Safety of IL-23/17 Antagonists in Patients with Psoriasis or Other Immune-mediated Inflammatory Diseases: A Systematic Meta-Analysis.

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Abstract

Background: The IL-23/17 axis plays central role in the pathogenesis of several immune-mediated inflammatory diseases (IMIDs). IL-23/17 antagonists showed significant improvement in the treatment for psoriasis and other IMIDs, including psoriasis(PSO), psoriatic arthritis(PsA), rheumatoid arthritis(RA) and ankylosing spondylitis(AS).

Objective: To assess the safety of IL-23/17 antagonists therapy on patients with psoriasis and other IMIDs.

Methods: Pooled analysis from thirty-nine placebo-controlled randomized clinical trials (RCTs) of IL-23/17 axis antagonists for IMIDs. Incidences of adverse events (AEs), serious adverse events (SAEs) and AEs of interest were applied to evaluate the safety profile.

Result: A Total of 15967 patients were exposed to IL-23/17 axis antagonists. The proportions of patients suffered at least one AE in antagonists group and placebo-control group are 67.5% and 51.1% respectively. Incidence of SAE was increased in patients treated with IL-23/17 axis antagonists compared to patients given placebo (relative risk 2.03; 95% CI, 1.62, 2.56). Incidence of AEs of interest were all increased in patients treated with IL-23/17 axis antagonists compared to patients given placebo.

Conclusion: In this analysis, we found increased risk of AEs, SAEs, nervous system disorder, cardiovascular disorder and hypertension among patients with IMIDs treated with IL-23/17 axis antagonists.

Introduction

Psoriasis is an immune-mediated inflammatory, genetic skin disorder, which affects over 2–3% of the world's population in broad outline[1] [2] [3] [4]. Patients with psoriasis suffer great physical and psychological burden and are unable to get a high quality of life. In clinical practice, a combination of glucocorticosteroids, vitamin D derivatives, phototherapies is common used for mild to moderate psoriasis treatment. Moreover, systemic therapies, such as methotrexate, ciclosporin, fumaric acid esters and biologic drugs are widely applied to moderate to severe psoriasis [5]. In the past decades, with a better understanding of the pathogenesis of psoriasis, biologics targeting to key inflammatory pathways, such as the TNF- α signaling and IL-23/17 axis, are developed and proved effective.

IL-23 drives the production of Th17 cells from naïve T cells and induce the differentiation of Th17 cells that produce several inflammatory cytokines such as IL-17A and IL-17F, which modulate hallmark inflammatory installed by noxious stimulus in immune-mediated inflammatory diseases (IMIDs) [6] [7]. IL-23/17 axis antagonists include IL-23 antagonist, a dimer composed of p40 and p19, and IL-17A antagonists. The efficiency of the latter was improved significantly in treatment for IMIDs, involving psoriasis(PSO), psoriatic arthritis(PsA), rheumatoid arthritis(RA) and ankylosing spondylitis(AS). Ustekinumab, targeting p40 subunit of IL-23, is the first IL-23/17 antagonist to be approved for psoriasis vulgaris after the TNF- α antagonists. In 2015, the first IL-17A antagonists, Secukinumab, was approved for psoriasis treatment[4] [5]. And Ixekizumab was another biological agent targeting to IL-17A. IL-23/17 axis antagonists have been related to potential adverse events(AEs), including hypertension, nervous system disorders, cardiovascular disorder, serious adverse events(SAEs). Nervous system disorders mainly include headache, Carotid artery occlusion, Cerebrovascular accident et.al also been taken into account.

As increased demands of patients for disease remission and quality of life, there are more therapeutic means for IMIDs. As doctors, it is necessary for adequately weigh the risk/benefit ratio of drugs before applying to patients, which including fully understanding the exact safety profile of IL-23/17 axis antagonists.

In this report, we analyze the potential AEs risk of IL-23/17 axis antagonists based on data from clinical randomized controlled trials. To our knowledge, this is the first safety analysis of three IL-23/17 axis antagonists as regards the four IMIDs. What's more, the risks of hypertension and nervous system disorders in patients with IMIDs receiving IL-23/17 axis antagonists therapy were rarely mentioned before.

