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# The risk of respiratory tract infections and interstitial lung disease with interleukin 12/23 and interleukin 23 antagonists in patients with autoimmune diseases: A systematic review and meta-analysis



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**Background:** Respiratory tract infections (RTIs) and interstitial lung disease (ILD) secondary to interleukin (IL) 12/23 or IL-23 antagonists have been reported in autoimmune diseases.

**Objective:** To assess the risk of RTIs and noninfectious ILD with these drugs.

**Methods:** We conducted a systematic review and meta-analysis of randomized controlled trials. Risk of RTIs and noninfectious ILD was compared to placebo by Mantel-Haenszel risk difference. We divided RTIs into upper RTIs (URTI), viral URTIs, and lower RTIs (LRTIs) including infectious pneumonia. Noninfectious ILD included ILD, eosinophilic pneumonia, and pneumonitis.

**Results:** We identified 54 randomized controlled trials including 10,907 patients with 6 IL-12/23 or IL-23 antagonists and 5175 patients with placebo. These drugs significantly increased the risk of RTIs (Mantel-Haenszel risk difference, 0.019; 95% confidence interval, 0.005-0.033;  $P = .007$ ), which was attributed to URTIs, but not viral URTIs or LRTIs. There was no significant difference in infectious pneumonia and noninfectious ILD between 2 groups.

**Limitations:** Because of the rarity of infectious pneumonia and ILD, sensitivity analysis was required.

**Conclusions:** The use of IL-12/23 or IL-23 antagonists for autoimmune diseases increased the risk of URTIs, but not viral URTIs, LRTIs, and noninfectious ILD. (J Am Acad Dermatol 2021;84:676-90.)

**Key words:** autoimmune diseases; IL12/23 and IL23 antagonists; meta-analysis; noninfectious interstitial lung disease; respiratory tract infections.

The clinical benefit of interleukin (IL) 12 and IL-23 inhibition has been shown in psoriasis and Crohn's disease (CD) by briakinumab<sup>1,2</sup> or ustekinumab.<sup>3,4</sup> Furthermore, IL-23-specific antagonists, such as tildrakizumab,<sup>5,6</sup> risankizumab,<sup>7,8</sup>

guselkumab,<sup>9,10</sup> and brazikumab,<sup>11</sup> have completed phase 2 or 3 trials. Currently, IL-12/23 or IL-23 antagonists are the second most commonly prescribed category of biologics for psoriasis and CD, behind anti-tumor necrosis factor agents.<sup>12</sup>

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However, randomized controlled trials (RCTs) of these drugs reported respiratory tract infections (RTIs) as the most common adverse events.<sup>13</sup> Furthermore, the surveillance conducted by the US Food and Drug Administration (FDA) reported the development of noninfectious interstitial lung disease (ILD) after ustekinumab.<sup>14</sup> Hence, physicians need evidence to decide whether to continue or hold these drugs, particularly during the current COVID-19 pandemic.<sup>15-17</sup>

This systematic review and meta-analysis aimed to determine the risk of RTIs and noninfectious ILD with anti-IL-12/23 or anti-IL-23 agents in autoimmune diseases.

## METHODS

### Search strategy and study selection

This meta-analysis was conducted according to an a priori defined protocol based on Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines.<sup>18</sup> The protocol of this meta-analysis has been submitted to the International Prospective Register of Systematic Reviews (PROSPERO).<sup>19</sup>

We searched PubMed/MEDLINE, Google Scholar, Scopus, Embase, [ClinicalTrials.gov](https://clinicaltrials.gov/) (<https://clinicaltrials.gov/>), and the Cochrane database from inception to February 1, 2019, to identify studies assessing the efficacy and safety of anti-IL-12/23 and anti-IL-23 therapies in autoimmune diseases. We also searched abstracts from medical conferences and bibliographies of identified articles for additional references. For Google Scholar, only the first 1000 articles were reviewed because this is the maximum number of results provided by the database. When a study registered in [ClinicalTrials.gov](https://clinicaltrials.gov/) or presented as an abstract became later available as an article, data were updated accordingly.<sup>20,21</sup>

As for inclusion criteria, we considered RCTs reporting the incidence of adverse events, including RTIs and noninfectious ILD, with anti-IL-12/23 and anti-IL-23 therapies. There were no restrictions regarding age, sex, or duration of the study. We imposed no geographic or language restrictions. Two authors (SA and DM) independently screened each of the potential trials, abstract, and/or full article to determine whether they were eligible for inclusion. Area of disagreement or uncertainty were resolved by

consensus among the authors. Studies were identified with the terms “briakinumab,” “ustekinumab,” “tildrakizumab,” “guselkumab,” “risankizumab,” “brazikumab,” “mirikizumab,” “LY2525623,” “anti-interleukin-12/23,” “anti-interleukin-23,” “anti-IL-12/23,” “anti-IL-23,” “anti-interleukin-12,” and “anti-IL-12” (both as medical subject headings and free text terms). RCTs without placebo-controlled groups were excluded. The search strategy is described in [Fig 1](#).

### Data extraction and quality assessment

All data were independently abstracted in duplicate by 2 authors (SA and DM) by using a data extraction form. Data on the study characteristics, such as author name, year of publication, study design, duration, sample size, age of patients, type of medications, and incidence of events were collected. Several published studies included data from multiple RCTs with different regimens or participant characteristics. For instance, the study published by Gordon et al included a comparison between ustekinumab and placebo and another comparison between risankizumab and placebo.<sup>7</sup> These comparisons were considered as separate individual RCTs in our meta-analysis to ensure proper comparison and to avoid selection bias. The Jadad score was used to assess the quality of RCTs.<sup>22</sup> We also used Cochrane risk-of-bias assessment instrument to evaluate the quality of the RCTs.<sup>23</sup> The Grading of Recommendations Assessment, Development, and Evaluation (GRADE) was applied to assess the certainty of evidence obtained from this meta-analysis.<sup>24</sup>

### Outcome assessment

The primary outcome measure of interest was the risk difference (RD) of the development of RTIs and noninfectious ILD among patients on anti-IL-12/IL-23 or anti-IL-23 agents compared with placebo. Subgroup analyses with each monoclonal antibody and underlying disease were performed. Data were analyzed based on the intention-to-treat principle except where indicated. We determined the number of each adverse event from the articles and the [ClinicalTrials.gov](https://clinicaltrials.gov/) database. We sorted RTIs into the following 3 categories: (1) upper RTIs (URTIs), (2) viral URTIs, and (3) lower RTIs (LRTIs). Based on Medical Dictionary for Regulatory

## CAPSULE SUMMARY

- This meta-analysis showed that IL-12/23 or IL-23 antagonists increased the risk of upper respiratory tract infections (URTIs), but not viral URTIs, lower RTIs, and noninfectious interstitial lung disease in autoimmune diseases.
- This result suggests their safe use even during the COVID-19 pandemic, but further observations are required.

