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Adverse Effects of Anti-Interleukin-23 Agents Employed in Patients with Psoriasis: A Systematic Review

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Keywords
Psoriasis · Anti-interleukin-23 · Adverse effects · Phase III trials · Nasopharyngitis

Abstract
Background: Psoriasis is an immune-mediated protracted ailment that perturbs about 100 million people globally. Anti-interleukin (IL)-23 agents have a distinctive status of safety and clinical efficacy. Anti-IL-23 operatives have demonstrated therapeutic prominences in cases of psoriasis in preceding global research. However, arrays of adverse events have been associated with the anti-IL-23 agents in the remedies of psoriasis. This systematic review aimed to assess the adverse developments of anti-IL-23 operatives for patients with psoriasis determined in phase III trials. ***Methodology:*** The PRISMA guidelines were wielded for this systematic review. The author systematically searched Google Scholar, PubMed, Scopus, and Cochrane databases to diagnosticate appropriate articles on adverse effects of anti-IL-23 agents in patients with psoriasis including the appropriate key terms (Medical Subject Headings). ***Results:*** A total of 18 studies were encompassed in this cutting-edge systematic review that met the selection criteria. In this review, the most prevailing adverse effect caused by anti-IL-23 agents was nasopharyngitis followed by headache, upper respiratory tract infection, and back pain, which are observed during the treatment with anti-IL-23 agents. The anti-IL-23 operatives, including ustekinumab and guselkumab, were significantly involved in the grade 3 stage of adverse effects for the treatment of psoriasis, whereas the anti-IL-23 agents including briakinumab, tildrakizumab, and risankizumab were significantly involved in the grade 4 stage of adverse effects. ***Conclusion:*** Targeted IL-23 therapy has expeditiously upsurged to the forefront as the importance of the IL-23 axis has been progressively identified, setting a new benchmark for psoriasis outcomes. Over the last 3 years, ustekinumab, guselkumab, tildrakizumab, and risankizumab have successively come to the market. However, these drugs caused several immunological and nonimmunological side effects, but they are customarily well-tolerated and have orderly safety vignettes.

Introduction

Psoriasis is an immune-mediated tenacious cutaneous disorder that affects about 3% of the US population and an estimated 125 million individuals globally [1, 2]. Plaque psoriasis is the most prevalent type, accounting for more than 80% of all cases. Plaque psoriasis is symbol-