Materials And Methods

Information Sources and Searches

The following databases were systematically searched: EMBASE, MEDLINE, and Cochrane Central Register of Controlled Trials (CENTRAL) from the beginning to March 2020. Search strategies included the following terms: ['L-23/17 axis antagonists' OR ('Ustekinumab' OR 'CNTO 1275') OR ('secukinumab' OR 'Cosentyx' OR 'AIN457') OR ('Ixekizumab' OR 'Taltz')] AND ['psoriasis' OR 'psoriatic arthritis' OR 'rheumatoid arthritis' OR 'ankylosing spondylitis'] AND ['safety' OR 'adverse events' OR 'hypertension' OR 'serious adverse events' OR 'nervous system disorders' OR 'cardiovascular disorder'] AND ['randomized controlled trial'].

Selected Studies and Integrated Data

Three authors (A, B ,C) join the program. Author A searched databases and deleted duplicates by title. The abstracts and full-text articles were screened by author A, B and C, and they checked whether the studies conform to the protocol or meet the criteria. If not, the study would be excluded. Common inclusion criteria for these trials included patients aged ≥ 18 years, placebo-controlled, and ensured that the index disease was present and that patients had active disease appropriate for clinical trial enrolment. Inclusion and exclusion criteria are shown in supplementary table1.

Two authors independently gathered information from each study and another author resolved the differences. Data collected included: NCT number, disease type, year of study, study design, drug name, study duration, number of patients, exposure definition, AEs (hypertension, nervous system disorders, cardiovascular disorder, SAEs).

Data Analysis

Data was summarized from placebo-controlled randomized clinical trials(RCTs) for meta-analysis, which published on ClinicalTrials.gov or other journals. Incidence rates of AEs, SAEs, hypertension, nervous system disorders and cardiovascular disorder were evaluated by Review Manager (RevMan) software (Version 5.3. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014). Forest plot are constructed by plotting the risks of SAE, nervous system disorders, cardiovascular disorder and hypertension between antagonists groups and placebo groups. Means of Chi Square and I^2 tests were used to evaluate Heterogeneity among studies. According to the Cochrane Handbook for Systematic Reviews of Interventions, it might not be important when I^2 is below 40%; the value of I^2 between 30–60% may represent moderate heterogeneity; the value of I^2 between 50–90% may represent substantial heterogeneity; there may be considerable heterogeneity when the value of I^2 is between 75–100%. Overall, $I^2 \leq 50\%$ is acceptable[8]. To allow for any heterogeneity among studies, random-effects models were used to give a more conservative estimate of the effect of individual therapies. Relative Risks (RR) and their corresponding 95% confidence intervals were described. All RCTs were judged risk of bias by random sequence, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data and other bias according to the Cochrane criteria guidelines. Grading of suggestions from Recommendations Assessment Development and Evaluation (GRADE) working group, authors determined the quality of evidence for each outcome.

Results

Data were derived from 36 global clinical randomized controlled trials of IL-23/17 axis antagonists, 15 in PSO, 11 in PsA, 4 in AS, 6 in RA, until March 2020 (Supplemental Fig. 1) [9] [10] [11] [12] [13] [14] [15] [16] [17] [18] [19] [20] [21] [22] [23] [24] [25] [26] [27] [28] [29] [30] [31] [32] [33] [34] [35] [36] [37] [38] [39] [40]. A Total of 13368 patients received IL-23/17 axis antagonists, 4833 patients received placebo. Among these, 9415 were patients with PSO, 5222 were patients with PsA, 1466 were patients with AS, 2098 were patients with RA. The main included study characteristics are listed in Table 1.

Table 1
Main characteristics of included studies.

Disease	Author	Patients, n	Mean age ,y	Female %	Study design	Exposure	Study Duration
Psoriasis							
	Paul C 2014	182	44.7	31.3	Phase 3, randomized, parallel assignment, double-blind, placebo-controlled study	Placebo; Secukinumab 150 or 300 mg	12weeks
	Gordon KB 2016	1296	45.7	31.9	Phase 3, randomized, parallel assignment, double-blind, placebo-controlled study	Placebo; Ixekizumab 80 mg	12weeks
	Gordon KB 2016	1224	45.0	32.9	Phase 3, randomized, parallel assignment, double-blind, placebo-controlled study	Placebo; Ixekizumab 80 mg	12weeks
	Gordon KB 2016	1346	45.8	31.8	Phase 3, randomized, parallel assignment, double-blind, placebo-controlled study	Placebo; Ixekizumab 80 mg	12weeks
	Krueger GG 2007	320	44.9	43.1	Phase 2, randomized, parallel assignment, double-blind, placebo-controlled study	Placebo; Ustekinumab 45 or 90 mg	36weeks
	Langley RG 2014	1306	44.4	28.9	Phase 3, randomized, parallel assignment, double-blind, placebo-controlled study	Placebo; Secukinumab 150 or 300 mg	52weeks
	Langley RG 2014	738	45.1	31.0	Phase 3, randomized, parallel assignment, double-blind, placebo-controlled study	Placebo; Secukinumab 150 or 300 mg	48weeks
	Leonardi C 2012	142	46.2	43.0	Phase 2, randomized, parallel assignment, double-blind, placebo-controlled study	Placebo; Ixekizumab 10, 25,75 or 150 mg	20weeks
	Leonardi CL 2008	766	45.3	30.7	Phase 3, randomized, parallel assignment, double-blind, placebo-controlled study	Placebo; Ustekinumab 45 or 90 mg	12weeks
	Novartis 2010	125	45.9	27.2	Phase 3, randomized, parallel assignment, double-blind, placebo-controlled study	Placebo; Secukinumab	37weeks
	Novartis 2012	177	45.9	33.9	Phase 3, randomized, parallel assignment, double-blind, placebo-controlled study	Placebo; Secukinumab 150 or 300 mg	12weeks