*Abbreviations used:*

CD:	Crohn's disease
CI:	confidence interval
FDA:	US Food and Drug Administration
IL:	interleukin
ILD:	interstitial lung disease
LRTI:	lower respiratory tract infection
MedDRA:	Medical Dictionary for Regulatory Activities
MH:	Mantel-Haenszel
OR:	odds ratio
RCT:	randomized controlled trial
RD:	risk difference
RR:	risk ratio
RTI:	respiratory tract infection
URTI:	upper respiratory tract infection

Activities (MedDRA) Terminology (<https://biportal.bioontology.org/ontologies/MEDDRA>), URTIs included the following diagnoses: nasopharyngitis, laryngitis, pharyngitis, rhinitis, sinusitis, tonsillitis, pharyngotonsillitis, tracheobronchitis, and upper respiratory infection. Viral URTIs included influenza and viral URTI. LRTIs were bronchitis, LRTI, and pneumonia. We included the following diseases in noninfectious IL: IL, eosinophilic pneumonia, and pneumonitis.

### Statistical analysis

We undertook a meta-analysis with a random effects model. Mantel-Haenszel (MH) RD was used as our primary method.<sup>25</sup> As for rare events, including infectious pneumonia and noninfectious IL, we performed the sensitivity analysis as described in the “Results” section because of uncertainty regarding the preferred method for rare events. First, we analyzed data by MH odds ratio (OR), Peto OR,<sup>26</sup> and MH risk ratio (RR) by excluding double-zero-event studies. Second, data were pooled among each drug, and then meta-analysis was performed by MH RD, MH OR, Peto OR, and MH RR.<sup>27</sup> Finally, data were assessed by MH OR, Peto OR, and MH RR by adding 0.5 continuity correction or treatment arm correction to zero-event studies.<sup>28</sup>

We evaluated the presence of heterogeneity across trials by using the  $I^2$  statistic. An  $I^2$  value of less than 25% indicated low heterogeneity, 25% to 75% indicated moderate heterogeneity, and greater than 75% indicated considerable heterogeneity.<sup>29</sup> Heterogeneity was evaluated by using the Cochran  $Q$  statistic with a significance level of  $P < .10$ .<sup>30</sup> Begg and Egger tests were performed to assess publication bias, and funnel plots were constructed to visualize possible asymmetry when 3 or more studies were available.<sup>31,32</sup>

Statistical analyses were performed using Comprehensive Meta-Analysis Software, version 2.0 (Biostat, Englewood, NJ). All statistical tests except for the  $Q$  statistic used a 2-sided  $P$  value of .05 for significance.

