg group compared to 7% in placebo reSURFACE 2 Week 12: PASI75 was achieved by 66% and 61% in 200 mg and 100 mg tildrakizumab respectively compared to 6% in placebo group and 48% in etanercept group PGA 0/1 was achieved by 59% in the 200 mg group and 55% in the 100 mg group compared to 4% in placebo and 48% in etanercept group	Most common AE was nasopharyngitis. Serious AEs were low in both groups, 1 patient in reSURFACE2 with alcoholic cardiomyopathy and steatohepatitis died and adjudication was undetermined	23

Table 3 (continued)

Clinical trial

Authors, year	Study type	No. of prt	Study design (study groups)	Study period	Efficacy	Safety	Ref
Papp et al., 2019	Post hoc analysis of 3 randomized, controlled, multicenter trials P05495 (phase 2), reSURFACE 1, and 2 (phase 3)	2081	See P05495, reSURFACE 1, and 2	28 weeks	Week 12: PASI 75 were better with tildrakizumab 100 and 200 mg (62.3% and 64.8%, respectively) than placebo (5.6%) Tildrakizumab was better for PASI90, PASI100, and PGA 0/1 versus placebo ($p < 0.0001$)	NR	79
Elewski et al., 2019	Analysis of two phase III, three-part, double-blind, randomized, placebo-controlled trials reSURFACE 1 and 2	1,862	See reSURFACE 1 and 2	52 weeks	Among patients who achieved PASI90, PASI75, or PASI50 at week 28, 89.4%, 91.1%, or 97.4% maintained the response achieved at week 52, respectively. Among patients that achieved PASI50-74, 75–89, or 90–99 at week 28, 64.8%, 33.7%, and 25.2% improved their 28th week response at week 52, respectively	NR	80
Reich et al., 2019	Pooled analysis of two phase III, three-part, double-blind, randomized, placebo-controlled trials reSURFACE 1 and 2	1,862	See reSURFACE 1, and 2	148 weeks	PASI75, 90, and 100 was achieved by 72.6%, 53.8%, and 28.9% of tildrakizumab 100 mg and 80.2%, 59.9%, and 32.6% of tildrakizumab 200 mg	Treatment-related AEs for tildrakizumab 100 mg, 200 mg, placebo, and etanercept were 35.2, 37.2, 148.6, and 148.6 events per 100 PYs, respectively. The most common AE was nasopharyngitis in all groups. 9 deaths occurred, none related to the study medication. The most common severe AEs were cellulitis, herpes zoster, and urosepsis	76

Table 3 (continued)

Clinical trial

Authors, year	Study type	No. of prt	Study design (study groups)	Study period	Efficacy	Safety	Ref
Kimball et al., 2020	Post hoc analysis of two phase III, three-part, double-blind, randomized, placebo-controlled trials reSURFACE 1 and 2	1,862	See reSURFACE 1, and 2	reSURFACE 1 64 weeks reSURFACE 1 52 weeks	In T100/T100 and T200/T200 partial responders at week 28 the proportion of patients that achieved PASI75 increased over time. In T100/T200 week 28 partial responders PASI75 increased from 38.5% at week 32 to 63.2% at week 52 and PASI75 remained constant in T200/T100. Among the patients that relapsed in T100/PBO and T200/PBO, 86% and 83% of those who reinitiated tildrakizumab achieved PASI75 by week 64	See reSURFACE 1, and 2	81
Menter et al., 2020	Post hoc analysis of a phase III, three-part, double-blind, randomized, placebo-controlled trial reSURFACE 1	463	See reSURFACE 1 Patients receiving tildrakizumab 100 mg and placebo were included	28 weeks	Week 12: 36.2% and 30.9% of patients with baseline PASIh ≥ 1.4 and ≥ 2.4, respectively achieved PASIh = 0.0 Week 28: 40.5% and 34% of patients with baseline PASIh ≥ 1.4 and ≥ 2.4, respectively, achieved PASIh = 0.0	NR	82
Gordon et al., 2020	Post hoc analysis of two phase III, three-part, double-blind, randomized, placebo-controlled trials reSURFACE 1 and 2	925	See reSURFACE 1 and 2 Patients on tildrakizumab 100 mg and placebo were included	28 weeks	Week 12: median PASI was 2.9, dichotomous PASI90 was 36.9%, and absolute PASI < 5, < 3, and < 1 were 64%, 50.8%, and 23.3%, respectively Week 28: median PASI was 1.7, PASI90 was 51.9%, and absolute PASI < 5, < 3, and < 1 were 75.3%, 62.8%, and 38%, respectively	NR	83

