Incidence of infections in patients with psoriatic arthritis and axial spondyloarthritis treated with biological or targeted disease-modifying agents: a systematic review and meta-analysis of randomised controlled trials, open-label studies and observational studies

Melanie Aureal, Milene Seauve, Soline Laplane, Jean-Christophe Lega, Natalia Cabrera, Fabienne Coury

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ORIGINAL RESEARCH

Incidence of infections in patients with psoriatic arthritis and axial spondyloarthritis treated with biological or targeted disease-modifying agents: a systematic review and meta-analysis of randomised controlled trials, open-label studies and observational studies

Melanie Aureal ,[1,2] Milene Seauve,[1,2] Soline Laplane,[1,2] Jean-Christophe Lega,[3,4] Natalia Cabrera,[5] Fabienne Coury[1,2,4,6]

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For numbered affiliations see end of article.

Correspondence to
Fabienne Coury;
fabienne.coury-lucas@chu-lyon.fr

ABSTRACT

Objective To estimate the incidence of infections among patients with psoriatic arthritis (PsA) or axial spondyloarthritis (axSpA), two distinct phenotypes included in the large group of spondyloarthritis (SpA), treated with tumour necrosis-factor-inhibitors, interleukin-17-inhibitors, Janus kinase-inhibitors, IL-23 or IL-12/23-inhibitors (IL-12/23i), phosphodiesterase 4-inhibitors or cytotoxic T-lymphocyte associated protein 4-Ig.

Methods A meta-analysis of randomised controlled trials (RCTs), open-label extension and observational studies was conducted. Serious infections were defined as infections that were life-threatening, required intravenous antibiotics and/or hospitalisation. Non-serious infections did not meet these severity criteria. The incidence rates (IR) were reported for each diagnosis by treatment class and study type using random-effect model to create a 95% CI.

Results Among 23 333 PsA patients and 11 457 axSpA patients, there were 1.09 serious infections per 100 patient-years (PY) (95% CI 0.85 to 1.35) with similar IR in PsA (0.96 per 100 PY 95% CI 0.69 to 1.28) and axSpA (1.09 per 100 PY 95% CI 0.76 to 1.46). The IR was lower in RCTs (0.77 per 100 PY 95% CI 0.41 to 1.20) compared with observational studies (1.68 per 100 PY 95% CI 1.03 to 2.47). In PsA patients, the lowest IR value was observed with IL-12/23i (0.29 per 100 PY 95% CI 0.00 to 1.03). There were 53.0 non-serious infections per 100 PY (95% CI 43.47 to 63.55) in 7257 PsA patients and 5638 axSpA patients. The IR was higher in RCTs (69.95 per 100 PY 95% CI 61.59 to 78.84) compared with observational studies (15.37 per 100 PY 95% CI 5.11 to 30.97).

Conclusion Serious infections were rare events in RCTs and real-life studies. Non-serious infections were common adverse events, mainly in RCTs.

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INTRODUCTION

Spondyloarthritis (SpA) is a group of inflammatory rheumatic diseases including distinct disorders with axial inflammation and/or peripheral arthritis, enthesitis or dactylitis. Axial SpA (axSpA) refer either to ankylosing spondylitis (AS) or non-radiographic axSpA (nr-axSpA) based on radiographic structural damage according to the modified New-York criteria. Psoriatic arthritis (PsA) is another subtype of SpA with skin inflammation associated to joint involvement.[1]

Six biologics or targeted (b/tsDMARD) modifying disease agents are currently prescribed in PsA or axSpA with large clinical efficacy in active disease, refractory to non-steroid anti-inflammatory drugs (NSAID). These treatments act either by inhibiting an inflammatory cytokine or its receptor (tumour necrosis factor (TNF), interleukin (IL)-17, IL-23, IL-12/23), molecules involved in cell activation (cytotoxic T-lymphocyte associated protein 4 (CTLA4)) with CTLA4-Ig, or intracellular signal pathways (Janus kinase (JAK) and phosphodiesterase 4 (PDE4)).[2 3] TNF-inhibitors (TNFi), IL-17-inhibitors (IL-17i) and JAK-inhibitors (JAKi) are used in PsA and axSpA, whereas IL-23-inhibitors (IL-23i), IL-12/23-inhibitors (IL-12/23i), PDE4-inhibitors (PDE4i) and CTLA4-Ig are only used in PsA due to their lack of efficacy on the axial symptoms.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ While the risk of infections in patients with rheumatoid arthritis or psoriasis treated with biological or targeted disease-modifying agents (b/tsDMARDs) has been extensively studied, there is limited research on the incidence of serious and non-serious infections in patients with spondyloarthritis, including psoriatic arthritis (PsA) and axial spondyloarthritis (axSpA).

WHAT THIS STUDY ADDS

⇒ This meta-analysis provides an assessment of the incidence rates of serious and non-serious infections, both overall and stratified by diagnosis (PsA or axSpA), for each class of treatment in randomised trials (RCTs), open-label extensions and observational studies.

⇒ Serious infections were rare events in patients with PsA or axSpA. In observational studies, the incidence tended to be higher compared with RCTs. The lowest incidence rate was observed with the use of IL-12/23 inhibitors (IL-12/23i) and phosphodiesterase 4 inhibitors, which were specifically used in patients with PsA.

⇒ Non-serious infections showed a trend of higher incidence in RCTs and were likely under-reported in observational studies.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ This meta-analysis reassures clinicians about prescription of b/tsDMARD in patients with PsA or axSpA regarding the risk of serious infections. However, it is important to note that non-serious infections were common adverse events that could have an impact on patient management.

Apart from the efficacy, safety and tolerance are two important parameters for therapeutic choice. Infections are a known side effect of these molecules, consistent with their mechanisms of action on the pathways of inflammation. A distinction is made between two types of infections. Serious infections are usually defined as life threatening, requiring intravenous antibiotics or hospitalisation. In the absence of consensual definition, we chose to define non-serious infections (NSI) as any infection which do not meet the criteria of serious infections.[4] NSI may include upper respiratory tract infections, influenza syndromes, nasopharyngitis, urinary tract infections, gastrointestinal infections, herpes infections, opportunistic infections, candida infections and skin infections. Although NSI are not life-threatening, their occurrence could be responsible for poor treatment compliance.[5]

Most of the data on the risk of infection in patients treated with b/tsDMARD are known from their use in other inflammatory diseases such as rheumatoid arthritis or psoriasis. However, characteristics of patients differ from one inflammatory disease to another, particularly in terms of age, comorbidities, pathophysiology of rheumatic diseases and associated treatments. Thus, it is difficult to extrapolate safety data from different populations.

Here, we present a meta-analysis to explore the incidence rate (IR) of serious and NSI in patients with SpA including PsA and axSpA stratified by diagnosis and according to class of treatment and study design (randomised controlled trials (RCTs), open-label extension (OLE) and observational studies).

MATERIAL AND METHODS

Literature research and study selection

The databases PubMed and Cochrane Central Register of Controlled Trial (CENTRAL) were searched from their date of inception to 30 March 2021, using a predefined search equation (online supplemental table 1). When necessary, additional studies were identified through hand searching.

The study was performed according to the Preferred Reporting the Items for Systematic Review and Meta-Analysis (PRISMA) statement for RCTs and OLE and in agreement with current recommendations of meta-analysis of observational studies in epidemiology group (MOOSE group) for observational studies (online supplemental table 2).