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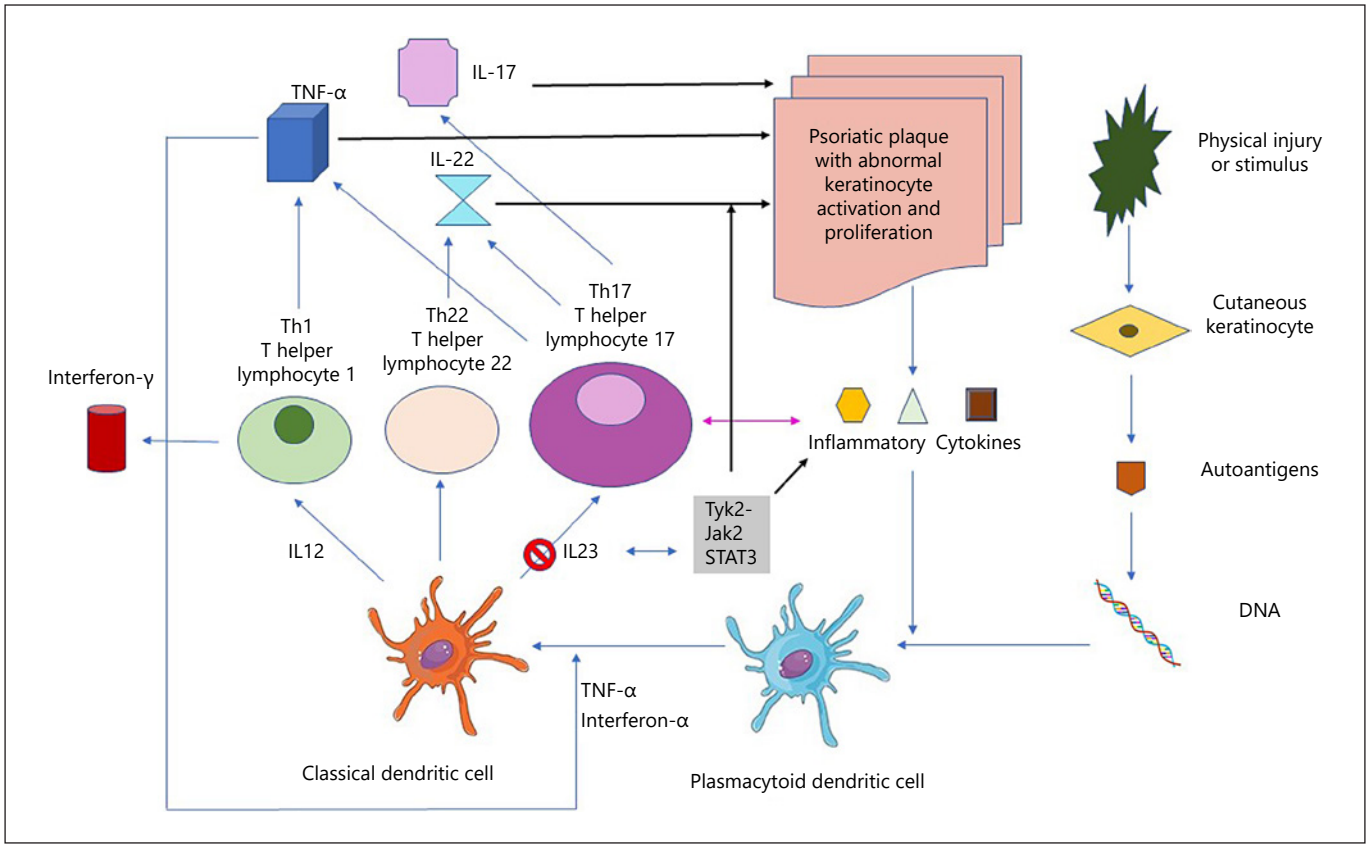

Fig. 1. Immune system involved in the treatment of anti-IL-23 agents. IFN-γ, interferon-gamma; IFN-α, interferon-alpha.

ized by erythematous, scaly patches, or plaques on extensor surfaces, but it can also involve intertriginous areas, nails, soles, and palms. Psoriasis affects both men and women equitably, although adults are further affected than youngsters [3, 4]. While psoriasis can appear at any age, there is a bimodal age assortment for commencement of psoriasis between the ages of 18–39 and 50–69 years [5]. Psoriasis inception age can be influenced by genetic and environmental factors. The omnipresence of the HLA-C*06 alleles is linked to the transpiration of psoriasis at a relatively young age [6]. The pathophysiology of psoriasis is convoluted and inadequately apprehended. Nonetheless, the pathogenesis of psoriasis is postulated to be linked to the over invigoration of integrals of the adaptive immune system [7]. Diverse cell categories, in conjunction with natural killer T cells, keratinocytes, plasmacytoid dendritic cells, and macrophages, exonerate cytokines that set in motion myeloid dendritic cells in the primeval junctures of psoriasis pathogenesis. DNA-LL37 complexes provoke plasmacytoid dendritic cells to emancipate interferon-alpha, which propels myeloid dendritic cells. On exhilaration, myeloid dendritic cells liberate interleukins (ILs) IL-12 and IL-23 subsequently. T-helper (TH) cell type 1 (TH1) cells are differentiated from naive T cells by IL-12. The endurance and amplification of TH17 and TH22 cells are provisory on IL-23. TNF-α and interferon-gamma are secreted by TH1 cells; IL-17, IL-22, and TNF-α are discharged by TH17 cells, and IL-22 is dispensed by TH22 cells [8]. The immune system involved in the treatment of anti-IL-23 was illustrated in Figure 1.