Table 3 (continued)

Clinical trial

Authors, year	Study type	No. of prt	Study design (study groups)	Study period	Efficacy	Safety	Ref
Imafuku et al., 2021	Subgroup analysis of phase III, three-part, double-blind, randomized, placebo-controlled trial reSURFACE 1	120 Japanese	See reSURFACE 1	192 weeks	Of Japanese patients with PASI75 / 90 / 100 and PGA 0/1 at week 64 85%/88% receiving T100/T200 maintained PASI75, 70%/96% maintained PASI100, and 68%/72% maintained PGA 0/1 at week 192	Incidence of severe infections, malignancies, adverse cardiac events, and hypersensitivity were low in both groups	84
Cantrell et al., 2021	Post hoc analysis of phase III, three-part, double-blind, randomized, placebo-controlled trial reSURFACE 1	221	See reSURFACE 1 Patients on tildrakizumab 100 mg were included	64 weeks	Patients continuously treated with tildrakizumab 100 mg 92.6%, 81.5%, and 49.6% achieved PASI50, 75, and 90 at week 64, respectively. Of patients re-randomized to placebo 80.8%, 48.1%, and 21.2% achieved PASI50, 75, and 90 at week 64. Of patients that relapsed and were retreated the proportion of PASI50, 75, and 90 was of 86.9%, 72.1%, and 31.2%	NR	85

Real world experience
No study available (last access January 22, 2021)

Abbreviations: *AEs*, adverse events; *PASI*, Psoriasis Area Severity Index; *PASIh*, head PASI; *PBO*, placebo; *PGA*, Physician's Global Assessment; *prt*, participants; *ref*, reference

study included 57 patients: PASI90 was reached by 63.2% at week 16 [67]. Reddy et al. [68] included patients who failed guselkumab treatment previously, and they found a 79.3% decrease in PGA and BSA, compared to an 84.3% decrease in patients without previous guselkumab treatment [68]. In the study by Megna et al. [69], NAPSI, palmo-plantar, and scalp area reduction were also reported. NAPSI reduced from 18.0 ± 8.5 to 7 ± 1.4, whereas palmo-plantar and scalp area showed a reduction of 67.5% and 99.9%, respectively [69]. Another important knowledge acquired by RWE is the possibility of using risankizumab in patients with other concomitant diseases, thus anticipating clinical therapeutic options under investigation. In fact, a case report described a patient with psoriasis and colonic diverticulitis, with achievement of PASI100 after 1 year of treatment with non-reported AEs [70]. In the CTs counterpart, risankizumab has been investigated in patients affected by moderately to severely active Crohn's disease [71].

A good safety profile for risankizumab was found in both CTs and RWE. Papp et al. [61] reported an incidence of 12–15% of serious AEs, including 2 basal cell carcinomas and a major cardiovascular event, while other CTs reported a percentage of severe AEs between 1.67 and 5.5% [21, 62–65]. The most frequently found AEs in CT were upper respiratory tract infection, nasopharyngitis, headache, and arthralgia [21, 62–66, 72–74]. Blauvelt et al. included a small subset of patients ($n = 31$) with latent tuberculosis (positive for Quantiferon TB gold assay) that did not receive tuberculous prophylaxis before treatment [63]. No active tuberculosis developed after risankizumab therapy for 55 weeks despite the lack of prophylaxis [63]. To date, no RWE reported cases of TB reactivation under risankizumab in real world settings. Most RWE denied AEs or failed to report them [68–70, 75–77].

Tildrakizumab

Since tildrakizumab was the last anti-IL23 approved for the treatment of moderate-to-severe psoriasis, a smaller number of clinical trials have been conducted. The P05495 and reSURFACE 1 study compared different doses of tildrakizumab to placebo, whereas the reSURFACE 2 CT compared different doses of tildrakizumab to etanercept [23, 24].