Disease	Author	Patients, n	Mean age, y	Female %	Study design	Exposure	Study Duration
	Novartis 2015	100	43.8	20.0	Phase 3, randomized, parallel assignment, double-blind, placebo-controlled study	Placebo; Secukinumab	52weeks
	Novartis 2017	543	40.2	24.1	Phase 3, randomized, parallel assignment, double-blind, placebo-controlled study		52weeks
	Papp KA 2008	1230	46.2	31.7	Phase 3, randomized, parallel assignment, double-blind, placebo-controlled study	Placebo; Ustekinumab 45 or 90 mg	12weeks
	Paul C 2015	404	44.1	24.3	Phase 2, randomized, parallel assignment, double-blind, placebo-controlled study	Placebo; Ustekinumab 45 or 90 mg	12weeks
Psoriatic Arthritis							
	Genovese MC 2013	237	54.9	77.2	Phase 2, randomized, parallel assignment, double-blind, placebo-controlled study	Placebo; Secukinumab 25, 75, 150 or 300 mg	20weeks
	Gottlieb A 2009	146	48.7	43.8	Phase 2, randomized, crossover assignment, double-blind, placebo-controlled study	Placebo; Secukinumab 63 mg	12weeks
	Kavanaugh A 2016	312	47.9	52.6	Phase 3, randomized, parallel assignment, double-blind, placebo-controlled study	Placebo; Ustekinumab 45 or 90 mg	44weeks
	Kivitz AJ 2019	341	49.0	42.2	Phase 3, randomized, parallel assignment, double-blind, placebo-controlled study	Placebo; Secukinumab 150 mg	112weeks
	McInnes IB 2013	598	47.1	46.3	Phase 3, randomized, parallel assignment, double-blind, placebo-controlled study	Placebo; Ustekinumab 45 or 90 mg	108weeks
	McInnes IB 2015	397	48.0	48.4	Phase 3, randomized, parallel assignment, double-blind, placebo-controlled study	Placebo; Secukinumab 75, 150 or 300 mg	52weeks
	Mease PJ 2015	606	49.0	54.5	Phase 3, randomized, parallel assignment, double-blind, placebo-controlled study	Placebo; Secukinumab 75 or 150 mg	24weeks
	Mease PJ 2017	417	49.5	54.0	Phase 3, randomized, parallel assignment, double-blind, placebo-controlled study	Placebo; Ixekizumab	24weeks