The incitement of the TH17 boulevard by IL-23 is reverenced to be the paramount of these pathways. Intracellularly, IL-23 gesticulation is arbitrated by Tyk2-Jak2 and STAT3, which manufactures pivotal inflammatory intermediaries. These cytokines kickoff keratinocyte proliferation, increased angiogenic mediators – endothelial adhesion molecules, and immune-cell intrusion into the lesioned cutaneous surfaces [7]. Anti-IL-23 operatives are generally safe and effective in clinical trials [9]. Ustekinu-

mab is the most often employed anti-IL-12/23-p40 agent, having been sanctioned for the treatment of psoriasis in 2009 and offering the expediencies of few drug injections, long-term maintenance, and high remission rates. Although inhibiting the IL-23 immune axis is enough to treat manyfold autoimmune ailments, there are perils of significant infections and other side effects [10, 11]. Briakinumab, a fully human monoclonal antibody directed against IL-12/23-p40 for the treatment of psoriasis, was found to cause intense complications and side effects in a phase III trial. In 2011, the drug's developer withdrew their application for clearance from the FDA and the European Agency for the Evaluation of Medicinal Products [12, 13]. As a result of this incidence, anti-IL-23 agents have come under expanded scrutiny. This contemporary systematic review aims to assess the adverse effects of anti-IL-23 agents for patients with psoriasis demonstrated in phase III trials.

Methodology

Study Design

The PRISMA guidelines were solemnized to execute this systematic review. This review incorporates a structured compilation of evidence-based articles and a systematic contemplation of their explorations based on the review's aim.

Search Strategy

The successive databases were used to conduct a literature search: Google Scholar, PubMed, Cochrane, and Scopus with the appropriate Medical Subject Headings. The author was primarily looking for studies on the side effects of anti-IL-23 agents in the patients of psoriasis. In addition to electronic search, manual probing of bibliographies of unearthed articles and previous systematic reviews on the topic were consummated. The Medical Subject Headings and keywords contain "psoriasis," "anti-interleukin-23 agents," "IL-23," "phase III trials," "phase 3 studies," "adverse effects," "adverse events," "side effects," "safety," "safety profile of IL-23," "Ustekinumab," "Briakinumab," "Risankizumab," "Tildrakizumab," and "Guselkumab."

Inclusion and Exclusion Criteria

Phase III trials that evaluated the adverse effects of anti-IL-23 agents employed for patients with psoriasis were included in this systematic review. Articles published between the years 2011–2021 in English were included. Exclusion criteria were (a) studies that evaluated the adverse effects of anti-IL-23 agents other diseases apart from psoriasis, phase I, II, and IV trials, prospective and retrospective studies; (b) gray literature, including presented abstracts, letters to the editors, commentaries, systematic review, or meta-analysis articles; and (b) unavailability of the full text of the article.

Article Screening

The author independently assesses the articles' screening operation and eligibility determination. The articles were initially screened based on their titles, followed by the abstract of the article. The case title and abstract of the articles were irrelevant to the present investigation; these were excluded from the secondary screening. The selected articles from the initial screening were assessed for full-text screening to find out the eligibility criteria of the present study. The full-text-assessed articles were further excluded based on insufficient information regarding the adverse effects of anti-IL-23 agents utilized for patients with psoriasis.

Data Extraction

The name of the authors and year, country, study design, sample size, gender, age, disease, anti-IL-23 agents, dose (mg/kg), mode of administration, adverse effects, and common terminology criteria for adverse events (CTCAE) grade were extracted from the selected articles.

Risk of Bias Assessments

The distinction of studies was determined using the Cochrane Handbook [14], including random sequence generation, allocation concealment, blinding of the outcome assessment, participants and personnel, incomplete outcome data, selective reporting, and other biases. The risk of bias of the included studies was classified as low, uncertain, and high risks of bias.

Outcome

The outcomes considered were the incidence and grade of adverse effects were determined using CTCAE v5.0 of the Department of Health and Human Services [15]. According to the CTCAE criteria, the adverse effects were classified into five grades based on the severity such as mild (grade 1), moderate (grade 2), severe (grade 3), life-threatening consequences; urgent intervention indicated (grade 4); and death related to adverse effects (grade 5).

Results

Eligible Studies

A total of 4,587 articles were discovered in multiple databases, including Google Scholar, PubMed, Scopus, and Cochrane databases, of which 3,904 were initially excluded due to repetition and irrelevance. After analyzing the titles and abstracts at the first screening level, 599 articles were further removed. For full-text evaluations, a total of 84 potentially relevant articles were chosen, of which 66 articles were further excluded as studies that did not evaluate psoriasis ($n = 31$), studies that related to other anti-IL agents ($n = 25$), and other study designs ($n = 10$). Finally, 18 studies that met the criteria for inclusion in the systematic review, as detailed in the PRISMA flow chart Figure 2, were included in this review.