Reich et al. [24] showed a good efficacy of tildrakizumab in the reSURFACE 1 and 2. In reSURFACE 1 at week 12, PASI75 was achieved by 62% and 64% in 200 mg and 100 mg tildrakizumab group, respectively. Also, PGA 0/1 was achieved by 59% in the 200 mg group and 58% in the 100 mg group of tildrakizumab. Temporarily, the reSUR-FACE 2 supported the efficacy by achieving a PASI75 by 66% and 61% in 200 mg and 100 mg tildrakizumab groups, respectively, compared to 48% in the etanercept group. PGA 0/1 was achieved by 59% in the 200 mg group and 55% in the

100 mg tildrakizumab group compared to 48% in etanercept group [23]. Later, the long-term efficacy was also agreed in a pooled analysis of reSURFACE 1 and 2 for 148 weeks [78]. A PASI75 response was attained by 72.6% of patients with 100 mg and 80.2% with 200 mg of tildrakizumab [78].

Regarding tildrakizumab safety profile, a low incidence of serious AEs was reported by both Papp et al. in 2015 [22] and Reich et al. in 2017 [23]. The most common AEs reported were nasopharyngitis and headache [22, 23]; the most frequent severe AEs at long-term were cellulitis, herpes zoster, and urosepsis [77].

Only two RWEs were found, one which is currently recruiting patients and the other one that has not yet started [79, 80]. RWE could open our horizons to different indications for tildrakizumab regarding comorbidities or previous treatment failures for our patients with moderate-to-severe psoriasis. Likewise, expand our knowledge regarding AEs, compared to CT. All mentioned studies, as well as some post hoc analysis from CTs, were included in Table 3 [81–87].

Discussion

Psoriasis treatment armamentarium is continuously growing with an increased number of different biologics being available so far, and another almost ready to expand the list: bimekizumab. Particularly, to date, 11 different biologics (adalimumab, brodalumab, certolizumab pegol, etanercept, guselkumab, infliximab, ixekizumab, risankizumab, secukinumab, tildrakizumab, and ustekinumab) belonging to 4 different classes (anti-TNF, anti-IL12/23, anti-IL17, and anti-IL23) are available for moderate-to-severe psoriasis treatment; apart from several distinct anti-TNF biosimilars [88]. As the psoriasis treatment goal is to obtain a complete or an almost complete skin clearance, dermatologist should not rely only on CTs data to perform the best treatment choice for their patients. In this context, RWE evidence is of indisputable importance since they evaluate the efficacy and safety in daily setting, which can be more complicated (multiple comorbidities, multifailure patients, difficult to treat areas, etc.) than those represented by CTs [89]. RWE also showed the efficacy and safety od anti-IL-23 in elderly patients, patients who are typically excluded from CTs, due to the multiple comorbidities and pharmacological treatments [90]. Furthermore, RWE also showed the safety during COVID-19 pandemic era, during which several concerns were raised about the use of biologics, which had been linked to eventual higher risk of COVID-19 infection or higher disease severity [91–95]. Our thorough review showed that RWE seems to confirm efficacy and safety of CTs on anti-IL23. More data are needed, especially for tildrakizumab whose RWE information is still scant due to its more recent availability on the market. Moreover, RWEs have already