Three authors (MA, MS and SL) independently assessed titles and abstracts to identify relevant studies for inclusion. Discrepancies were discussed and when necessary, a fourth reviewer (FC-L) resolved any disagreements. The full text of the studies was obtained when necessary to confirm inclusion.

Inclusion criteria

The studies were included if they: (1) investigated the number of serious infections defined as life-threatening, requiring intravenous antibiotics or hospitalisations or NSI defined as any event coded in the MedDRA SOC Infection and Infestation (MedDRA or Medical Dictionary for Regulatory Activities https://www.meddra.org) in RCTs and OLE and defined as any infection which do not meet the criteria of serious infections in observational studies; (2) involved patients with AS fulfilling modified New-York criteria, nr-AxSpA fulfilling Assessment of SpondyloArthritis International Society classification criteria for PsA and axSpA fulfilling Classification Criteria for Psoriatic Arthritis and (3) included patients treated with bDMARD or tsDMARD (TNF inhibitors(TNFi): etanercept, infliximab, golimumab, adalimumab and certolizumab pegol; IL-17i: secukinumab, ixekinumab, bimekizumab and brodalumab; IL-23i: ustekinumab, guselkumab and risankizumab; CTLA4-Ig: abatacept; JAKi: tofacitinib, upadacitinib and filgotinib; PDE4i: apremilast).

Studies with other design than RCTs, OLE or observational studies, such as mixed data of several pathologies other than AS, nr-AxSpA or PsA and studies in other languages than English were excluded. In addition, OLE should comprise RCTs data to be included.

Data extraction and quality assessment

The following data were independently extracted by two authors (MA and MS) for each study: NCT (National Clinical Trial) number, year of publication, study design, country, pathology, population description, type and dose of b/tsDMARD, follow-up time, characteristics of population (sex, age, disease duration, disease activity,

C-reactive protein, body mass index, concomitant treatment, previous biological therapy and smoking status), number of serious infections and number of NSI. The included studies used a variety of methods to report incidence. We used patient year (PY) when it was available in studies, or we calculated it if necessary.

If data were missing in the article, the corresponding authors were contacted by e-mail. Disagreements about data extraction were resolved by discussion with another independent author (FC-L). Revised Cochrane risk-of-bias tool for randomised trials (RoB V.2, www.riskofbias.info) was used to assess the quality of RCTs and the Newcastle-Ottawa Scale (NOS) was used to assess the quality of OLE and observational studies (online supplemental table 3).

Statistical analysis

The IR of infections was separated into two major groups, according to whether these events were serious infections or NSI. Then, we performed subgroup analyses by dividing all studies according to study type and treatment class. Those analysis were stratified according to the disease (PsA, axSpA and SpA).

Forest plots were constructed from the extracted data to create a 95% CI using R V.3.4 with package 'meta' (V.4.9–2) and 'metafor' (V.2.0–0). The IR of events (serious or NSI) and their 95% CI were estimated using inverse variance method and Freeman-Tukey double arcsine transformation. IR was expressed in events per 100 PY. Heterogeneity was assessed using inconsistency index (I^2). If substantial heterogeneity was observed (I^2>50%), a random-effects model was used based on Hartung-Knapp adjustment. The planned subgroup analyses were the following: study design, class of treatment and disease.

RESULTS

Search results

The initial search strategy identified 379 citations on PubMed and 348 citations on CENTRAL of which 96 were included (60 RCTs, 20 OLEs and 16 observational studies). A total of 89 studies (56 RCTs, 19 OLEs and 14 observational studies) about serious infections (n=33 892 patients with 33 168 PY of follow-up; 849 events) and 55 studies (37 RCTs, 8 OLEs and 10 observational studies) about NSI (n=13 008 patients with 12 451 PY of follow-up; 5339 events) were included (figure 1, table 1). The characteristics of patients are available in online supplemental table 4.

Serious infections

The IR of serious infections was estimated at 1.09 events per 100 PY (95% CI 0.85 to 1.35, I^2=67%) in patients with SpA (PsA and axSpA). The IRs were 1.68 per 100 PY (95% CI 1.03 to 2.47, I^2=91%) for observational studies, 1.48 per 100 PY (95% CI 1.26 to 1.72, I^2=0%) for OLE and 0.77 per 100 PY (95% CI 0.41 to 1.20, I^2=24%) for RCT (figure 2).

For patients with PsA, the IR of was estimated at 0.96 per 100 PY (95% CI 0.69 to 1.28, I^2=52%). For patients with axSpA, the IR of was estimated at 1.09 per 100 PY (95% CI 0.76 to 1.46, I^2=28%) (figure 3).

In subgroup analysis by therapeutic classes in PsA patients, the IRs were 1.36 per 100 PY (95% CI 0.72 to 2.16, I^2=55%) with TNFi, 0.97 per 100 PY (95% CI 0.49 to 1.57, I^2=47%) with IL-17i, 1.51 per 100 PY (95% CI 0.00 to 14.74, I^2=31%) with JAKi, 0.29 per 100 PY (95% CI 0.00 to 1.03, I^2=15%) with IL-12/23i and IL-23i, 0.38 per 100 PY (95% CI 0.00 to 1.19, I^2=0%) with PDE4i and 1.71 per 100 PY (95% CI 0.00 to 43.38, I^2=1%) with CTLA4-Ig (figure 4A).

In axSpA patients, the IRs were 1.24 per 100 PY (95% CI 0.78 to 1.77, I^2=28%) with TNFi, 1.20 per 100 PY (95% CI 0.59 to 1.96, I^2=40%) with IL-17i, 1.28 per 100 PY (95% CI 0.00 to 13.77, I^2=0%) with JAKi (figure 4B).

Non-serious infections

The IR of NSI was estimated at 53.04 NSI per 100 PY (95% CI 43.47 to 63.55, I^2=99%) in patients with SpA (PsA or axSpA). The IRs were 69.95 per 100 PY (95% CI 61.59 to 78.84, I^2=84%) for RCTs, 41.91 per 100 PY (95% CI 21.85 to 68.41, I^2=99%) for OLE and 15.37 per 100 PY (95% CI 5.11 to 30.97, I^2=99%) for observational studies (figure 5).

Similar IR was found for patients with PsA (54.08 (95% CI 40.96 to 68.99, I^2=98%)) or with axSpA (58.02 per 100 PY (95% CI 44.79 to 72.94, I^2=98%)) (*data not shown*). Subgroup analyses by class of treatment in RCTs was not performed because it resulted in too few studies in each subgroup.

Quality assessment

Concerning the quality assessment, 58% of RCTs were judged as low risk, 42% of RCTs were judged with some concerns and none of the RCTs included were judged as high risk (online supplemental table 9).

The mean NOS score in observational studies was 5.9 ranging from four to seven stars, with four stars in one study,[6] five stars in five studies,[7–11] six stars in four studies[12–15] and seven stars in six studies.[16–21]

For serious infections in observational studies, meta-regression analyses did not reveal any significant association; therefore, the source of heterogeneity could not be clearly identified (see online supplemental tables 5 and 6). The visual inspection of funnel plot and Egger's regression test (p<0.004) were in favour of small effect studies (online supplemental figure 1).