Baseline Characteristics of the Included Studies

Table 1 shows the baseline characteristics of the studies that were included. Out of 18 included studies, seven

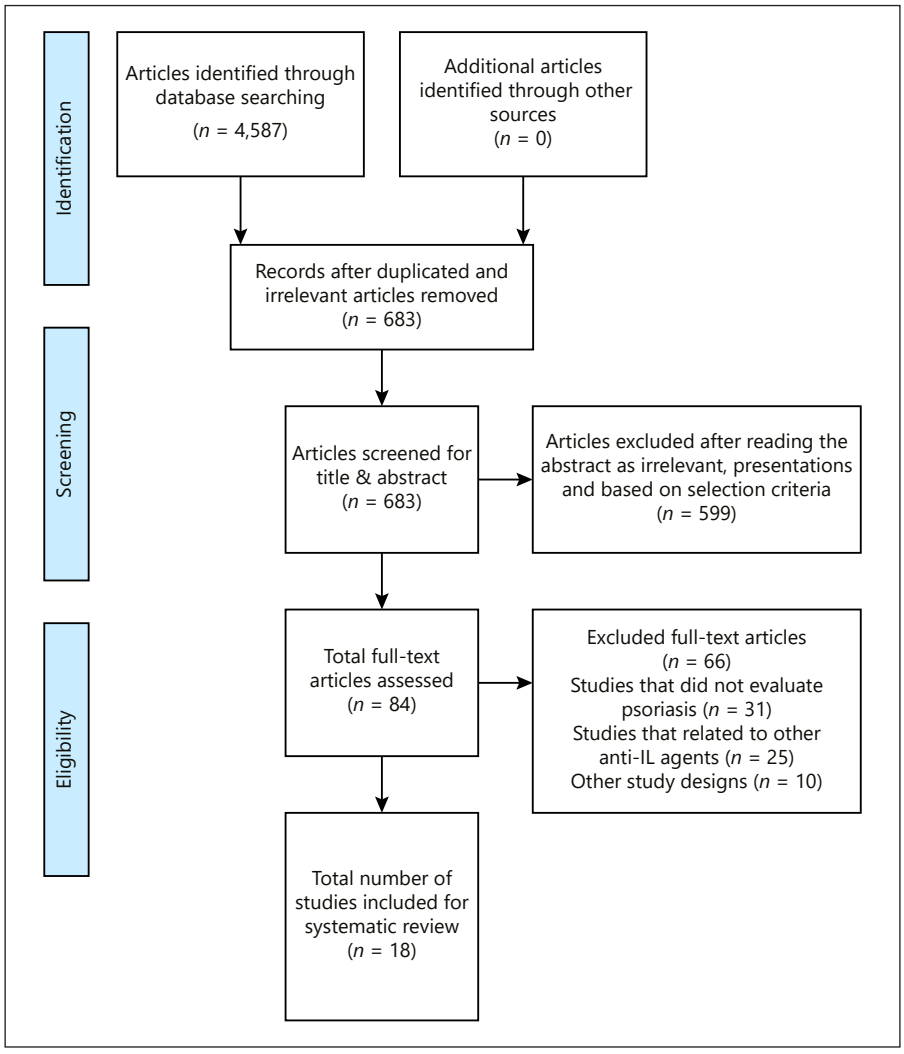

Fig. 2. PRISMA chart.

studies [13, 16–21] were published in the USA, five studies [22–26] were published in Germany, two studies [27, 28] were published in Canada, whereas the remaining four studies were published in different countries including Taiwan [29], Japan [30], Korea [31], and France [32]. In addition, all the included 18 studies in the systematic review were phase III trials. A total of 9,567 psoriasis patients were involved in the included 18 studies, of which 6,487 patients' were male, and 3,080 patients were female, with sample sizes ranging from 62 to 1,465. The age of the included patients was raging between 15.2 and 60 years. All the included studies in this review were evaluated the adverse drug effects of anti-IL-23 agents for psoriasis. The risk of bias was low in 16 studies, whereas two studies showed an uncertain risk of bias (Appendix A).