Disease	Author	Patients, n	Mean age, y	Female %	Study design	Exposure	Study Duration
	Nash P 2017	363	51.9	53.4	Phase 3, randomized, parallel assignment, double-blind, placebo-controlled study	Placebo; Ixekizumab 80 mg	24weeks
	Nash P 2018	414	49.8	54.8	Phase 3, randomized, parallel assignment, double-blind, placebo-controlled study	Placebo; Secukinumab 150 or 300 mg	24weeks
	Novartis 2015	42	47.0	64.3	Phase 2, randomized, parallel assignment, double-blind, placebo-controlled study	Placebo; Secukinumab	3weeks
	Van Der Heijde D 2019	997	48.8	49.8	Phase 3, randomized, parallel assignment, double-blind, placebo-controlled study	Placebo; Secukinumab 150 or 300 mg	24 weeks
Ankylosing Spondylitis							
	Baeten D 2015	371	41.8	30.7	Phase 3, randomized, parallel assignment double-blind, placebo-controlled study	Placebo; Secukinumab	16weeks
	Baeten D 2015	219	43.3	30.1	Phase 3, randomized, parallel assignment, double-blind, placebo-controlled study	Placebo; Secukinumab 75 or 150 mg	16weeks
	Pavelka K 2017	226	42.5	39.8	Phase 3, randomized, parallel assignment, double-blind, placebo-controlled study	Placebo; Secukinumab 150 or 300 mg	16weeks
	Kivitz AJ 2019	463	43.0	31.4	Phase 3, randomized, parallel assignment, double-blind, placebo-controlled study	Placebo; Secukinumab 150 mg	16weeks
Rheumatoid arthritis							
	Blanco FJ 2017	551	54.5	81.7	Phase 3, randomized, parallel assignment, double-blind, placebo-controlled study	Placebo; Secukinumab	24weeks
	Tlustochowicz W 2016	221	54.0	79.6	Phase 2, randomized, parallel assignment, double-blind, placebo-controlled study	Placebo; Secukinumab	16weeks
	Tahir H 2017	637	52.9	87.3	Phase 3, randomized, parallel assignment, double-blind, placebo-controlled study	Placebo; Secukinumab	16weeks

Disease	Author	Patients, n	Mean age, y	Female %	Study design	Exposure	Study Duration
	Smolen JS 2017	274	51.5	83.2	Phase 2, randomized, parallel assignment, double-blind, placebo-controlled study	Placebo; Ustekinumab 90 mg	48weeks
	Dokoupilova E 2018	242	54.2	83.5	Phase 3, randomized, parallel assignment, double-blind, placebo-controlled study		24weeks

The Cochrane manual recommends authors Cochrane risk bias assessment tools, which believes that bias can better reflect the quality of an RCT. All RCTs show low risk. The quality of evidence was high for every outcome.

All RCTs reported AEs and SAEs. Compared with placebo group, drug group obtained higher rate of AEs (64.2% VS 49.5%). Figure 1 shows the forest plot representing the pooled analysis of all studies on SAEs: The IL-23/17 axis antagonists treatment had significant effect on SAEs when analyzing the total population [RR = 1.95 (1.55, 2.44)]. As for heterogeneity, $I^2 \leq 50\%$ is acceptable based on the Cochrane Book ($I^2 = 22\%$ and $p = 0.12$).

Nervous system disorders were assessed in all studies, which included 13368 patients exposed to IL-23/17 axis antagonists. Overall, 8.3% (1109) patients suffered nervous system disorders in drug group, which was higher than placebo-control group (5.2%). Figure 2 shows the forest plot representing the pooled analysis of all studies on nervous system disorders: The IL-23/17 axis antagonists treatment had significant effect on nervous system disorder when analyzing the total population [RR = 1.56 (1.32, 1.84)]. As for heterogeneity, $I^2 \leq 50\%$ is acceptable based on the Cochrane Book ($I^2 = 14\%$ and $p = 0.42$).

Cardiovascular disorders were assessed in 31 studies, which included 12648 patients on IL-23/17 axis antagonists exposure. The global incidence was 1.6%, whereas the incidence of patients exposed to the placebo was 0.5%. Figure 3 shows the forest plot representing the pooled analysis of 31 studies on Cardiovascular disorders: The IL-23/17 axis antagonists treatment had significant effect on Cardiovascular disorders when analyzing the total population [RR = 2.06 (1.39, 3.06)]. There was no evidence of heterogeneity in the outcome of incidence rate of cardiovascular disorder ($I^2 = 0\%$ and $p = 0.94$).

Hypertension was assessed in 26 studies, which included 8909 patients exposed to IL-23/17 axis antagonists. Among them, 461 (5.2%) of 5324 patients had hypertension, whereas the incidence of patients exposed to the placebo was 2.5%. Figure 4 shows the forest plot representing the pooled analysis of 26 studies on hypertension: The IL-23/17 axis antagonists treatment had significant effect on hypertension when analyzing the total population [RR = 1.97 (1.50, 2.57)].

Discussion

This analysis is the first to evaluate the safety of IL-23/17 axis antagonists (Ustekinumab, Secukinumab, Ixekizumab) in patients with four IMIDs: PSO, PsA, AS, and RA. Our study synthesized the incident rates of AEs, SAEs and interested AEs (nervous system disorders, cardiovascular disorder, hypertension) from 36 RCTs.

Benefiting from the newly-developed therapies on IMIDs, patients with IMIDs are now having more options for the treatment. IL-23/17 axis antagonists have shown significant efficacy in IMIDs, and were used more frequently worldwide. It was paramount to define the safety profile of the medication. Overall, AEs and SAEs obtained higher incident rate in antagonists group. However, most of AEs were mild, and few of them led to drug discontinuation.