For NSI, meta-regression analyses did not reveal any significant association; therefore, the source of heterogeneity could not be clearly identified (see online supplemental tables 7 and 8). The visual inspection of funnel plot was in favour of effect studies (online supplemental figure 2).

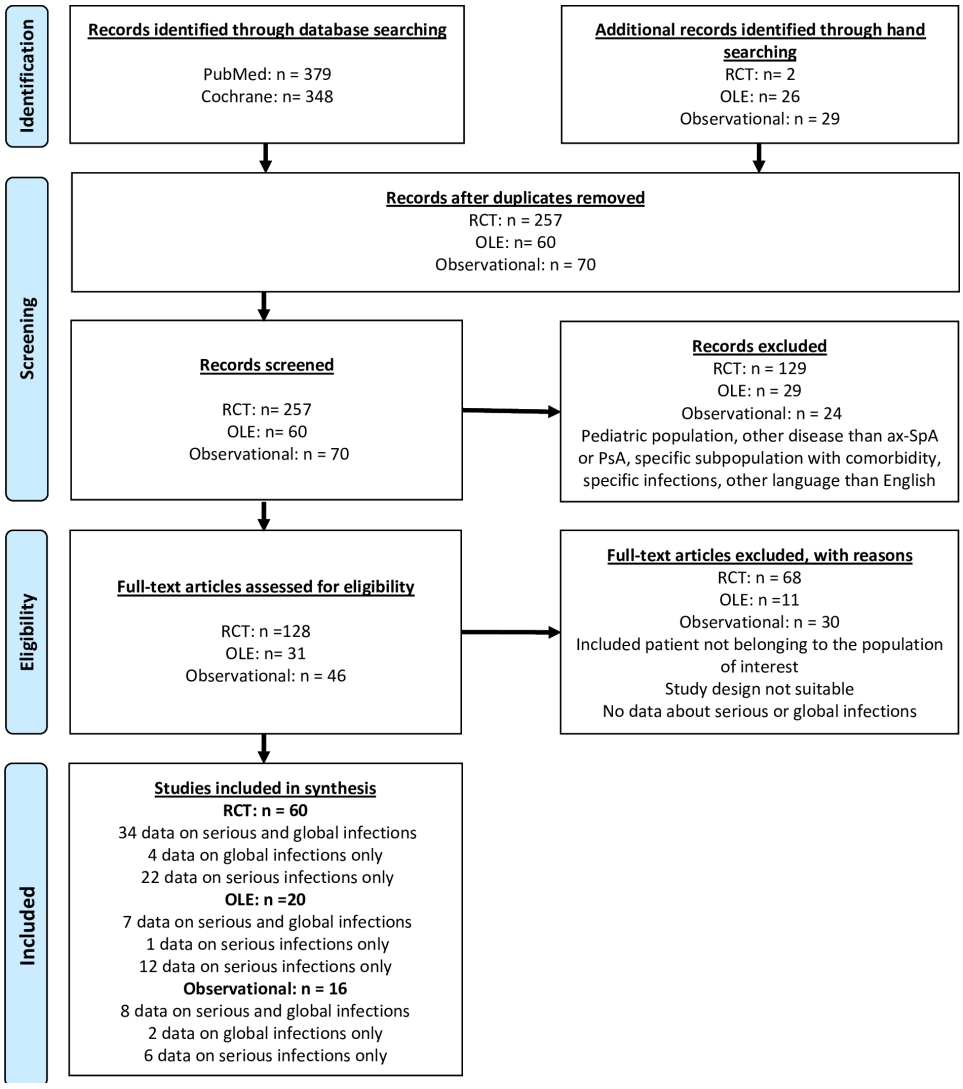

Figure 1 Flowchart. axSpA, axial spondyloarthritis; PsA, psoriatic arthritis; RCT, randomised controlled trial; OLE, open-label extension.

DISCUSSION

This large meta-analysis suggests that serious infections are rare events in the population of patients with PsA and axSpA treated with different classes of b/tsDMARD. For every 100 patients with SpA and treated with b/tsDMARD, we reported a rate of 1.09 serious infections and 53.0 NSI. In our study, the IRs of serious and NSI were similar in patients with PsA and axSpA.

We choose to focus our study on the IR of infections to describe the absolute risk of infection in the population of patients with PsA or axSpA treated with b/tsDMARD. Indeed, while physicians and patients have a better understanding of the differences in risk when results are presented as absolute risk rather than relative risk, few studies in the literature have focused on the assessment of this absolute risk in population of patients with PsA and axSpA.[22 23]

Compared with rheumatoid arthritis, there is a trend toward a lower IR of serious infections in patients with PsA and axSpA. In fact, a meta-analysis including 66 RCTs and 22 OLEs, estimated the IR of serious infections at 4.90 per 100 PY in patients with rheumatoid arthritis treated with TNFi and 3.04 per 100 PY with CTLA4-Ig.[24] In observational registries, IR of serious infections varies between 3.1 and 6.4 infections per 100 PY.[25–33] Compared with psoriasis, the IR of serious infections in patients with PsA and axSpA appears to be similar. In a meta-analysis of RCTs, the IR of serious infections was estimated at 1.29 per 100 PY with IL-17i.[34] In trials PHOENIX 1, 2 and ACCEPT, the IR of serious infections in patients treated with ustekinumab was estimated at 1.4 per 100 PY.[35] In a nationwide cohort study from France involved data from the National Health Data System, IR of serious infections in was 25.0 (95% CI (23.8 to 26.2)) per 1000 PY among patients newly treated with biological treatment.[36]There is very limited data in the literature about IR of serious infections in patients without inflammatory disease or immunosuppressive treatment. In a large population-based study, Smollen *et al* found that patients with rheumatoid arthritis treated with any type of therapy (biological or not) have an IR of serious infections at 3.86

Table 1 Characteristics of the studies included in the meta-analysis of severe and global infections.