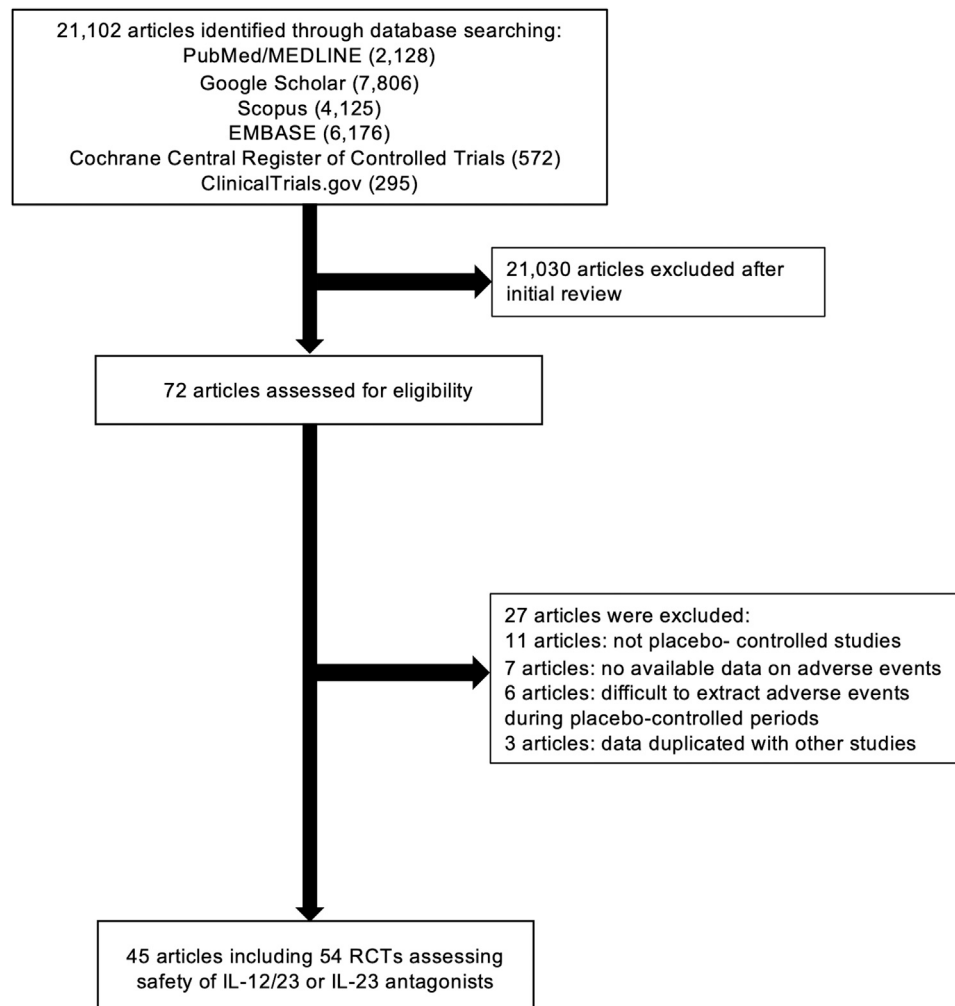
## RESULTS

### Study characteristics

We identified 21,102 citations through the literature search, excluded 21,030 titles and abstracts after the initial screening, and assessed 72 studies for eligibility. A final number of 43 full-text articles and 2 studies registered only in [ClinicalTrials.gov](https://clinicaltrials.gov) met all eligibility criteria and included 54 RCTs with a total of 10,907 patients with anti-IL-12/IL-23 or anti-IL-23 antibodies and 5175 with placebo (Fig 1). The 54 RCTs included 1 study of brazikumab (59 patients), 8 of briakinumab (1817 patients), 9 of guselkumab (1321 patients), 5 of risankizumab (830), 5 of tildrakizumab (1596 patients), and 26 of ustekinumab (5284 patients). All of the included studies are randomized, double-blind, placebo-controlled studies and have high scores in the Jadad scoring system. The characteristics and outcomes of the included studies are summarized in Table I.<sup>33-60</sup> The mean ages of patients and percentages of male patients were 43.8 years and 66.6% for guselkumab, 42.8 years and 65.4% for risankizumab, 37.6 years and 62.4% for tildrakizumab, 43.3 years and 49.5% for briakinumab, and 43.3 years and 54.0% for ustekinumab. The percentages of studies that permitted use of concomitant drugs (eg, corticosteroids, budesonide, thiopurines, methotrexate, calcineurin inhibitors, or aminosaliclates) during the trials were 40.0% for risankizumab, 38.5% for ustekinumab, 37.5% for briakinumab, 0% for guselkumab, and 0% for tildrakizumab. As for brazikumab, 1 study for CD was included in this analysis and permitted concomitant drugs (Table I).

### RTIs

Meta-analysis with a random effects model showed that the overall risk of RTIs with anti-IL-12/IL-23 or anti-IL-23 agents was significantly higher than that of placebo (MH RD, 0.019; 95% confidence interval [CI], 0.005-0.033;  $P = .007$ ) (Fig 2). The number needed to harm of RTIs was 58.8. Subgroup analysis showed a significantly increased risk of RTIs with briakinumab (MH RD, 0.021; 95% CI, 0.001-0.041;  $P = .036$ ) and risankizumab (MH RD, 0.040; 95% CI, 0.005-0.076;  $P = .026$ ). Heterogeneity was absent ( $I^2 = 0\%$ ) in overall and subgroup analyses except for briakinumab ( $I^2 = 31\%$ ). Funnel plot showed no asymmetry, therefore suggesting there were no



**Fig 1.** Flow chart of the assessment of the studies identified in the meta-analysis. *IL*, Interleukin; *RCT*, randomized controlled trial.

small-study effects or publication biases, which was supported by Begg and Egger tests (Supplemental Fig 1; available via Mendeley at <https://doi.org/10.17632/j7dfkr2s8v.1>). We also assessed the differential risk of RTIs by underlying disease and showed a significantly increased risk of RTIs in psoriasis (MH RD, 0.023; 95% CI, 0.010-0.036;  $P < .001$ ) and ankylosing spondylitis (MH RD, 0.136; 95% CI, 0.006-0.265;  $P = .040$ ) (Supplemental Fig 2; available via Mendeley at <https://doi.org/10.17632/j7dfkr2s8v.1>).

We divided RTIs into URTIs, viral URTIs, and LRTIs and investigated each risk with IL-12/23 or IL-23 inhibitors. The overall risk of URTIs was significantly higher in the treatment group compared to placebo (MH RD, 0.017; 95% CI, 0.005-0.029;  $P = .006$ ) (Supplemental Fig 3, *A*;

available via Mendeley at <https://doi.org/10.17632/j7dfkr2s8v.1>). Subgroup analysis showed an elevated risk of URTIs with risankizumab (MH RD, 0.028; 95% CI, 0.004-0.053;  $P = .024$ ). No publication bias was detected by Begg and Egger tests (Supplemental Fig 3, *B*).

Anti-IL-12/IL-23 or anti-IL-23 agents did not increase the overall risks of viral URTIs (MH RD, 0.001; 95% CI, -0.002 to 0.003;  $P = .60$ ) and LRTIs (MH RD, 0; 95% CI, -0.002 to 0.002;  $P = .71$ ) (Supplemental Figs 4, *A* and 5, *A*; available via Mendeley at <https://doi.org/10.17632/j7dfkr2s8v.1>). Heterogeneity was absent ( $I^2 = 0\%$ ) in these analyses. Publication bias was indicated in the analysis of viral URTIs (Begg:  $P < .001$ ; Egger:  $P = .019$ ) (Supplemental Fig 4, *B*) and LRTIs (Begg:  $P < .001$ ; Egger:  $P = .55$ ) (Supplemental Fig 5, *B*), but

the funnel plots did not appear asymmetric on visual inspection.

### Infectious pneumonia and noninfectious ILD

The total numbers of infectious pneumonia were 9 and 4 cases in the treatment group and placebo, respectively. *Mycobacterium tuberculosis* and viral pneumonia were not reported. The overall risk of infectious pneumonia was not significantly increased in the treatment group compared to placebo (MH RD, 0; 95% CI, -0.002 to 0.002;  $P = .87$ ) (Fig 3). Heterogeneity was absent ( $I^2 = 0\%$ ). The funnel plot was not asymmetric, indicating no publication bias, which was supported by Egger test ( $P = .93$ ) but not Begg test ( $P < .001$ ) (Supplemental Fig 6; available via Mendeley at <https://doi.org/10.17632/j7dfkr2s8v.1>).

In terms of noninfectious ILD, 2 and 1 cases were identified in the treatment and placebo groups, respectively. All 3 cases were reported in trials of ustekinumab and occurred within 16 weeks after initiation of the trial.<sup>61-63</sup> The overall risk of ILD was not significantly increased in the treatment group (MH RD, 0; 95% CI, -0.002 to 0.002;  $P = .99$ ) (Fig 4). Heterogeneity was absent ( $I^2 = 0\%$ ). Begg ( $P < .001$ ) test was suggestive of publication bias, however the funnel plot was not asymmetric (Supplemental Fig 7; available via Mendeley at <https://doi.org/10.17632/j7dfkr2s8v.1>).

The sensitivity analysis showed consistent results (Supplemental Tables 1-6; available via Mendeley at <https://doi.org/10.17632/rdxgpw9yxk.2>), except the analysis with 0.5 constant correction of zero-event studies showed a lower risk of infectious pneumonia (Supplemental Table 7; available via Mendeley at <https://doi.org/10.17632/rdxgpw9yxk.2>) and ILD in the treatment group (Supplemental Table 8; available via Mendeley at <https://doi.org/10.17632/rdxgpw9yxk.2>).

