Impact of biologic therapies on risk of adverse cardiovascular events in patients with Ankylosing Spondylitis or Psoriatic Arthritis: a systematic literature review.

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Abstract

Background: Recent evidence highlights increased mortality and morbidity due to cardiovascular disease (CVD), especially within the two major forms of Spondyloarthropathies (SpAs), Ankylosing Spondylitis (AS) and Psoriatic Arthritis (PsA). Healthcare professionals and patients in these populations should be alerted regarding the high risk of cardiovascular (CV) events and thus, customize the treatment strategy accordingly.

Objective: This systematic literature review aimed to determine the effects of biological therapies on serious CV events in AS and PsA.

Methods: Screening for the study was carried out using PubMed and Scopus databases from the database's inception to the 17th of July 2021. The literature search strategy for this review is based on the Population, Intervention, Comparator, Outcomes (PICOs) framework. Randomized controlled trials (RCTs) of biologic therapies for the treatment of AS and/or PsA were included. The primary outcome measure was the number of serious CV events reported during the placebo-controlled phase.

Results: 4,422 articles were generated from keywords, eligibility criteria, and databases. Following the screening, we retained 13 studies for analysis: 3 in AS and 10 in PsA. Meta-analysis of results was not feasible due to the small number of the identified studies, the heterogeneity of the biologic treatment and the included populations, as well as the infrequently reported requested endpoint. According to our review, biologic treatments are safe options as for CV risk in patients with PsA or AS.

Conclusion: Further and more extensive trials in AS/PsA patients at high risk of CV events are needed before firm conclusions can be drawn.

Keywords: Spondyloarthropathies; Ankylosing Spondylitis; Psoriatic Arthritis; Serious cardiovascular events; Biologic therapies.

Key Messages

- AS and PsA have higher incidence of CV events in respect to the general population.
- Healthcare professionals and the patients of these populations should be alarmed regarding the high risk of CV events.
- Biologic therapies reviewed did not significantly affect the risk of serious CV events in patients with AS or PsA.
- Additional clinical trials and more-well executed are needed before firm conclusions can be drawn.

Introduction

SpAs encompass many different forms of inflammatory arthritis and can impact on the spine (axial SpA) and/or peripheral joints (peripheral SpA). AS and PsA are both forms of SpAs that cause skeletal disease[1]. Moll *et al.,* concluded that there is a group of closely inter-related "seronegative spondarthritides" which include PsA, Reiter's disease, intestinal arthropathies, AS and Behçet's syndrome[2].

PsA is a heterogeneous disease with complex musculoskeletal and extra-articular manifestations. It was initially defined as Psoriasis (Pso) associated with inflammatory arthritis[1]. AS is an inflammatory disease known to affect the axial joints and may impair spinal mobility[3]. Most of the patients with SpAs suffer from comorbidities, which contribute to the patient's overall disease burden. Common comorbidities of SpAs are osteoporosis as well as CVD[4].

According to recent studies, the two main forms of SpAs, AS and PsA have increased mortality and morbidity because of CVD. Chronic inflammation may be a direct cause of CVD, acting as an independent risk factor, or as an indirect cause by affecting known risk factors for atherosclerosis[5]. Therefore, it should be highlighted that both healthcare professionals as well as the patients of these populations should be alarmed regarding the high risk of CV events[6].

Developing treatment guidelines for SpAs is challenging due to the heterogeneity of the disease but also due to several comorbidities including, obesity, and metabolic disease (diabetes, hypertension, hyperlipidaemia, fatty liver disease, CV outcomes), which are associated with the disease[7]. It's interesting to note that the evaluation of comorbidities has been highlighted as a crucial component of therapy planning and can result in the escalation of treatment for associated disorders[8].

According to the European Guidelines on CV disease prevention in clinical practice (2016), RA enhances CV risk independently of traditional risk factors. However, the available evidence is less robust for PsA and AS[9].

Likewise, the role of antirheumatic drugs in CVD prevention has been an intensively researched field in recent years[10]. In contrast to the strong evidence suggesting a beneficial effect of TNF inhibitors on CV risk in patients with Rheumatoid Arthritis (RA)[11,12] such information in PsA[13] or AS[14] is limited[15].

Given the above unmet medical need, we decided to systematically review the existing literature in order to determine the effects of biological therapies on serious CV events in AS and PsA. This is the first systematic study of randomized, controlled trials that has been done, as far as we are aware, to assess the impact of biologic therapies on the risk of adverse CV events in patients with AS/PsA.

Methods

This study was conducted in accordance with the recommendations of the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) statement [16]. The systematic review protocol is not registered.

Eligibility criteria

The literature search strategy for this review is based on the PICO framework [17].

The population included is adult (≥18 years) patients with PsA or AS.

The intervention is defined as any biologic therapy: Infliximab or Remicade or Adalimumab or Humira or Etanercept or Enbrel or Golimumab or Simponi or Certolizumab pegol or Cimzia or Ustekinumab or Stelara or Secukinumab or Cosentyx or Ixekizumab or Taltz or Abatacept or Orencia or Guselkumab or Tremfya in all formulations and treatment durations.