Author (study name)	Year	Study design registry number	Molecule	Dose	Diagnosis	Patient in treatment group (n)	Study duration (weeks)	Outcome	
								SI	NSI
TNF-inhibitors studies									
Antoni (IMPACT)	2005	RCT phase 3	Infliximab	5 mg / kg / 6 w	PsA	52	16	X	
Van der Heijde (ASSERT)	2005	RCT phase 3	Infliximab	5 mg / kg / 6 w	AS	201	24	X	X
Sieper (INFAST)	2014	RCT phase 3 NCT00844805	Infliximab	5 mg / kg / 6 w	AS	105	28	X	X
Park (PLANETAS)	2016	OLE	Infliximab	5 mg / kg / 6 w	AS	174	102	X	X
Davis	2003	RCT phase 3	Etanercept	25 mg / 2 w	AS	138	24	X	
Mease	004	RCT phase 3	Etanercept	25 mg / 2 w	PsA	101	24	X	
Braun	2011	RCT phase 3 NCT00247962	Etanercept	50 mg / 1 w	AS	379	16	X	
Dougados	2014	RCT phase 3	Etanercept	50 mg / 1 w	Nr-AxSpA	106	12	X	X
Mease	2019	RCT phase 3 NCT02376790	Etanercept	50 mg / 1 w	PsA	567	48	X	
Davis	2007	OLE	Etanercept	25 mg / 2 w and 50 mg / 1 w	AS	257	192	X	X
Martin-Mola	2010	OLE	Etanercept	25 mg / 2 w and 50 mg / 1 w	AS	56	156	X	X
Inman (GO RAISE)	2008	RCT phase 3 NCT00265083	Golimumab	50 or 100 mg / 4 w	AS	278	24	X	X
Kavanaugh (GOREVEAL)	2009	RCT phase 3 NCT00265096	Golimumab	50 or 100 mg / 4 w	PsA	292	24	X	X
Kavanaugh (GOVIBRANT)	2017	RCT phase 3 NCT02181673	Golimumab	2 mg / kg / 8 w IV	PsA	240	24	X	X
Deodhar (GO ALIVE)	2018	RCT phase 3 NCT02186873	Golimumab	2 mg / kg / 8 w IV	AS	105	16	X	X
Kavanaugh (GO REVEAL)	2013	OLE	Golimumab	50 or 100 mg / 4 w SC	PsA	394	268	X	
Deodhar (GO RAISE)	2014	OLE	Golimumab	50 or 100 mg / 4 w SC	AS	353	268		X
Mease (ADEPT)	2005	RCT phase 3 NCT00195689	Adalimumab	40 mg / 2 w SC	PsA	151	24	X	X
Van der Heijde (ATLAS)	2006	RCT phase 3	Adalimumab	40 mg / 2 w SC	AS	208	24	X	X
Genovese	2007	RCT phase 3	Adalimumab	40 mg / 2 w SC	PsA	51	12	X	X
Huang	2012	RCT phase 3 NCT01114880	Adalimumab	40 mg / 2 w SC	AS	229	12	X	X
Sieper (ABILITY 1)	2013	RCT phase 3 NCT00939003	Adalimumab	40 mg / 2 w SC	Nr-AxSpA	91	12	X	X
Mease (ADEPT)	2008	OLE	Adalimumab	40 mg / 2 w SC	PsA	298	144	X	X
Van der Heijde (ATLAS)	2009	OLE	Adalimumab	40 mg / 2 w SC	AS	311	104	X	X
Van der Heijde (ABILITY1)	2018	OLE	Adalimumab	40 mg / 2 w SC	Nr-AxSpA	190	156	X	
Mease (RAPID-PsA)	2014	RCT phase3 NCT01087762	Certolizumabpegol	200 mg / 2 w or 400 mg / 4 w SC	PsA	273	24	X	X

Continued

Table 1 Continued

Author (study name)	Year	Study design registry number	Molecule	Dose	Diagnosis	Patient in treatment group (n)	Study duration (weeks)	Outcome	
Landewe (RAPID-AxSpA)	2014	RCT phase 3 NCT01087762	Certolizumabpegol	200 mg / 2 w or 400 mg / 4 w SC	AS	218	24	X	X
Kristensen	2007	Observational	Several TNF-inhibitors	NA	PsA	261	105.1	X	
Saad	2010	Observational	Several TNF-inhibitors	NA	PsA	596	156	X	
Modesti	2012	Observational	Several TNF-inhibitors	NA	AS/PsA	225	132.6	X	X
Moura	2019	Observational	Several TNF-inhibitors	NA	SA	369	103	X	
Wallis	2014	Observational	Several TNF-inhibitors	NA	Nr-AxSpA	264	134.7	X	X
Ruberson Da Silva	2018	Observational	Several TNF-inhibitors	NA	PsA	122	24		X
Rusman	2018	Observational	Several TNF-inhibitors	NA	AS	122	221	X	X
Wroński	2019	Observational	Several TNF-inhibitors	NA	AS	103	72	X	X
IL-17 inhibitors									
Baeten	2013	RCT phase 2 NCT00809159	Secukinumab	10 mg / kg / 3 w IV	AS	24	28	X	X
McInnes	2014	RCT phase 2 NCT00809614	Secukinumab	10 mg / kg / 3 w IV	PsA	28	24	X	
Baeten (MEASURE 2)	2015	RCT phase 3 NCT01649375	Secukinumab	150 or 75 mg / 4 w SC	AS	145	16		X
Mease (FUTURE 1)	2015	RCT phase 3 NCT01392326	Secukinumab	150 or 75 mg / 4 w, after IV loading infusion 10 mg / kg	PsA	406	24		X
McInnes (FUTURE 2)	2016	RCT phase 3 NCT01752634	Secukinumab	75 or 150 or 300 mg SC	PsA	299	16		X
Kivitz (MEASURE 4)	2018	RCT phase 3 NCT02159053	Secukinumab	150 mg / 4 w SC	AS	233	16	X	
Mease (FUTURE 5)	2018	RCT phase 3 NCT02404350	Secukinumab	150 or 300 mg / 4 w SC	PsA	664	24	X	
Huang (MEASURE 5)	2020	RCT phase 3 NCT02896127	Secukinumab	150 mg / 4 w SC	AS	305	16	X	
Deodhar (PREVENT)	2021	RCT phase 3 NCT02696031	Secukinumab	150 mg / 4 w SC	Nr-AxSpA	369	20	X	
McInnes (FUTURE 2)	2017	OLE	Secukinumab	75 or 150 or 300 mg SC	PsA	387	104	X	X
Kivitz (MEASURE 4)	2018	OLE	Secukinumab	150 mg / 4 w SC	AS	346	104	X	
Nash (FUTURE 3)	2018	OLE	Secukinumab	150 or 300 mg / 4 w SC	PsA	406	52	X	
Baraliakos (MEASURE 1)	2019	OLE	Secukinumab	150 or 75 mg / 4 w SC, after IV loading	AS	360	260	X	
Kivitz (FUTURE 4)	2019	OLE	Secukinumab	150 mg / 4 w SC	PsA	334	104	X	
Huang (MEASURE 5)	2020	OLE	Secukinumab	150 mg / 4 w SC	AS	453	52	X	
Van der Heijde (FUTURE 5)	2020	OLE	Secukinumab	150 or 300 mg / 4 w SC	PsA	255	52	X	
Deodhar	2021	OLE	Secukinumab	150 mg / 4 w SC	Nr-AxSpA	369	104	X	
Kiltz	2020	Observational	Secukinumab	MD	AS/PsA	1001	NA		X
Klavdianou	2020	Observational	Secukinumab	300 mg / 4 w SC	PsA	75	52	X	X
Ramonda	2020	Observational	Secukinumab	150 or 300 mg / 4 w SC	PsA	608	104	X	X
Mease (SPIRIT P1)	2017	RCT phase 3 NCT01695239	Ixekizumab	80 mg / 2 w / 4 w SC	PsA	210	24	X	X