### Grading the quality of evidence

Based on the GRADE criteria, the overall quality of evidence for this analysis was moderate because infectious pneumonia and ILD were rare events (Supplemental Tables 9 and 10; available via Mendeley at <https://doi.org/10.17632/rdxgpw9yxk.2>).

## DISCUSSION

Our meta-analysis showed that IL-12/23 or IL-23 inhibitors increased the risk of RTIs, especially URTIs, but not viral URTIs and LRTIs, and noninfectious ILD in autoimmune diseases.

We found that risankizumab and briakinumab particularly enhanced the risk of RTIs and hypothesized that concomitant therapies during the trials might differentiate the risk of RTIs. In terms of anti-IL-23 agents, risankizumab showed a higher rate of RCTs that permitted concomitant therapies (40.0%) compared with guselkumab (0%) and tildrakizumab (0%). Among RCTs of risankizumab, the only study reporting an increased risk of RTIs was performed in patients with ankylosing spondylitis, who were permitted to use conventional disease-modifying antirheumatic drugs or low-dose systemic steroids.<sup>64</sup> This suggests that combination therapy of anti-IL-23 agents with immunosuppressants might work synergistically to surface the risk of RTIs. As for anti-IL-12/IL-23 agents, each of briakinumab and ustekinumab has a similar percentage of RCTs that permitted concomitant drugs (37.5% for briakinumab and 38.5% for ustekinumab). Other potential risk factors such as age and sex were not different among the drugs. Given that briakinumab has been withdrawn from the application with the FDA because of severe adverse events,<sup>1</sup> the difference in risk of RTIs among the 2 drugs would be explained by different properties of these drugs.

Our study might support that anti-IL-12/23 and anti-IL-23 therapies can be safely used for autoimmune diseases even during the current COVID-19 pandemic. However, given that influenza vaccination is generally recommended for patients with autoimmune diseases receiving immunosuppressive therapies,<sup>65</sup> viral URTIs caused by influenza virus could be prevented in both the treatment and placebo groups, and our finding regarding the risk of viral URTIs might be affected. In addition, studies included in this analysis were conducted before the pandemic and the risk of severe acute respiratory syndrome coronavirus 2 in patients with anti-IL-12/23 or anti-IL-23 therapies could not be assessed. Further studies, particularly during the current pandemic, are necessary to provide enough evidence to ensure the safety of these drugs. Additional investigations are also needed to understand the differential risk of RTIs in psoriasis and ankylosing spondylitis and the mechanism of ILD by IL-12/23 inhibition because patients who are indicated for these drugs, namely psoriasis, rheumatoid arthritis, and inflammatory bowel disease, all carry an increased risk of lung disease.<sup>66-68</sup>

IL-12 and IL-23 have fundamental functions in host defense. IL-12 promotes the differentiation of

**Table I.** Characteristics of randomized controlled trials of IL-12/23 or IL-23 antagonists\*

Drugs	Target	Disease	References	Age, y	Sex, % male	Study duration, wk	Concomitant therapies during trials	Regimen, mg (unless noted otherwise)	Jadad score	Patients, N		RTIs, n		Infectious pneumonia, n		Non infectious ILLD, n	
										IL-12/23	Placebo	IL-12/23	Placebo	IL-12/23	Placebo	IL-12/23	Placebo
Brazikumab	IL-23	CD	Sands et al (2017) <sup>11</sup>	37	38	12	Yes	700 IV at wk 0, 4	5	59	60	9	11	0	0	0	0
Guselkumab	IL-23	Psoriasis	Ohtsuki et al (2018) <sup>33</sup>	50	68	16	No	50, 100 SC at wk 0, 4, 12	5	128	64	22	7	0	0	0	0
			†NCT02905331 <sup>20</sup>	46	68	16	No	100 SC at wk 0, 4, 12	4	62	16	13	1	0	0	0	0
			Nemoto et al (2018) <sup>34</sup>	NA	60	24	No	10, 30, 100, 300 SC (s)	5	20	4	2	0	0	0	0	0
			Blauvelt et al (2017) <sup>35</sup>	44	73	16	No	100 SC at wk 0, 4, 12	5	329	174	55	26	0	0	0	0
			Reich et al (2017) <sup>10</sup>	44	70	16	No	100 SC at wk 0, 4, 12	5	494	248	51	26	0	0	0	0
			Gordon et al (2015) <sup>9</sup>	44	72	16	No	5, 50, 200 SC at wk 0, 4, q12 wk; 15, 100 SC q8 wk	5	207	42	25	3	0	0	0	0
			Sofen et al (2014) <sup>36</sup>	43	63	24	No	10, 30, 100, 300 SC (s)	4	20	4	5	0	0	0	0	0
Healthy volunteer			Terui et al (2018) <sup>37</sup>	52	29	24	No	200 SC at wk 0, 4	5	25	24	8	9	0	0	0	0
			Zhuang et al (2016) <sup>38</sup>	27	96	16	No	0.03, 0.1, 0.3, 1, 3, 10 mg/kg IV; 3 mg/kg SC (s)	5	36	11	5	1	0	0	0	0
Risankizumab	IL-23	Psoriasis	Gordon et al (2018) <sup>7</sup>	48	71	16	No	150 SC at wk 0, 4	5	304	102	37	8	0	0	0	0
			Gordon et al (2018) <sup>7</sup>	47	68	16	No	150 SC at wk 0, 4	5	294	98	21	4	0	0	0	0
			Krueger et al (2015) <sup>39</sup>	42	81	24	No	0.01, 0.05, 0.25, 1, 3, 5 mg/kg IV; 0.25, 1 mg/kg SC (s)	5	31	8	11	2	0	0	0	0
			Baeten et al (2018) <sup>64</sup>	38	70	16	Yes	18 SC (s); 90, 180 SC at wk 0, 8, 16	5	119	40	31	5	0	0	0	0
		Ankylosing spondylitis															