showed additional features respect to CTs such as anti-IL23 efficacy in erythrodermic psoriasis, pustular psoriasis, as well as in possible psoriasis comorbidities such as hidradenitis suppurativa. Outstanding progresses have been done in the last few decades regarding psoriasis pathogenesis and the development of innovative therapies [90]. It is now well known that psoriasis is a chronic inflammatory multifactorial disease with dysregulation of immune cells (Th1 and Th17 above all) being its key features [96]. In this context, a major role is played by inflammatory cytokines such as TNF-α and IL-17, and IL-23 [96]. Advances in psoriasis pathogenesis have put the basis for the development of new effective drugs for its treatment. Nowadays, 11 different biologics belonging to 4 diverse classes are available for moderate to psoriasis treatment: anti-TNF (adalimumab, certolizumab pegol, etanercept, and infliximab), anti-IL12/23 (ustekinumab), anti-IL17 (brodalumab, ixekizumab, secukinumab), and anti-IL23 (guselkumab, risankizumab, and tildrakizumab). In addition, anti-TNF biosimilars as well as small molecules (apremilast) are also available as therapeutic weapon for psoriasis management. Psoriasis is a chronic relapsing disease which requires long-term treatment. Although biologics have dramatically improved psoriasis therapy, currently available biological agents are not curative; relapse or rebound of the disease could occur when a therapy is discontinued or even during the treatment (primary or secondary inefficacy) with some patients being non responders even after several weeks of treatment [97]. Since our goal is to find the right treatment for the right patient at the right time, in order to guarantee the best clinical outcomes in long term together with the best quality of life improvement and safety level, treatment selection has to be performed case by case with clinical decision which should not rely only on CTs data. Indeed, even if CTs represent the fundamental first step for new drugs approval which ensure their efficacy and safety profile, RWE studies are needed to increase the knowledge about new drugs in clinical practice, particularly in patients and/or conditions which are typically excluded by CTs. Moreover, although CTs and RWE-related data may differ one another, together, they complement information and current knowledge on both efficacy and safety of recent available biological therapies [89]. Particularly, RWE studies allow to confirm data of efficacy and safety in patients which are usually excluded from CTs study populations. Indeed, CTs require strongly selective inclusion criteria, resulting in the selection of study populations which may not reflect the cohort of patients to manage in daily clinical practice. These patients include ones affected by multiple comorbidities, including elderly psoriatic patients in which disease management may be frequently challenging due to several factors such as common multiple comorbidities and linked polypharmacy, infections, and cancer vulnerability due to immunosenescence. Furthermore, CTs data are usually

referred to plaque psoriasis type, excluding patients suffering from non-plaque psoriasis (erythrodermic psoriasis, guttate psoriasis, or pustular psoriasis) which may also benefit from biologics. Moreover, RWE may also give additional information on multifailure patients; in fact, the need for a prompt and new available therapy in case of clinical failure is not always compatible with the timing for a complete wash out required in CTs. Other examples of the importance of RWE and their complementation with CTs are represented by their utility for pharmacovigilance and monitoring long-term treatment emergent AEs which may not be highlighted by CTs as the case of eczematous eruptions for anti-IL17 as well as clinical issues which have not been posted in CTs as the case of COVID-19, COVID-19 vaccines as well as their influence on psoriasis natural course and biologics efficacy [98–106]. Indubitably, all these issues are particularly actual and true for anti-IL-23, the latest class of biologics approved for moderate to severe psoriasis. Indeed, real life studies are still limited due to their recent availability on the market respect other classes of biologics. Since another anti-IL23 as mirikizumab will be available in the future for psoriasis [107], as well as the fact that these drugs are being also evaluated for PsA as well as inflammatory bowel diseases treatment [108], RWE for anti-IL23 and their correlation with CTs represent a hot topic in dermatology, which could help to highlight eventual peculiarities and differences among anti-IL23s performances in order to guide the dermatologist among the jungle of biologics treatment for psoriasis management.

Conclusions

Our review showed that guselkumab, risankizumab, and tildrakizumab confirmed the promising data showed by clinical trials, in terms of both safety and efficacy profile. The anti-IL-23 biologic class confirmed to be safe with no concerns about the use of these drugs even in more fragile patients, such as elderly, and/or in those suffering from several comorbidities, and many concomitant medications. Hence, although more real-life studies, with longer follow-up periods, and larger study populations are still needed, our review confirm the important role that anti-IL-23 s have in the management of moderate to severe forms of psoriasis.

approved the final version to be published. He agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Professor Gabriella Fabbrocini contributed to the design of the work, data interpretation, and she revised the work critically for important intellectual content. She approved the final version to be published and she agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Doctor Sonia Sofía Ocampo-Garza contributed to the conception of the work, data acquisition, and interpretation. She drafted the work and she approved the final version to be published. She agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Data availability Data from the study are reported in the text, the table, and the figure of the article.

Declarations

Ethics approval Not require.

Conflict of interest Doctor Matteo Megna acted as speaker or consultant for Novartis, Eli Lilly, and Abbvie. Doctor Angelo Ruggiero has no conflict of interest to declare. Professor Gabriela Fabbrocini acted as speaker or consultant for Janssen, Leo Pharma, Novartis, Eli Lilly, Abbvie, and Almirall. Doctor Sonia Sofía Ocampo-Garza has no conflict of interest to declare.

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