Continued

Table 1 Continued

Author (study name)	Year	Study design registry number	Molecule	Dose	Diagnosis	Patient in treatment group (n)	Study duration (weeks)	Outcome	
Nash (SPIRIT P2)	2017	RCT phase 3 NCT02349295	Ixekizumab	80 mg / 2 w / 4 w SC	PsA	245	24	X	X
Van der Heijde (COASTV)	2018	RCT phase 3 NCT02696785	Ixekizumab	80 mg / 2 w4 w SC	AS	164	16	X	X
Deodhar (COAST X)	2019	RCT phase 3 NCT02757352	Ixekizumab	80 mg / 2 w / 4 w SC	Nr-AxSpA	198	52	X	X
Deodhar (COAST W)	2019	RCT phase 3 NCT02696798	Ixekizumab	80 mg / 2 w / 4 w SC	AS	212	16	X	X
Dougados (COAST V/W)	2020	OLE	Ixekizumab	80 mg / 2w / 4 w SC	AS	641	52	X	X
Orbai (SPIRIT P2)	2021	OLE	Ixekizumab	80 mg / 2w / 4 w SC	PsA	337	156	X	X
Ritchlin (BE ACTIVE)	2020	RCT phase 2 NCT02969525	Bimekizumab	16, 160 or 320 mg / 4 w SC	PsA	164	12	X	
Van der Heijde (BEAGILE)	2020	RCT phase 2 NCT02963506	Bimekizumab	16, 64, 160 or 320 mg / 4 w SC	AS	243	12	X	
Coates (BE ACTIVE)	2021	OLE	Bimekizumab	16, 64, 160 or 320 mg / 4 w SC	PsA	204	152	X	
Mease	2014	RCT phase 2 NCT01516957	Brodalumab	140 or 280 mg / 2 w SC	PsA	113	12	X	
Mease (AMVISION 1–2)	2021	RCT phase 3 NCT02029495NCT02024646	Brodalumab	140 or 210 mg / 2 w SC	PsA	640	24	X	X
IL-23 inhibitors									
Gottlieb	2009	RCT phase 2 NCT00267956	Ustekinumab	90 or 63 mg / 1 w SC	PsA	76	12	X	X
McInnes (PSUMITT 1)	2013	RCT phase 3 NCT01009086	Ustekinumab	45 or 90 mg SC	PsA	409	16	X	X
Ritchlin	2014	RCT phase 2 NCT01077362	Ustekinumab	45 or 90 mg w0–w4, then every 12 w SC	PsA	207	24	X	X
Chimenti	2017	Observational	Ustekinumab	MD	PsA	65	104	X	X
Deodhar	2018	RCT phase 2 NCT02319759	Guselkumab	100 mg / 8 w SC	PsA	100	24	X	X
Deodhar (DISCOVER 1)	2020	RCT phase 3 NCT03162796	Guselkumab	100 mg / 4 w / 8 w SC	PsA	255	24	X	X
Mease (DISCOVER 2)	2020	RCT phase 3 NCT03158285	Guselkumab	100 mg / 4 w / w SC	PsA	493	24	X	X
McInnes	2021	OLE	Guselkumab	100 mg / 4 w / 8 w SC	PsA	731	52	X	
Baeten	2018	RCT phase 2 NCT02047110	Risankizumab	18, 90, 180 mg / 8 w SC	AS	119	16	X	X
CTLA4-Ig									
Mease	2011	RCT phase 2 NCT00534313	Abatacept	3 or 10 mg / kg (±2 initial doses of 30 mg / kg) IV / 28 days	PsA	128	24	X	
Mease (ASTRAEA)	2017	RCT phase 3 NCT01860976	Abatacept	125 mg / 1 w SC	PsA	213	24	X	X
JAK-inhibitors									
Gladman (OPAL Beyond)	2017	RCT phase 3 NCT01882439	Tofacitinib	5 mg or 10 mg 2x / day	PsA	263	12	X	

Continued

Table 1 Continued

Author (study name)	Year	Study design registry number	Molecule	Dose	Diagnosis	Patient in treatment group (n)	Study duration (weeks)	Outcome	
Mease (OPAL Broaden)	2017	RCT phase 3 NCT01877668	Tofacitinib	5 mg or 10 mg 2x / day	PsA	211	12	X	
Van der Heijde	2017	RCT phase 2NCT01786668	Tofacitinib	2, 5 or 10 mg 2x / day	AS	156	16	X	X
Mease (EQUATOR)	2018	RCT phase 2 NCT03101670	Filgotinib	200 mg / day	PsA	65	16	X	X
Van der Heijde (TORTUGA)	2018	RCT phase 2 NCT03117270	Filgotinib	200 mg / day	AS	58	12	X	X
Van der Heijde (SELECT-AXIS 1)	2019	RCT phase 2 NCT03178487	Upadacitinib	15 mg / day	AS	93	14	X	X
PDE4 inhibitors									
Schett	2012	RCT phase 2 NCT00456092	Apremilast	20 mg 2x / day or 40 mg / day	PsA	136	12	X	
Kavanaugh (PALACE 1)	2014	RCT phase 3 NCT01172938	Apremilast	20 or 30 mg 2x / day	PsA	336	24	X	
Cutolo (PALACE 2)	2016	RCT phase 3 NCT01212757	Apremilast	20 or 30 mg 2x / day	PsA	325	16	X	
Edwards (PALACE 3)	2016	RCT phase 3 NCT01212770	Apremilast	20 or 30 mg 2x / day	PsA	336	24	X	
Nash (ACTIVE)	2018	RCT phase 3 NCT01925768	Apremilast	30 mg 2x / day	PsA	110	24	X	
Wells (PALACE 4)	2018	RCT phase 3 NCT01307423	Apremilast	20 or 30 mg 2x / day	PsA	350	24	X	
Several treatments									
Ritchlin	2019	Observational	Ustekinumab, adalimumab, etanercept, infliximab	NA	PsA	2041	256.4	X	
Li	2020	Observational	Ixekizumab, secukinumab, ustekinumab, adalimumab, certolizumab pegol, etanercept, golimumab, infliximab	NA	PsA	5520	31.2	X	
Rahman	2020	Observational	Golimumab, infliximab, ustekinumab	NA	PsA	462	416	X	X
Krabbe	2021	Observational	Abatacept, adalimumab, certolizumab pegol, etanercept, golimumab, infliximab, secukinumab, ustekinumab	NA	AS/PsA	5387	52	X	

AS, ankylosing spondylitis; CTLA4, cytotoxic T-lymphocyte associated protein 4-Ig; IV, intravenous; JAK, Janus kinase; MD, missing data; NA, not applicable; nr-axSpA, non-radiographic axial spondyloarthritis; NSI, non-serious infections; OLE, open-label extension; PDE4, phosphodiesterase 4; PsA, psoriatic arthritis; RCT, randomised controlled trials; SC, subcutaneous; SI, serious infections; TNF, tumour necrosis factor; w, week.