Continued

Table I. Cont'd

Drugs	Target	Disease	References	Age, y	Sex, % male	Study duration, wk	Concomitant therapies during trials	Regimen, mg (unless noted otherwise)	Jadad score	Patients, N		RTIs, n		Infectious pneumonia, n		Non infectious ILD, n	
										IL-12/23	Placebo	IL-12/23	Placebo	IL-12/23	Placebo	IL-12/23	Placebo
Tildrakizumab	IL-23	Psoriasis	Feagan et al (2017) <sup>8</sup>	39	37	12	Yes	200, 600 IV at wk 0, 4, 8	5	82	39	10	5	1	1	0	0
			Reich et al (2017) <sup>5</sup>	46	67	12	No	100, 200 SC at wk 0, 4	5	617	154	69	17	0	0	0	0
			Reich et al (2017) <sup>5</sup>	46	71	12	No	100, 200 SC at wk 0, 4	5	621	156	76	12	0	0	0	0
		Healthy volunteer	Papp et al (2015) <sup>6</sup>	43	74	16	No	5, 25, 100, 200 SC at wk 0, 4, 16	5	308	45	63	11	0	0	0	0
			Khalilieh et al (2018) <sup>40</sup>	26	38	28	No	0.1, 0.5, 3, 10 mg/kg IV (s)	5	22	7	0	0	0	0	0	0
Briakinumab	IL-12 IL-23	Psoriasis	Khalilieh et al (2018) <sup>40</sup>	27	62	20	No	50, 200 SC (s)	5	28	9	0	0	0	0	0	0
			Gordon et al (2012) <sup>1</sup>	46	69	12	No	200 SC wk 0, 4; 100 SC wk 8	5	981	484	114	40	2	0	0	0
			Gottlieb et al (2011) <sup>41</sup>	43	67	12	No	200 SC wk 0, 4; 100 SC wk 8	5	138	68	19	8	0	0	0	0
			Strober et al (2011) <sup>42</sup>	45	64	12	No	200 SC wk 0, 4; 100 SC wk 8	5	139	72	20	6	0	0	0	0
		Kimball et al (2008) <sup>43</sup>	46	75	12	No	200 SC (s); 100 SC q2wks for 12 wk; 200 SC q1wk for 4 wk; 200 SC q2wks or q1wk for 12 wk	5	150	30	38	3	0	0	0	0	
	CD		Panaccione et al (2015) <sup>2</sup>	36	51	12	Yes	200, 400, 700 IV at wk 0, 4, 8	5	200	46	0	0	0	0	0	0
			Mannon et al (2004) <sup>44</sup>	43	25	28	Yes	1, 3 mg/kg SC at wk 0; q1wk from wk 4 to 10	5	32	8	2	0	0	0	0	0
			Mannon et al (2004) <sup>44</sup>	40	20	25	Yes	1, 3 mg/kg SC q1wk for 7 wk	5	31	8	2	0	0	0	0	0
	MS		Vollmer et al (2011) <sup>45</sup>	47	25	24	No	200 SC q2wk; 200 SC q1wk	5	146	69	51	29	0	0	0	0

Ustekinumab IL-12 IL-23	Psoriasis	Gordon et al (2018) <sup>7</sup>	48	71	16	No	45 SC (wt ≤ 100 kg); 90 SC (wt > 100 kg) at wk 0, 4	5	100	102	12	8	0	0	0	0
		Gordon et al (2018) <sup>7</sup>	47	68	16	No	45 SC (wt ≤ 100 kg), 90 SC (wt > 100 kg) at wk 0, 4	5	99	98	9	4	0	0	0	0
		Landells et al (2015) <sup>46</sup>	15	49	12	No	0.75 mg/kg SC (wt ≤ 60 kg); 45 SC (60 < wt ≤ 100 kg); 90 SC (wt > 100 kg); 0.375 mg/kg SC (wt ≤ 60 kg); 22.5 SC (60 < wt ≤ 100 kg); 45 SC (>100 kg) at wk 0, 4	5	73	37	16	13	0	0	0	0
		Lebwohl et al (2015) <sup>47</sup>	45	69	12	No	45 SC (wt ≤ 100 kg); 90 SC (wt > 100 kg) at wk 0, 4	5	300	309	38	37	0	0	0	0
		Lebwohl et al (2015) <sup>47</sup>	45	68	12	No	45 SC (wt ≤ 100 kg), 90 SC (wt > 100 kg) at wk 0, 4	5	313	313	32	39	0	0	0	0
		Zhu et al (2013) <sup>48</sup>	40	77	12	No	45 SC at wk 0, 4	5	160	161	28	21	0	0	0	0
		Igarashi et al (2012) <sup>61</sup>	46	80	12	No	45, 90 SC at wk 0, 4	5	126	32	21	4	0	0	1	0
		Tsai et al (2011) <sup>49</sup>	40	85	12	No	45 SC at wk 0, 4	5	61	60	12	10	0	0	0	0
		Papp et al (2008) <sup>3</sup>	45	69	12	No	45, 90 SC at wk 0, 4	5	820	410	119	59	1	1	0	0
		Leonardi et al (2008) <sup>50</sup>	45	69	12	No	45, 90 SC at wk 0, 4	5	510	255	109	52	0	1	0	0