Adverse Effects Associated with the Anti-IL-23 Agents

Among the included 18 studies in this review were used different types of anti-IL-23 agents to treat moderate-to-severe psoriasis, including ustekinumab, tildrakizumab, briakinumab, guselkumab, and risankizumab with the dose of 45–300 mg. Most of the included studies were administrated the anti-IL-23 agents through subcutaneous injection. Among the included 18 studies in this review, 13 reported that nasopharyngitis was the most common adverse event associated with the anti-IL-23 agents for treating psoriasis, followed by headache and back pain (Table 2). The reported adverse effects were observed during the treatment with anti-IL-23 agents.

In the phase III randomized controlled trial of briakinumab for moderate-to-severe Psoriasis; Gordon et al. [13] documented the adverse effects in the treatment

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Table 1. Baseline characteristics and the adverse effects caused by anti-IL-23 agents [13, 17–21, 23–32, 44]

S.No	Author [ref.]	Country	Study design	Sample size	Gender	Age	Disease	Anti-IL-23 agents	Dose, mg/kg	Mode of administration	Adverse effects	CTCAE (grade)
1	Tsai et al. [29]	Taiwan; Korea	Phase III	*N* = 121	Male 103, female 18	40.6 years	Moderate-to-severe psoriasis	Ustekinumab	45 mg	Subcutaneous injection	Upper respiratory tract infection, hyperglycemia, nasopharyngitis, pruritus, cough, eosinophilia, psoriasis, anemia, injection site reactions, eczema, abnormal hepatic function, psoriatic arthropathy	3
2	Kimball et al. [21]	USA, Chicago	Phase III	*N* = 766	Male 531, female 235	45.5 years	Moderate-to-severe psoriasis	Ustekinumab	45 mg or 90 mg	Not reported	Cardiovascular event	3
3	Gordon et al. [13]	USA, Skokie	Phase III	*N* = 1,465	Male 1,009, female 456	45.5 years	Moderate-to-severe psoriasis	Briakinumab	100–200 mg	Not reported	Nasopharyngitis, headache, upper respiratory tract infection, back pain	4
4	Landells et al. [27]	Canada, Newfoundland	Phase III	*N* = 110	Male 54, female 56	15.2 years	Moderate-to-severe plaque psoriasis	Ustekinumab	45 or 90 mg	Intravenous injection	Infections, infestations, nasopharyngitis, headache, and psoriasis	3
5	Thaçi et al. [26]	Germany, Schleswig-Holstein	Phase III	*N* = 676	Male 252, female 424	>18 years	Moderate-to-severe plaque psoriasis	Ustekinumab	300 mg	Subcutaneous injection	Headache, nasopharyngitis, diarrhea, fatigue, arthralgia	3
6	Langley et al. [28]	Canada, Nova Scotia	Phase III	*N* = 1,212	Male 828, female 384	46.2 years	Moderate-to-severe psoriasis	Ustekinumab	45 or 90 mg	Not reported	Cardiovascular event	3
7	Blauvelt et al. [18]	USA, Oregon	Phase IIIb	*N* = 676	Male 252, female 424	45.2 years	Moderate-to-severe plaque psoriasis	Ustekinumab	300 mg	Subcutaneous injection	Nasopharyngitis, headache, upper respiratory tract infection, arthralgia, diarrhea, back pain	4
8	Blauvelt et al. [44]	USA, Oregon	Phase III	*N* = 837	Male 608, female 129	43.7 years	Moderate-to-severe psoriasis	Guselkumab	100 mg	Not reported	Nasopharyngitis, upper respiratory tract infection, injection site erythema, headache, arthralgia, pruritus, back pain	3
9	Blauvelt et al., [17]	USA, Portland	Phase IIIb	*N* = 378	Male 236, female 142	45.3 years	Moderate to severe psoriasis	Ustekinumab	45 or 90 mg	Subcutaneous injection	Myocardial infarction	3
10	Reich et al. [23]	Germany, Hamburg	Phase IIIb	*N* = 302	Male 202, female 100	44 years	Moderate-to-severe psoriasis	Ustekinumab	80 or 160 mg	Subcutaneous injection	Nasopharyngitis, headache, arthralgia, hypertension, rhinitis, back pain	3
11	Reich et al. [24]	Germany, Hamburg	Phase III	*N* = 992	Male 692, female 300	43.7 years	Moderate-to-severe psoriasis	Guselkumab	100 mg	Subcutaneous injection	Nasopharyngitis, headache, upper respiratory tract infection	3
12	Ohtsuki et al. [30]	Japan, Tokyo	Phase III	*N* = 192	Male 145, female 47	47.8 years	Moderate-to-severe plaque-type psoriasis	Guselkumab	50–100 mg	Subcutaneous injection	Nasopharyngitis	3
13	Lee et al. [31]	Korea, Seoul	Phase III	*N* = 62	Male 49, female 13	60 years	Moderate-to-severe plaque psoriasis	Ustekinumab	300 mg	Subcutaneous injection	Upper respiratory tract infection, nasopharyngitis, rhinorrhea, arthralgia, allergic conjunctivitis, diarrhea, eczema, headache, oropharyngeal pain, vomiting, acne, contusion, cough, fatigue, myalgia, nausea, pruritus, allergic rhinitis, skin abrasion, tinea pedis, back pain, urticaria, psoriatic arthropathy, ligament sprain	3