The comparator could be the same drug (different dose or regimen), any diffe-rent drug, or placebo.

The study design includes RCTs in adults. Systematic reviews/meta-analyses, reviews, case reports, case series, observational studies, correspondences, short communications, editorials, commentaries, guidelines, and other study designs were excluded.

Major adverse CV events and significant uncontrolled cerebrocardiovascular events [18,19] during the placebo-controlled phase are the primary outcomes and are defined as either coronary artery disease (including myocardial infarction, coronary artery by-pass grafting and percutaneous coronary intervention) stroke, peripheral arterial disease, heart failure, unstable angina, unstable arterial hypertension, cerebrovascular accident, or CV-related mortality.

Search strategy

Research papers were identified through web-based searches in PubMed and Scopus. Searching in the before-mentioned bibliographical databases was conducted with the title and abstract on the grounds of all potential combinations of two groups of terms. The included studies are dated from the database's inception to July 17, 2021. Cited references from previously conducted systematic reviews and selected articles were screened to find additional studies that were not retrieved in the initial search. Conference abstracts were not searched because they do not contain sufficient data for quality assessment.

Study selection

Following the literature search, identified studies were checked to exclude duplicates. One researcher (KM) screened the remaining articles to identify studies that met the predetermined eligibility criteria. The studies were selected following specific methodologically driven steps. Firstly, all identified studies were exported into an excel document and were evaluated based on titles and/or abstracts against the pre-specified eligibility criteria. Subsequently, study abstracts and titles were reviewed and those, deemed irrelevant, were excluded, and the exclusion reasons were documented. Rejected studies were those not relevant to the subject of investigation. Whenever the information provided in titles/abstracts was insufficient to reach a clear decision for their inclusion or exclusion and/or when the titles/abstracts indicated that studies met the inclusion criteria, the full papers were retrieved to be further reviewed. Moreover, only studies published in English with available full text and studies concerning human subjects were included.

Data extraction

A data extraction excel file was developed based on the review aims and objectives, including the following information: First author, year of publication, study location, autoimmune disease, trial duration, duration of treatment during the randomized-controlled phase, dosage and treatment regimen of each arm, the total number of patients, number of patients in each arm, number of major adverse CV event/significant uncontrolled cerebrocardiovascular events in each arm during the randomized-controlled phase, the incidence of CV event/significant uncontrolled cerebrocardiovascular events in each arm during the randomized-controlled phase.

Quality Assessment

The quality of included studies was evaluated using the Critical Appraisal Skills Programme (CASP) Randomised Controlled Trials checklist (20). This is a checklist with 11 questions designed to review studies systematically. This checklist was designed as an educational/teaching tool not as a scoring system. Studies were not excluded based on quality since the quality assessment of existing literature pertained to the study objectives.

Results

A total of 4,422 articles were generated from keywords, eligibility criteria, and databases. Of the 4,422 articles, 4,376 were from PubMed and 46 were obtained from Scopus. Following deduplication, 4,418 articles were screened, and 221 full-text articles were assessed for eligibility. Finally, after reading the full text of the remaining 221 articles, we retained 13 studies for analysis: 3 in AS and 10 in PsA. Our PRISMA[16] (preferred reporting items for systematic reviews and meta-analyses) flow diagram is shown below in Figure 1.

Characteristics of Included Studies

Among these RCTs, 3[21–23] were based on AS patients and 10[24–33] on PsA patients (Tables I, II). The total number of AS patients was 781, while the total number of PsA patients was 4,253. People with AS were included in trials testing Etanercept[21], Golimumab[22] and Ixekizumab[23]. People with PsA were included in trials testing Adalimumab[24,25], Certolizumab pegol[26], Secukinumab[27,28], Ixekizumab[25,29], Golimumab[30] and Guselkumab[31–33]. The blinded - controlled period ranged from 12 weeks to 24 weeks.

Effects on CV events

AS patients

Integrated CV safety data of the selected studies in AS patients are presented in Table III.

Treatment with Etanercept [21], Golimumab [22] and Ixekizumab [23] has significantly improved disease activity compared with the placebo-controlled arm. In these studies, only one serious CV event was reported for each biological agent of our interest. In detail, one Etanercept treated patient experienced acute myocardial infarction and underwent angioplasty but continued in the study [21]. Similarly, one patient in the 50-mg Golimumab group had a myocardial infarction on day 67, despite a normal screening cardiac evaluation 4 months prior[14]. In regards with

Ixekizumab, one cerebrocardiovascular event was identified in the Q4W treatment arm. Although the presented cerebrocardiovascular event was not further specified, it must be noted that data on terms relating to cerebrocardiovascular events was adjudicated by external clinical events committees[15].

PsA patients

Integrated CV safety data of the selected studies in PsA patients are presented in table IV.

Treatment with the biological agents of our interest has significantly improved disease activity compared with the placebo-controlled arm in PsA patients[16–25].