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Table I. Cont'd

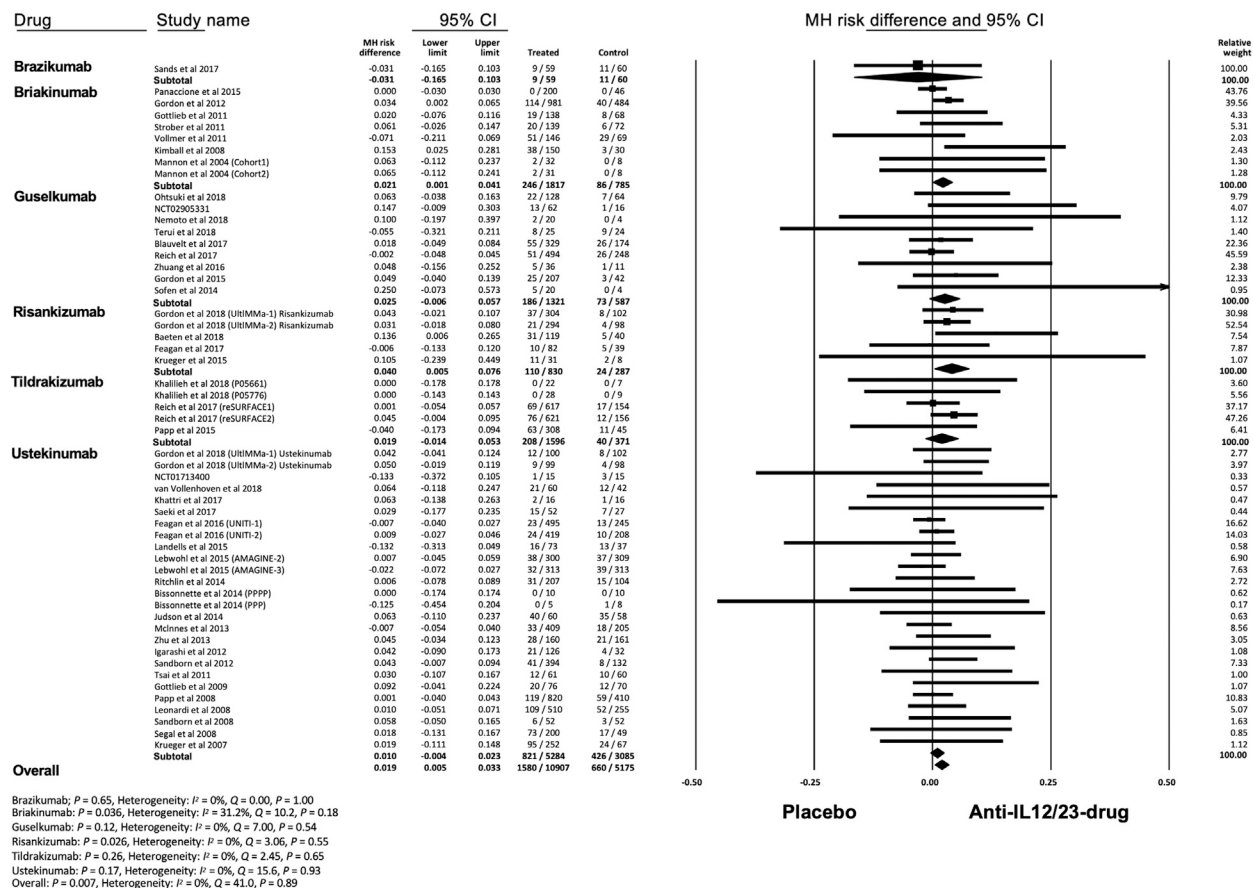
Drugs	Target	Disease	References	Age, y	Sex, % male	Study duration, wk	Concomitant therapies during trials	Regimen, mg (unless noted otherwise)	Jadad score	Patients, N		RTIs, n		Infectious pneumonia, n		Non infectious IILD, n	
										IL-12/23	Placebo	IL-12/23	Placebo	IL-12/23	Placebo	IL-12/23	Placebo
			Krueger et al (2007) <sup>51</sup>	46	59	20	No	45, 90 SC at wk 0, q4wk	5	252	67	95	24	1	0	0	0
		PsA	Ritchlin et al (2014) <sup>62</sup>	49	47	16	Yes	45, 90 SC at wk 0, 4, 16	5	207	104	31	15	0	0	0	1
			McInnes et al (2013) <sup>52</sup>	48	52	16	Yes	45, 90 SC at wk 0, 4, 16	5	409	205	33	18	0	0	0	0
			Gottlieb et al (2009) <sup>53</sup>	50	59	12	Yes	90 SC q1wk for 4 wk	5	76	70	20	12	0	0	0	0
		CD	Feagan et al (2016) <sup>54</sup>	37	40	8	Yes	130 mg, 6 mg/kg IV (s)	5	495	245	23	13	0	0	0	0
			Feagan et al (2016) <sup>54</sup>	39	50	8	Yes	130 mg, 6 mg/kg IV (s)	5	419	208	24	10	0	0	0	0
			Sandborn et al (2012) <sup>4</sup>	39	41	8	Yes	1, 3, 6 mg/kg IV (s)	5	394	132	41	8	0	0	0	0
			Sandborn et al (2008) <sup>55</sup>	40	55	8	Yes	90 SC at wk 0, 1, 2, 3; 4.5 mg/kg IV at wk 0	5	52	52	6	3	0	0	0	0
		Atopic dermatitis	Khattari et al (2017) <sup>56</sup>	37	63	16	No	45 SC (wt ≤ 100 kg), 90 SC (wt > 100 kg) at wk 0, 4, 16	5	16	16	2	1	0	0	0	0
			Saeki et al (2017) <sup>51</sup>	39	71	24	No	45, 90 SC at wk 0, 4	5	52	27	15	7	0	0	0	0
		GVHD	†NCT01713400 <sup>21</sup>	53	63	52	Yes	45 SC (wt ≤ 100 kg), 90 SC (wt > 100 kg) at day -1 and day 20 after transplantation	5	15	15	1	3	0	0	0	0
		SLE	van Vollenhoven et al (2018) <sup>58</sup>	40	3	24	Yes	260 (wt 35-55 kg), 390 (55 < wt ≤ 85), 520 (wt > 85 kg)	5	60	42	21	12	1	0	0	0

Sarcoidosis	Judson et al (2014) <sup>63</sup>	50	51	44	Yes	IV wk 0; 90 SC q8wk 180 SC wk 0; 90 SC wk 8, 16, 24	5	60	58	40	35	3	0	1	0
MS	Segal et al (2008) <sup>59</sup>	37	36	37	No	27, 90, 180 SC wk 0, 1, 2, 3, 7, 11, 15, 1990 SC q8wks	5	200	49	73	17	0	0	0	0
PPPP	Bissonnette et al (2014) <sup>60</sup>	55	10	16	No	45 SC (wt < 100 kg), 90 SC (wt ≥ 100 kg) at wk 0, 4, 16	5	10	10	0	0	0	0	0	0
PPP	Bissonnette et al (2014) <sup>60</sup>	50	0	16	No	45 SC (wt < 100 kg); 90 SC (wt ≥ 100 kg) at wk 0, 4, 16	5	5	8	0	1	0	1	0	0

CD, Crohn's disease; GVHD, graft-versus-host disease; IL, interleukin; ILD, interstitial lung disease; IV, intravenous; MS, multiple sclerosis; NA, not available; PPP, palmoplantar pustulosis; PPPP, palmoplantar pustular psoriasis; PsA, psoriatic arthritis; q, every; RTI, respiratory tract infection; (s), single dose; SC, subcutaneous; SLE, systemic lupus erythematosus; wt, weight.

\*Regarding age and sex, data from overall patients in each trials or patients treated IL-12/23 or IL-23 antagonists were used.

<sup>†</sup>This study was registered in [ClinicalTrials.gov](http://ClinicalTrials.gov) but later became available as an article.