Table 1 (continued)

S.No	Author [ref.]	Country	Study design	Sample size	Gender	Age	Disease	Anti-IL-23 agents	Dose, mg/kg	Mode of administration	Adverse effects	CTCAE (grade)
14	Paul et al. [32]	France, Toulouse	Phase IIIb	*N* = 302	Male 202, female 100	44 years	Psoriasis	Ustekinumab	80–160 mg	Subcutaneous injection	Nasopharyngitis, headache, arthralgia, hypertension, back pain, diarrhea, influenza, cough, injection site erythema, pruritus, bronchitis, upper respiratory tract infection, rhinitis, injection site reaction, musculoskeletal pain	3
15	Reich et al. [25]	Germany, Hamburg	Phase III	*N* = 772	Male 533, female 239	>18 years	Moderate-to-severe psoriasis	Tildrakizumab	100–200 mg	Subcutaneous injection	Nasopharyngitis, injection site erythema, upper respiratory tract infection, headache, injection site reaction, influenza, urinary tract infection, cough, pruritus, viral upper respiratory Tract infection, arthralgia, back pain, hypertension, gastroenteritis, diarrhea, oropharyngeal pain, sinusitis, bronchitis, nausea	4
16	Blauvelt et al. [19]	USA, Oregon	Phase III	*N* = 507	Male 356, female 151	>18 years	Moderate-to-severe plaque psoriasis	Risankizumab	150 mg	Subcutaneous injection	Cardiovascular events	4
17	Thaçi et al. [26]	Germany, Lubeck	Phase IIIb	*N* = 119	Male 382, female 37	39 years	Moderate-to-severe plaque psoriasis	Guselkumab	100 mg	Subcutaneous injection	Nasopharyngitis, diarrhea, abdominal pain, flushing, lymphopenia	3
18	Ferris et al. [20]	USA, Pittsburgh	Phase III	*N* = 78	Male 53, female 25	46 years	Moderate-to-severe psoriasis	Guselkumab	100 mg	Subcutaneous injection	Injection site pain, injection site coldness, injection site pruritus, injection site swelling, injection site induration, viral upper respiratory tract infection, injection site erythema, upper respiratory tract infection, injection site bruising	3

Table 2. Adverse effects associated with anti-IL-23 agents demonstrated by included studies

Adverse effects associated with anti-IL-23 agents	Studies reported
Nasopharyngitis	[13, 16, 31, 32, 17, 22,23, 25–27, 29, 30]
Headache	[13, 16, 17, 22, 23, 25, 27, 31, 32]
Back pain	[13, 16, 17, 23, 25, 31, 32]
Upper respiratory tract infection	[13, 16, 17,29, 31, 32]
Arthralgia	[16, 17, 22, 23, 25, 31, 32]
Pruritus	[17, 25, 29, 31, 32]
Diarrhea	[16, 22, 25, 26, 31, 32]
Injection site erythema	[17, 20, 25, 32]
Cardiovascular event	[18, 21, 28]
Hypertension	[23, 25, 32]
Viral upper respiratory tract infection	[20, 25]
Cough	[29, 31]
Psoriasis	[27, 29]
Injection site reactions	[25, 29]
Eczema	[29, 31]
Fatigue	[22, 31]
Rhinitis	[23, 32]
Nausea	[25, 31]
Cough	[25, 32]
Influenza	[25, 32]
Bronchitis	[25, 32]
Musculoskeletal pain	[32]
Abdominal pain, flushing, lymphopenia	[26]
Injection site pain, injection site coldness, injection site pruritus, injection site swelling, injection site induration, injection site bruising	[20]
Urinary tract infection, gastroenteritis, oropharyngeal pain, sinusitis	[25]
Eosinophilia, hyperglycemia, anemia, abnormal hepatic function psoriatic arthropathy	[29]
Infections, infestations	[27]
Rhinorrhea, allergic conjunctivitis, oropharyngeal pain, vomiting, acne, contusion, myalgia, allergic rhinitis, skin abrasion, tinea pedis, urticaria, psoriatic arthropathy, ligament sprain	[31]