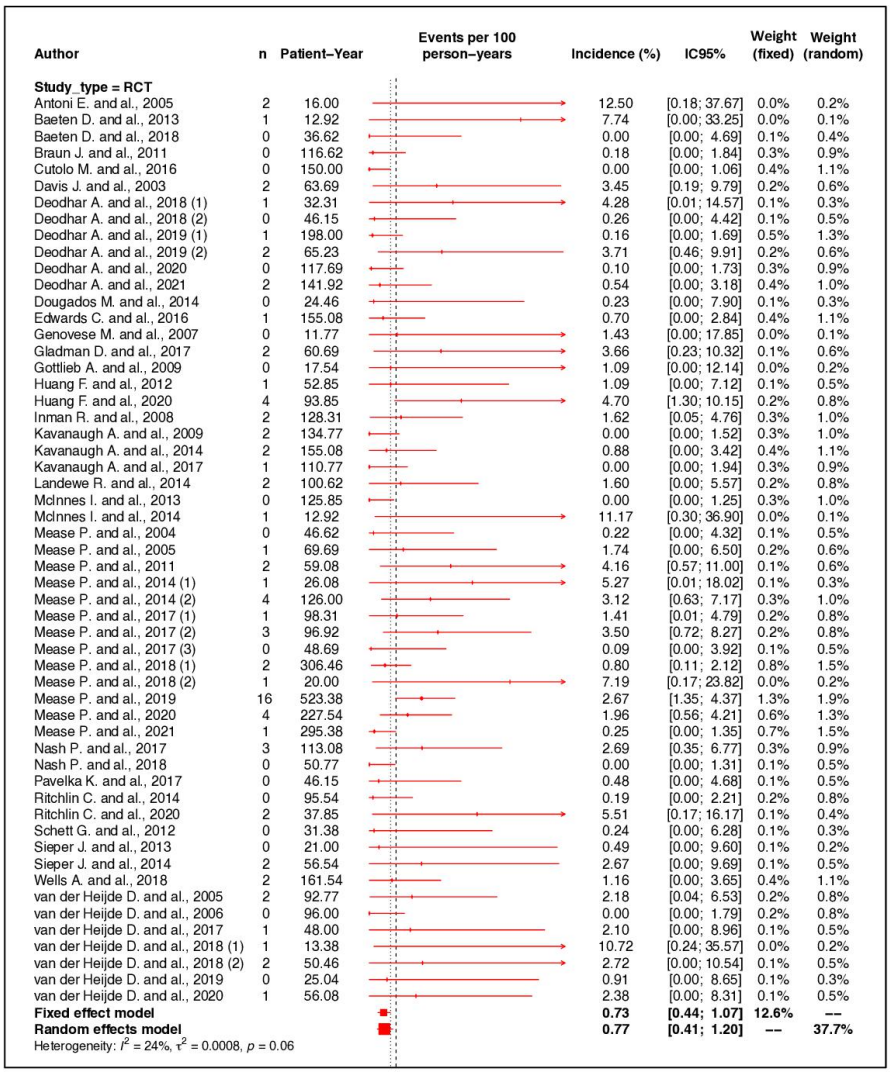

Figure 2 Forest plot of incidence rate of serious infections according to type of study. RCT, randomised controlled trial.

per 100 PY and estimated IR of SI of healthy individuals of general population at 1.25 per 100 PY.[37]

To estimate the IR of infections, we have included many studies with various designs. We found a trend towards a higher IR of serious infections in observational studies than in RCTs. This could be explained by differences in population characteristics. In fact, despite RCTs are the gold standard as only randomisation and double blinding can allow for proper group comparison, these studies are of limited duration and often apply very strict inclusion criteria. Because of the longer time of follow-up and the inclusion of less selected patients sometimes with comorbidities, observational studies offer a valuable source of information for rare serious adverse events such as serious infections and might be more representative of the population encountered in daily practice.[38 39] In our study, mean treatment exposure was 6 months in RCTs, 2.4 years in OLE and 2.5 years in observational studies, which could imply an increase in the risk of infection with increasing duration of exposure to treatment. However, it is known from studies in rheumatoid arthritis, that risk of serious infections is increased in the first 6 months of treatment and higher IR of serious infections were reported for shorter study duration in rheumatoid arthritis.[24 27 28] On this issue, our results are mixed. On the one hand, there is a trend of a higher incidence of infection in OLE than in RCTs. This hypothesis is supported by an observational study in which mean serious infections onset time was 25.5 months in patients with AS.[6] However, we excluded many OLE during data extraction because of missing data or because they reported number of patients with serious infections instead of number of serious infections.[40] In this context, the population of OLE included in our study is not strictly comparable with that of RCTs and other confounding factors besides the duration of follow-up could explain differences in IR of serious infections. On the other hand, when we look at the IR of serious infections in RCTs and in their corresponding OLE, we also observe mixed results with some studies finding a higher IR of serious infections in RCTs[41–46] and other studies where the IR of serious infections seems higher in OLE.[47–49] More studies designed to evaluate the IR of serious infections over time in SpA are therefore needed. Also, in our meta-analysis, patients of

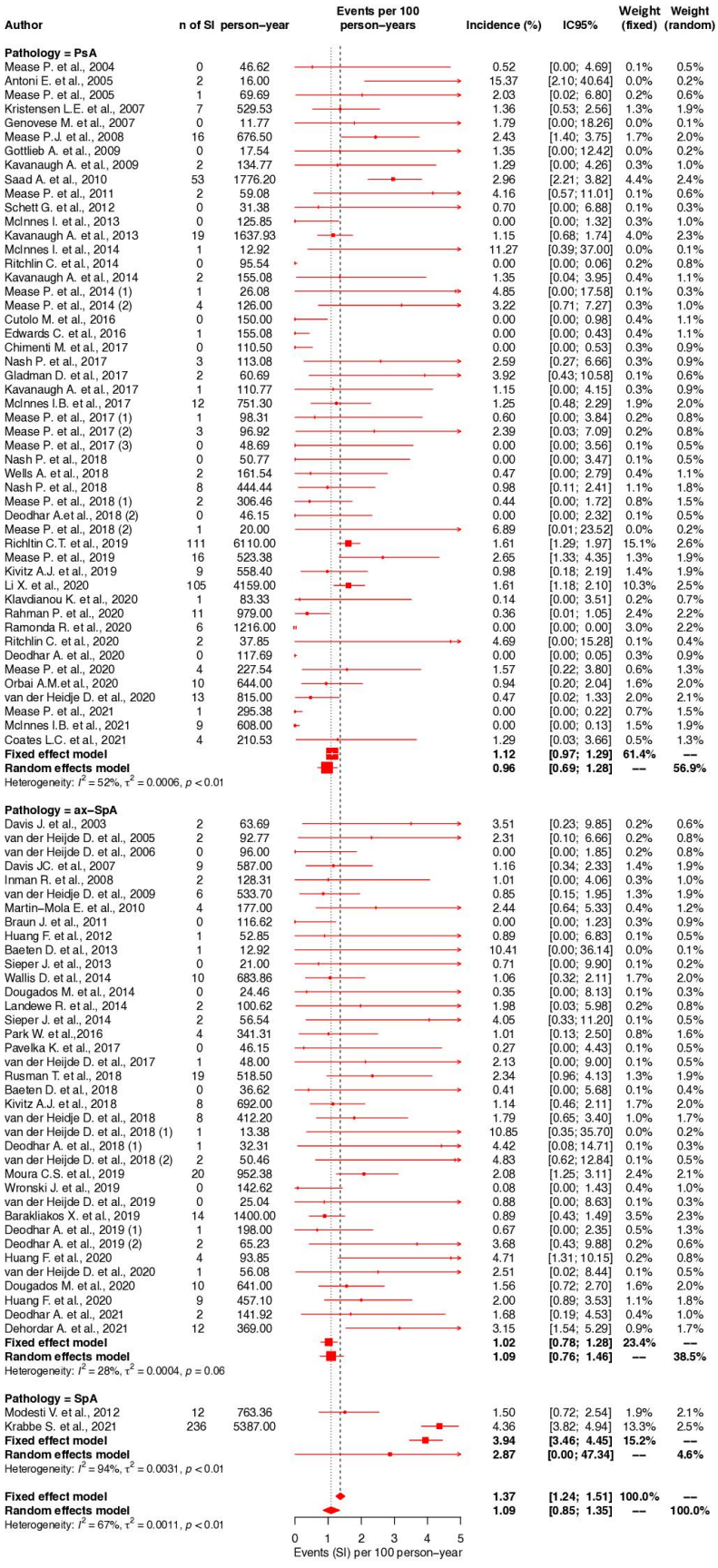

Figure 3 Forest plot of incidence rate of serious infections according to diagnosis. axSpA, axial spondyloarthritis; PsA, psoriatic arthritis; SpA, spondyloarthritis.