Brazikumab:  $P = 0.65$ , Heterogeneity:  $I^2 = 0\%$ ,  $Q = 0.00$ ,  $P = 1.00$   
 Briakinumab:  $P = 0.036$ , Heterogeneity:  $I^2 = 31.2\%$ ,  $Q = 10.2$ ,  $P = 0.18$   
 Guselkumab:  $P = 0.12$ , Heterogeneity:  $I^2 = 0\%$ ,  $Q = 7.00$ ,  $P = 0.54$   
 Risankizumab:  $P = 0.026$ , Heterogeneity:  $I^2 = 0\%$ ,  $Q = 3.06$ ,  $P = 0.55$   
 Tildrakizumab:  $P = 0.26$ , Heterogeneity:  $I^2 = 0\%$ ,  $Q = 2.45$ ,  $P = 0.65$   
 Ustekinumab:  $P = 0.17$ , Heterogeneity:  $I^2 = 0\%$ ,  $Q = 15.6$ ,  $P = 0.93$   
 Overall:  $P = 0.007$ , Heterogeneity:  $I^2 = 0\%$ ,  $Q = 41.0$ ,  $P = 0.89$

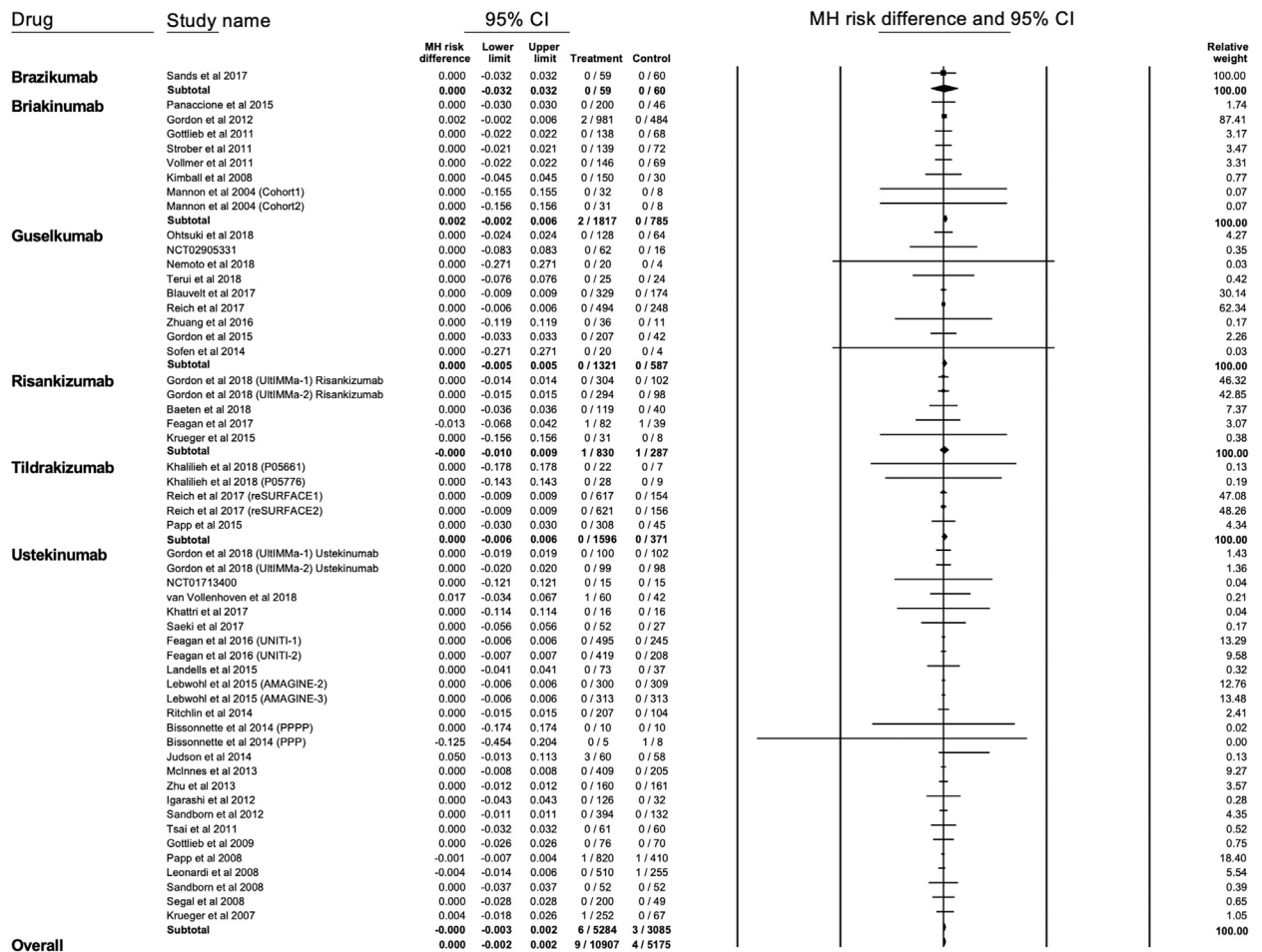
**Fig 2.** Meta-analysis of the Mantel-Haenszel (MH) risk difference of respiratory tract infections with IL-12/23 and IL-23 antagonists. *CI*, Confidence interval; *IL*, interleukin.

naive T cells into interferon gamma-producing T helper type (Th) 1 cells, which contribute to viral clearance<sup>69</sup> and prevent infections of *Mycobacterium* and *Salmonella* species.<sup>70</sup> Meanwhile, IL-23 maintains IL-17-producing Th17 cells, and the deficiency of IL-17 immunity results in infections of *Candida* species.<sup>71,72</sup> Our results showed that IL-12/23 or IL-23 antagonists did not increase the risk of LRTIs and infectious pneumonia, including *Mycobacteria tuberculosis* or any virus. As for viral RTIs, previous studies showed that IL-17-knockout mice had lower levels of lung inflammation by influenza virus compared with the wild type.<sup>73</sup> A study of the Middle East respiratory syndrome coronavirus showed that a patient with a poor outcome had an increased level of IL-17 expression in the lung.<sup>69</sup> These data suggest that IL-12/23 or IL-23 inhibitors might theoretically be preventive for severe acute

respiratory syndrome coronavirus 2-induced pneumonia rather than detrimental in autoimmune diseases during the COVID-19 pandemic.