groups during the induction and maintenance phases. About 2.7% participants discontinued the briakinumab due to any AEs. In a similar safety assessment of risankizumab, 0.5% cases discontinued the medicine due to AEs in the A1 part, while this rate was 3.6% in part B [19]. In a 16-week therapeutic period of a CLEAR study, the discontinuation rate due to ustekinumab's AEs was 1.2% [16]. Discontinued percentage patients for guselkumab in VOYAGE 1 trial during the placebo-controlled period was 1.2% and 2.7% in active comparator-controlled period [17]. In a pooled analyses of randomized phase III clinical trials (reSURFACE 1 and reSURFACE 2) evaluating tildrakizumab for moderate-to-severe psoriasis, the rate of discontinuation due to AEs in the 100-mg tildrakizumab treatment group was 1.7 per 100 patient-years, and in the 200-mg tildrakizumab cohort, the discontinuation rate was 1.2 per 100 patient-years [25].

Classification of Adverse Effects according to CTCAE Criteria

Out of 18 included studies, 14 studies observed grade 3 stage of adverse effects for the treatment of anti-IL-23 agents in patients with psoriasis, whereas four studies observed grade 4 stage of adverse effects. The anti-IL-23 agents, including ustekinumab and guselkumab, were significantly involved in the grade 3 stage of adverse effects for the treatment of psoriasis, whereas the anti-IL-23 agents including briakinumab, tildrakizumab, and risankizumab were significantly involved in the grade 4 stage of adverse effects. However, the anti-IL-23 agent guselkumab did not participate in the grade 4 stage of adverse effects for the treatment of psoriasis among the included phase III trials (Table 1).

Discussion

Psoriasis is an inflammatory disease caused by the immune system. Biologics are frequently utilized to treat people with severe psoriasis. The discovery of the Th17 pathway and its role in psoriasis inflammation has resulted from advances in pathogenesis [9]. Recently, biologics that inhibit the Th17 pathway, either upstream or downstream, have been introduced to the market [33]. Because IL-23 is a crucial upstream regulator, anti-IL-23 drugs exhibited a broad spectrum of antagonistic activity. Early in the disease inflammatory cascade, IL-23 encourages downstream effectors to maintain the TH17 cell phenotype [34]. These procedures are generally well tolerated and regarded as safe. However, as compared to placebo, adverse events are more common. IL-23 is produced by various immune cells in response to microbial products and inflammatory cytokines, and it functions as a link between the innate and adaptive immune systems, driving early local immunity [35]. The unique IL-23-p19 subunit is linked to the shared p40 subunit found in IL-12 to form the structure of IL-23. IL-23 and IL-12 are also involved in differentiating naive TH cells into TH17 and TH1 cells, respectively [36]. TH17 cells release several proinflammatory cytokines, which drive keratinocyte growth and activate downstream inflammatory signaling pathways [37].

In this review, the most common adverse effect caused by anti-IL-23 agents was nasopharyngitis followed by headache, upper respiratory tract infection, and back pain. To this point, the safety profiles of IL-23 inhibitors appear to be generally benign, with nasopharyngitis, upper respiratory tract infection, and headache being the most prevalent side effects across all classes [38]. Previously, several PHOENIX and ACCEPT trials reported that the most common adverse events of anti-IL-23 agents were nasopharyngitis, upper respiratory tract infections, headache, arthralgia, and injection site erythema [39, 40], which is similar to the current review. The anti-IL-23 agents, including ustekinumab and guselkumab, were significantly involved in the grade 3 stage of adverse effects for the treatment of anti-IL-23 agents in patients with psoriasis, whereas the anti-IL-23 agents including briakinumab, tildrakizumab, and risankizumab were significantly involved in the grade 4 stage of adverse effects. While the ustekinumab trials have not shown significantly more cardiovascular events than the placebo, IL-23 inhibitors' association with such events has remained controversial [41, 42]. The anti-IL-23 agent guselkumab did not participate in the grade 4 stage of adverse effects for the treatment of psoriasis among the included phase III trials in this review. The FDA recently approved guselkumab as the first selective IL-23 inhibitor for the treatment of psoriasis. Also, several mild adverse effects were associated with the guselkumab [43].