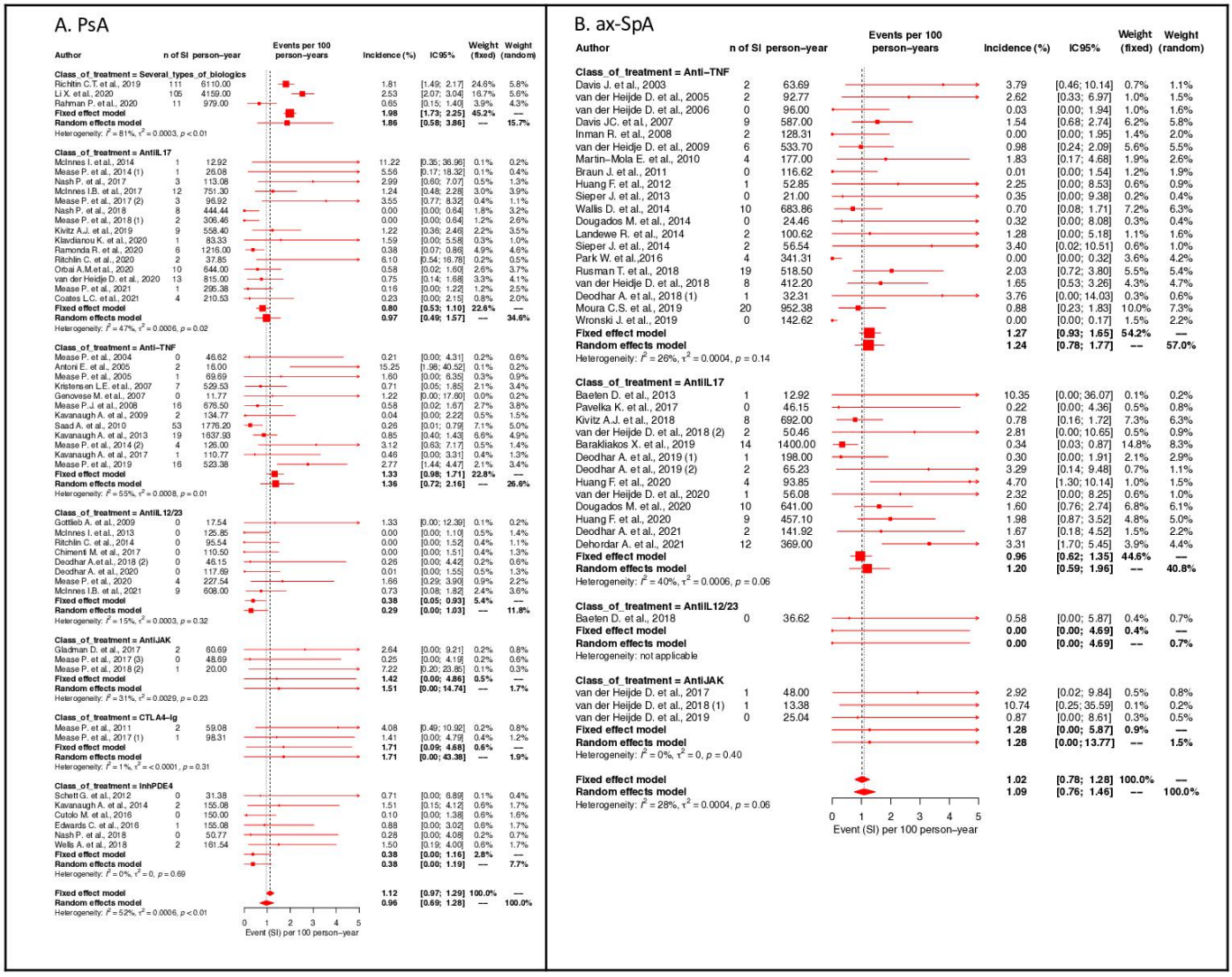

Figure 4 Forest plot of incidence rate of serious infections according to PsA (A) or axSpA (B), subgroup analysis by class of treatment. axSpA, axial spondyloarthritis; PDE4, phosphodiesterase 4; PsA, psoriatic arthritis; TNF, tumour necrosis factor.

observational studies have longer disease duration and were treated with more concomitant drugs than in RCTs (concomitant corticoid was used by 28% of patients in observational studies and 14% of patients in RCTs). A prospective study assessing the IR of serious infections in a cohort of rheumatoid arthritis patients before the era of b/tsDMARD showed an increased risk in the presence of corticosteroid therapy (RR 2.2; 95% CI 1.5 to 3.4).[50] Another study showed a dose-dependent effect of corticosteroid therapy on the risk of severe pneumonia in patients with rheumatoid arthritis.[51] Another explanation is the more regular follow-up of patients in RCTs which benefit from closer monitoring and therefore more antibiotic prescriptions.

In the case of NSI, we found a trend towards a lower IR of NSI in observational studies compared with RCTs. Indeed, because these infections are not serious, patients are more likely to under-report them in studies with an observational design. It is not possible to compare the rates obtained in our study with existing data in the literature as the methods of collecting this adverse event vary from one study to another. In rheumatoid arthritis, a prospective observational cohort study BSBR-RA was estimated IR of NSI at 27 NSI per 100 PY from clinician questionnaires and patients diaries every 6 months for 3 years.[52] In a meta-analysis of 33 RCTs including patients with any inflammatory diseases treated with TFNi, IR of NSI range from 30 NSI per 100 PY with infliximab to eight NSI per 100 PY with etanercept.[53] RCTs therefore appear to be the best source for estimating the occurrence of NSI, as those are systematically recorded. It may be interesting to study whether NSI represent a risk factor for serious infections and could be used as a surrogate endpoint in RCTs.

Regarding therapeutic choice, the lowest IR of serious infections were found for IL-23i and PDE4i prescribed exclusively in PsA. This result is in agreement with a recent cohort study in patients with PsA or psoriasis showing that patients treated with ustekinumab had 1.3–3.0 times lower risk of hospitalised serious infections than patients initiating other biologics as TNFi.[54] Li *et al* reported in a cohort of patients with psoriasis (8010 PY)