Incidence rates of AEs and SAEs were 95.4 per 100 person-years and 9.3 per 100 person-years (Supplementary Table 2). In contrast to JAK antagonists exposure, incidence rates of AEs and SAEs were 42.69 per 100 person-years and 9.98 per 100 person-years, according to Olivera et al[41]. IL-23/17 antagonists show advantage in reducing SAEs. SAEs include major adverse cardiovascular event, cancer and other events which could be enough to death. In this aspect, IL-23/17 antagonists are safer than JAK antagonists. However, the high incidence of AEs might directly affect patients' quality of life. Thus, a further study in relationship between prevalence of AEs and patients' quality of life will be carried out.

There were also higher proportions of patients with nervous system disorders in the antagonists groups than placebo group. Mean incidence rate of nervous system disorders is 12.3 per 100 person-years (Supplementary Table 2). The majority of nervous system disorders is headache, of which the incidence rate on Ustekinumab therapy (10.3 per 100 person-years) is lower than Secukinumab (12.4 per 100 person-years) and Ixekizumab (15.5 per 100 person-years). This difference could be due to the fact that both Secukinumab and Ixekizumab block IL-17A, whereas Ustekinumab targets p40 subunit of IL-23. McGinley AM et al reported that IL-17A recruits IL-1 β -secreting myeloid cells mainly including $\gamma\delta$ T17 and Th17 cells, both of which are prime pathogenic cells in central nervous system (CNS) autoimmunity [42]. Nevertheless, exact immunopathogenesis of high prevalence of nervous system disorders in patients with IMIDs exposure to IL23/17 antagonists are needed to explore.

Cardiovascular disorders were considered to be one of the biggest killers leading to death around the worldwide. Mean incidence rate of Cardiovascular disorders is 5.7 per 100 person-years (Supplementary Table 2). As the forest plot shows, more patients on antagonists therapy sustained cardiovascular disorders. Interestingly, the incidence rate of hypertension also increased in patients on IL23/17 antagonists therapy. Though, the exact pathogenic mechanism of the higher incidence rate of hypertension on IL23/17 antagonists therapy was not reported, it must be associated with the inflammatory cytokines and immune response on IL23/17 axis pathway. Anton Gisterå et al proved that IL-17–dependent pathway promotes stabilization of atherosclerotic plaques [43]. Konstantinos Savvatis et al proved that IL-23 play a key role in prognosis of myocardial infarction [44]. It accounts for patients undergoing therapeutic IL23/17 antagonists with higher incidence rate of cardiovascular disorder.

There are several limitations in our study. First, present study only focused on the most commonly used IL-23/17 axis antagonists such as Ustekinumab, Secukinumab and Ixekizumab, therefore other medications involved in IL-23/17 axis inhibition need to be further studied. Secondly, most of the included studies were conducted in PSO, followed by PsA, and the number of studies regarding to AS and RA was limited. Thirdly, this analysis only included placebo-controlled RCTs to assure the quality of the evidence. It may influence the rate of AEs in total. Fourthly, the patient eligible for analysis are 18 years old or older, not including juveniles. Additionally, regard as the absence of enough data from long-term studies

In conclusion, the results of present analysis support that the use of IL-23/17 antagonists for the treatment of PSO, PsA, AS and RA increased the incidence rates of AEs, SAEs and interest of AEs (nervous system disorders, cardiovascular disorder, hypertension). To fully evaluate the safety profile of the different IL-23/17 antagonists, there need to be more long-term studies.

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Availability of data and materials

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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Conflicts of Interest

The authors have declared that no conflict of interest exists.

Authors' contributions

All authors were involved in this meta-analysis. SL designed the study and was a major contributor in this work. All authors collected data from studies conformed to selection criteria. All authors read and approved the final manuscript.

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Figures

Figure 1

Forest plot comparing the incidence rate of serious adverse events for IL-23/17 axis antagonists group versus placebo-controlled group.

Figure 2

Forest plot comparing the incidence rate of nervous system disorders for IL-23/17 axis antagonists group versus placebo-controlled group.

Figure 3

Forest plot comparing the incidence rate of cardiovascular disorders for IL-23/17 axis antagonists group versus placebo-controlled group.

Figure 4

Forest plot comparing the incidence rate of hypertension for IL-23/17 axis antagonists group versus placebo-controlled group.

Supplementary Files

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