**Limitations**

First, this study did not assess the long-term effect of IL-12/23 or IL-23 antagonists on RTIs and ILD. However, 92.6% (50/54) of the included studies reported RTIs during placebo-controlled phases. The FDA reported whether the onset of ILD was acute or subacute,<sup>14</sup> so our data would most likely include the incidence of these events. Second, regarding infectious pneumonia and ILD, many studies had zero events in both arms (87% [47/54] and 94% [51/54], respectively). Thus, we undertook comprehensive analyses that either included or excluded double-zero-event studies. The analysis with 0.5 constant correction showed a lower risk of



Brazikumab:  $P = 1.00$ , Heterogeneity:  $I^2 = 0\%$ ,  $Q = 0.00$ ,  $P = 1.00$   
 Briakinumab:  $P = 0.38$ , Heterogeneity:  $I^2 = 0\%$ ,  $Q = 0.19$ ,  $P = 1.00$   
 Guselkumab:  $P = 1.00$ , Heterogeneity:  $I^2 = 0\%$ ,  $Q = 0.00$ ,  $P = 1.00$   
 Risankizumab:  $P = 0.93$ , Heterogeneity:  $I^2 = 0\%$ ,  $Q = 0.29$ ,  $P = 0.99$   
 Tildrakizumab:  $P = 1.00$ , Heterogeneity:  $I^2 = 0\%$ ,  $Q = 0.00$ ,  $P = 1.00$   
 Ustekinumab:  $P = 0.79$ , Heterogeneity:  $I^2 = 0\%$ ,  $Q = 4.63$ ,  $P = 1.00$   
 Overall:  $P = 0.87$ , Heterogeneity:  $I^2 = 0\%$ ,  $Q = 5.46$ ,  $P = 1.00$

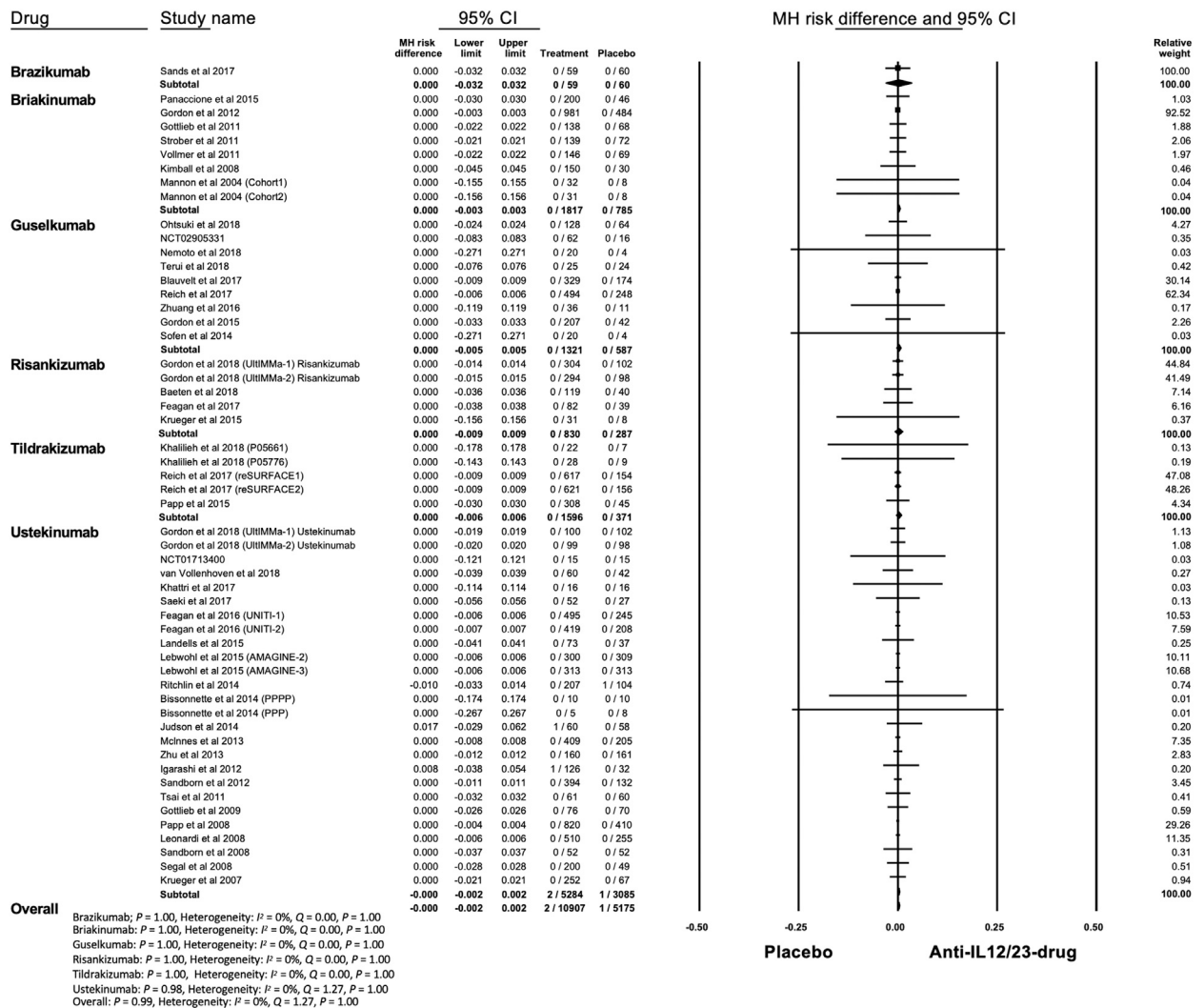
**Fig 3.** Meta-analysis of Mantel-Haenszel (MH) risk difference of infectious pneumonia with IL-12/23 and IL-23 antagonists. *CI*, Confidence interval; *IL*, interleukin.

these events in the treatment group. We also used treatment arm correction because this method performed better than 0.5 constant correction to examine rare events.<sup>74</sup> Third, our study may not reflect the risk in patients at high risk for RTIs because of the possible exclusion of patients with recent RTIs or chronic lung disease in clinical trials. Fourth, we categorized RTIs into URTIs, viral URTIs, and LRTIs based on MedDRA, which is widely used in clinical trials, but not so much in clinical research. Furthermore, the included studies were conducted before the pandemic. Hence, it does not provide evidence of whether there is an increase

in RTIs or ILD during the pandemic in patients receiving IL-12/23 or IL-23 antagonists, nor whether these agents can be continued after a diagnosis of COVID-19. A meta-analysis of real-world studies of COVID-19 in patients with autoimmune diseases is needed.

### CONCLUSION

This meta-analysis showed that IL-12/23 or IL-23 antagonists had an increased risk of URTIs, but not viral URTIs, LRTIs including infectious pneumonia, and noninfectious ILD.



**Fig 4.** Meta-analysis of the Mantel-Haenszel (MH) risk difference of noninfectious interstitial lung disease with IL-12/23 and IL-23 antagonists. CI, Confidence interval; IL, interleukin.

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