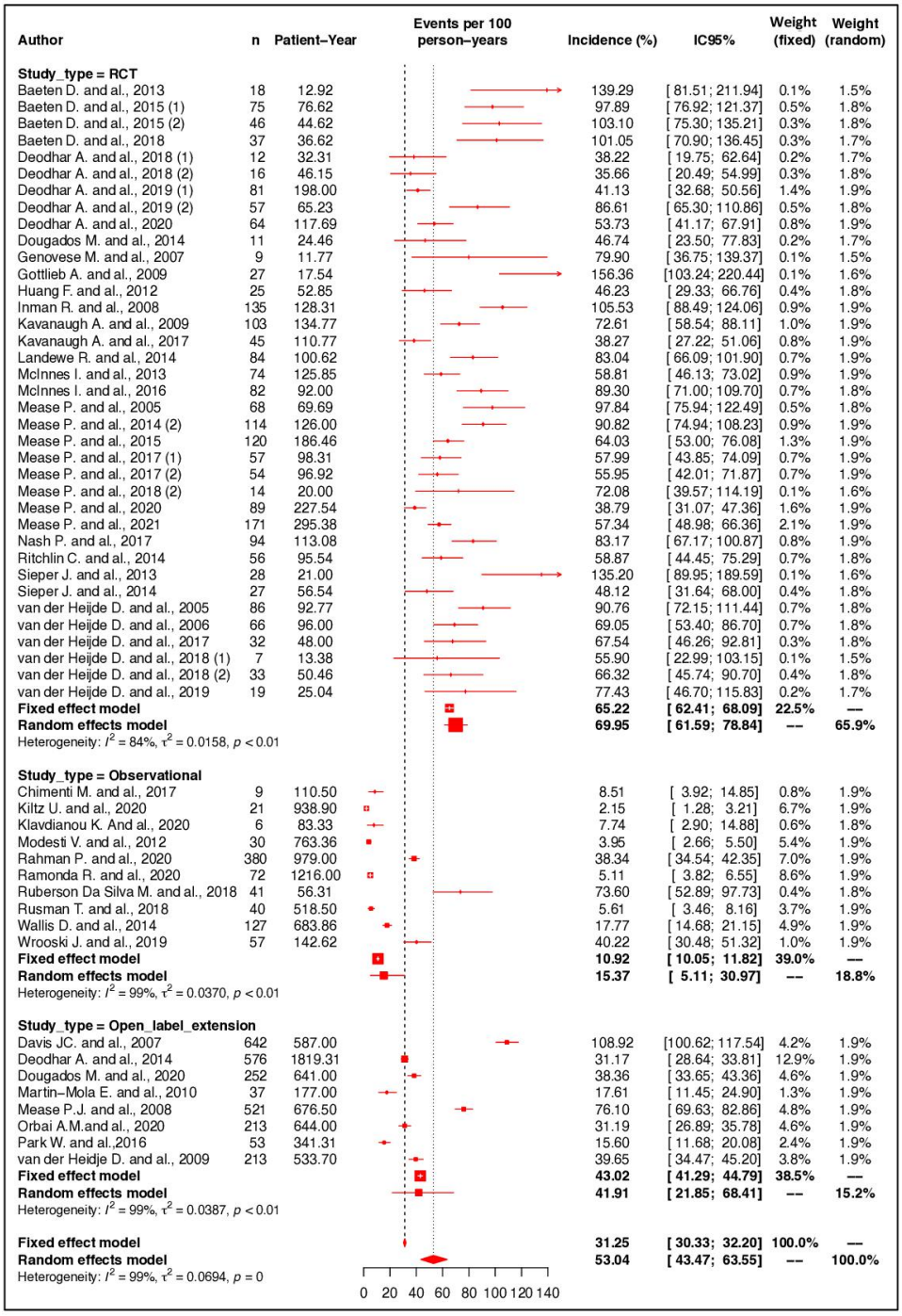

Figure 5 Forest plot of incidence rate of non-serious infections according to type of study. RCT, randomised controlled trial.

or PsA (4159 PY of follow-up) that patients treated with an IL-23i were less likely to display a hospitalised serious infections than patients treated with a TNFi.[12] In a meta-analysis of patient with psoriasis, the rate of overall adverse event including serious infections was significantly higher in biologics targeting the IL-17 compared with biologics targeting IL-23.[55] The IR of serious infections with TNFi in axSpA was estimated at 1.24 events per 100 PY. To the best of our knowledge, only one other meta-analysis of nine RCTs estimated the IR of serious infections with TNFi at 1.9 per 100 PY.[56] The lower rate of serious infections in this study could be explained by the inclusion of more recent publications in which the population benefited of the current European Alliance of Associations for Rheumatology recommendations of vaccination against influenza and pneumococcal disease and systematic pretherapeutic assessment of infection. In SpA, IR of serious infections were similar with TNFi (1.29 events per 100 PY), IL-17i (1.05 events per 100 PY) and JAKi (1.30 events per 100 PY). Those results are in line with observational studies included in our meta-analysis which evaluated risk of infection in patients with PsA or psoriasis treated with IL-17i or TNFi and found no significant difference regarding serious infections.[12 54] However,

a recent observational study from the Nordic Countries suggest a higher risk of infection with secukinumab than TNFi in patients with SpA. The authors moderate this result as the crude excess risk seemed largely explained by more frequent secukinumab use in difficult-to-treat patients especially in patients older, with longer disease duration and who were not naïve from biologic (53% bionaive in TNF group vs 11% bionaive in secukinumab group).[57]

The main limitation of this meta-analysis was the substantial heterogeneity in observational studies, without source identification. Higher methodological and clinical heterogeneity is often expected in MOOSE compared with RCTs. Subgroup analyses did not improve the heterogeneity and meta-regression analyses for year of publication, duration of follow-up and number of patients with concomitant corticoid, NSAID or conventional synthetic DMARD were not significant in univariate analysis. This high heterogeneity could explain a part of the funnel plot asymmetry. Moreover, we could not exclude publication bias given the results of Egger's regression test and funnel plot, although the asymmetry of funnel plot may be related to the smaller cohorts being at increased risk of infection or, in observational studies, related to the easier publication of positive studies with significant results.

We attempted to estimate the IR as precisely as possible using data from various study designs. However, we found a lack of large observational studies evaluating the IR of serious infections in this population, in particular in national cohorts, unlike in rheumatoid arthritis. Because of the absence of a control group in observational studies, it was not possible to evaluate the relative risk of serious and NSI in those studies. We did not include studies concerning biosimilars because our search equation was based on the international non-proprietary nomenclature of drugs, whereas biosimilars have names specific to each laboratory that develops them. Only one study with a biosimilar was included (PLANETAS OLE) as the biosimilar was compared with the reference originator infliximab arm and only this last one was included in our meta-analysis.

CONCLUSION

Our meta-analysis highlights that serious infections are rare events in the specific population of patients with PsA or axSpA treated with b/tsDMARD despite a trend of a higher incidence in observational studies compared with RCTs.

NSI were frequent in RCTs although their impact is currently poorly studied in the literature. The impact of the frequent finding of NSI in patients treated with b/tsDMARD, mainly in RCTs studies, needs to be explored.

Author affiliations
[1]Departement of rheumatology, Lyon-Sud Hospital Hospices civiles de Lyon, Pierre-Benite, France
[2]University of Lyon, University of Lyon 1 Claude Bernard, Lyon, Rhône-Alpes, France
[3]Department of Internal and Vascular Medicine, Hospices Civils de Lyon, Lyon, France
[4]Lyon Immunopathology Federation (LIFe), Hospices Civils de Lyon, Lyon, France
[5]University of Lyon, Laboratoire de Biométrie et Biologie Évolutive UMR - CNRS 5558, Lyon, France
[6]University of Lyon, INSERM UMR 1033, Lyon, France

Twitter Natalia Cabrera @ncabroj

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ORCID iD
Melanie Aureal http://orcid.org/0000-0001-6905-8735

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