This study has several strengths. First, the included trials were randomized controlled trials of good quality, which helped reduce selection bias caused by differences in researchers and medical settings. Second, long-term follow-up studies with significant implications were added, which were discovered by compiling rare or nonimmune adverse effects induced by anti-IL-23 agents. However, the current systematic review has some limitations. First, eligible studies included in the review regarding the adverse effects of anti-IL-23 agents for patients with psoriasis were used a wide range of anti-IL-23 agents such as ustekinumab, briakinumab, guselkumab, tildrakizumab, and risankizumab. The lack of a standardized, universal, and appropriate anti-IL-23 agent for the treatment of psoriasis was demonstrated by these variance points. Second, only phase III trials were included in this review. Despite these limitations, this updated systematic review provides an evidence-based report on the adverse effects of anti-IL-23 agents for patients with psoriasis demonstrated by the pooled effect of different studies using rigorous methodology.

Conclusion

The vast proportion of studies into the pathophysiology of psoriasis has resulted in new medication classes that have revolutionized the treatment of psoriasis. Targeted IL-23 therapy has quickly risen to the forefront as the importance of the IL-23 axis has been progressively identified, setting a new benchmark for psoriasis outcomes. Over the last 3 years, ustekinumab, guselkumab, tildrakizumab, and risankizumab have successively come to the market. However, these drugs caused several immunological and nonimmunological side effects, but they are generally well-tolerated and have high safety profiles.

Key Message

Anti-IL-23 agents caused several side effects, but they are customarily well-tolerated and have orderly safety vignettes.

Statement of Ethics

Dr. Piyu Parth Naik has nothing to disclose and complied with ethics guidelines. This article is based on previously conducted studies and does not contain any new studies with human participants or animals performed by any of the authors.

Conflict of Interest Statement

The author has no conflicts of interest to declare.

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Author Contributions

Dr. Piyu Parth Naik has solely contributed to manuscript writing. Named author meets the International Committee of Medical Journal Editors (ICMJE) criteria for authorship for this article, takes responsibility for the integrity of the work, and has given her approval for this version to be published.

Data Availability Statement

Data sharing is not applicable to this article as no datasets were generated during the current study.

Appendix A

Risk of bias assessment of the included studies

S.No	Author [ref.]	Random sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome data	Selective outcome reporting	Other source of bias
1	Thaci et al. [26]	+	*	+	+	+	+	*
2	Kimball et al. [21]	+	*	+	+	+	+	*
3	Gordon et al. [13]	+	+	+	–	+	+	*
4	Landells et al. [27]	+	*	+	+	+	+	*
5	Thaçi et al. [26]	+	*	+	+	+	+	*
6	Langley et al. [28]	+	+	+	–	+	+	*
7	Blauvelt et al. [18]	+	*	+	+	+	+	*
8	Blauvelt et al. [44]	+	+	+	+	+	+	*
9	Blauvelt et al. [17]	*	*	+	+	+	+	*
10	Reich et al. [24]	+	+	+	+	+	+	*
11	Reich et al. [23]	+	+	+	+	+	+	*
12	Ohtsuki et al. [30]	+	+	+	+	+	+	*
13	Lee et al. [31]	–	*	*	*	+	+	*
14	Paul et al. [32]	–	*	+	+	+	+	*
15	Reich et al. [25]	+	+	+	+	+	+	*
16	Blauvelt et al. [19]	+	+	+	+	+	+	*
17	Thaçi et al. [26]	+	+	+	+	+	+	*
18	Ferris et al. [20]	+	+	+	+	+	+	*

(+), low risk; (–), high risk; (*), uncertain risk.

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