In the ADEPT study, serious adverse events in the placebo-treated patients were cerebrovascular accidents and aggravation of coronary artery disease, whereas zero CV events were reported in the Adalimumab-treated patients[24]. On the contrary, in the SPIRIT-P1 study, comparing two regimens of Ixekizumab and an active reference arm of Adalimumab to treatment with placebo, three cerebrocardiovascular events were reported in the Adalimumab-treated patients and zero similar events were reported in the remaining treatment arms [25].

In the RAPID-PsA trial, one death occurred in a Certolizumab pegol-treated patient during the first 24 weeks: one myocardial infarct in the 200 mg Q2W group, while zero events of our interest were identified in the other treatment groups[26].

The safety profile of Secukinumab was consistent in both selected studies involving patients with PsA [27,28]. In FUTURE 1 study, throughout the placebo-controlled period, one patient receiving 75 mg of Secukinumab had a stroke, while zero CV events were observed in the placebo group[27]. Similarly, in FUTURE 2 study, only one myocardial infarction was recorded in a high-risk patient who received Secukinumab 75 mg; the patient continued in the study[28].

In both phase III randomized clinical trials, SPIRIT-P1 and SPIRIT-P2, zero confirmed major adverse cardiac events were reported in the Ixekizumab treatment groups[25,29].

Kavanaugh *et al.,* demonstrated that patients with PsA treated with IV Golimumab experienced significantly greater improvements in measures of disease activity compared with patients receiving placebo. In terms of CV safety, one death occurred, in the placebo group due to acute CV failure while, in the Golimumab group one patient experienced a SAE: myocardial infarction [30].

Two phase III studies, DISCOVER-1, and DISCOVER-2, and one phase 2a study demonstrated that Guselkumab is efficacious in treating the signs and symptoms of active PsA[31–33]. Two MACE events that occurred in 2 patients (i.e., cardiac failure in a patient receiving placebo[32] and ischemic stroke in a patient receiving Guselkumab 100 mg Q4W[33] were identified. Both patients receiving Guselkumab presented with multiple risk factors[31,33].

Quality assessment results

All review studies focused on the characteristics and endpoints of interest and used acceptable methods to answer the research questions. Recruitment of participants had been conducted in an acceptable way in all RCTs studies. Patients, health-care professionals, and investigators remained blinded to treatment in all studies. Results were well-described in all studies (Table V).

Discussion

Traditional CV risk factors have a well-established role in the general population (36). The burden of CVD on the morbidity of autoimmune rheumatic disorders is significant. Subclinical atherosclerosis exists in SpAs even though patients show an elevated prevalence of standard CV risk factors. It appears that endothelial dysfunction is brought on by chronic inflammation, and this, in turn, causes atherosclerosis and CV complications[37]. This implies that in order to reduce the risk of CV morbidity and death in these patients, proper diagnosis and management of CV risk factors should be regarded as being just as critical as the management of SpAs symptoms.

To our knowledge, this is the first systematic literature review of RCTs undertaken to date that aims to evaluate how biological therapies affect the cardiovascular events in AS and PsA patients. Although meta-analysis couldn't be conducted, this narrative review indicates that biologic treatments are safe options as for CV risk in patients with PsA or AS.

In 2015, Roubille and colleagues conducted a systematic literature review and meta-analysis of controlled studies and randomized trials to determine the association between CV events and antirheumatic drugs in RA and PsA/Pso. The treatment options were biologics, non-biological disease-modifying antirheumatic drugs (DMARDs), non-steroidal anti-inflammatory drugs (NSAIDs) and corticosteroids. In PsA/Pso, limited evidence suggested that systemic therapies are associated with decreasing in the risk of all CV events [38].

In 2019, Champs et al., conducted a systematic review and meta-analysis of RCTs to investigate the short-term risk of major adverse CV events or congestive heart failure in patients with PsA or Pso initiating a biological therapy. Likewise, their meta-analysis showed no statistically significant difference in the short-term risk of major adverse cardiac events (MACEs) in patients with PsA or Pso initiating a biological therapy[39].

This systematic literature review has some limitations. First, the complete screening and data extraction was led by one fellow (KM). The placebo-controlled phase of the trials identified

was short due to ethical considerations. Therefore, the studies identified were neither large enough nor long enough to evaluate uncommon serious adverse events or the risks associated with long-term use. Since the requested endpoint was infrequently reported and the heterogeneity of the treatments (in terms of active substances, dosages, duration etc.) and the populations (in terms of age, comorbidities, time of diagnosis etc.) was high, we concluded that meta-analysis of results was not feasible to perform. Third, investigators used only 2 databases, PubMed, and Scopus as they had not access to other high-quality databases like Embase. Therefore, it was decided to conduct a broader search without applying filters to avoid missing any relevant studies. As such, keywords for population were included that were combined with keywords for intervention but no keywords for outcomes were considered.

In conclusion, the presence of certain comorbidities can influence negatively or, on the contrary, drive the physician to choose certain treatments and, therefore, it should be systematically evaluated and be considered when choosing a treatment. However, there is a gap in the research on the effect of biological therapies in CVD. Based on the available evidence in AS and PsA patients, further, well executed, larger trials in people at high risk of CV events are needed before firm conclusions can be drawn.

Figures and Tables

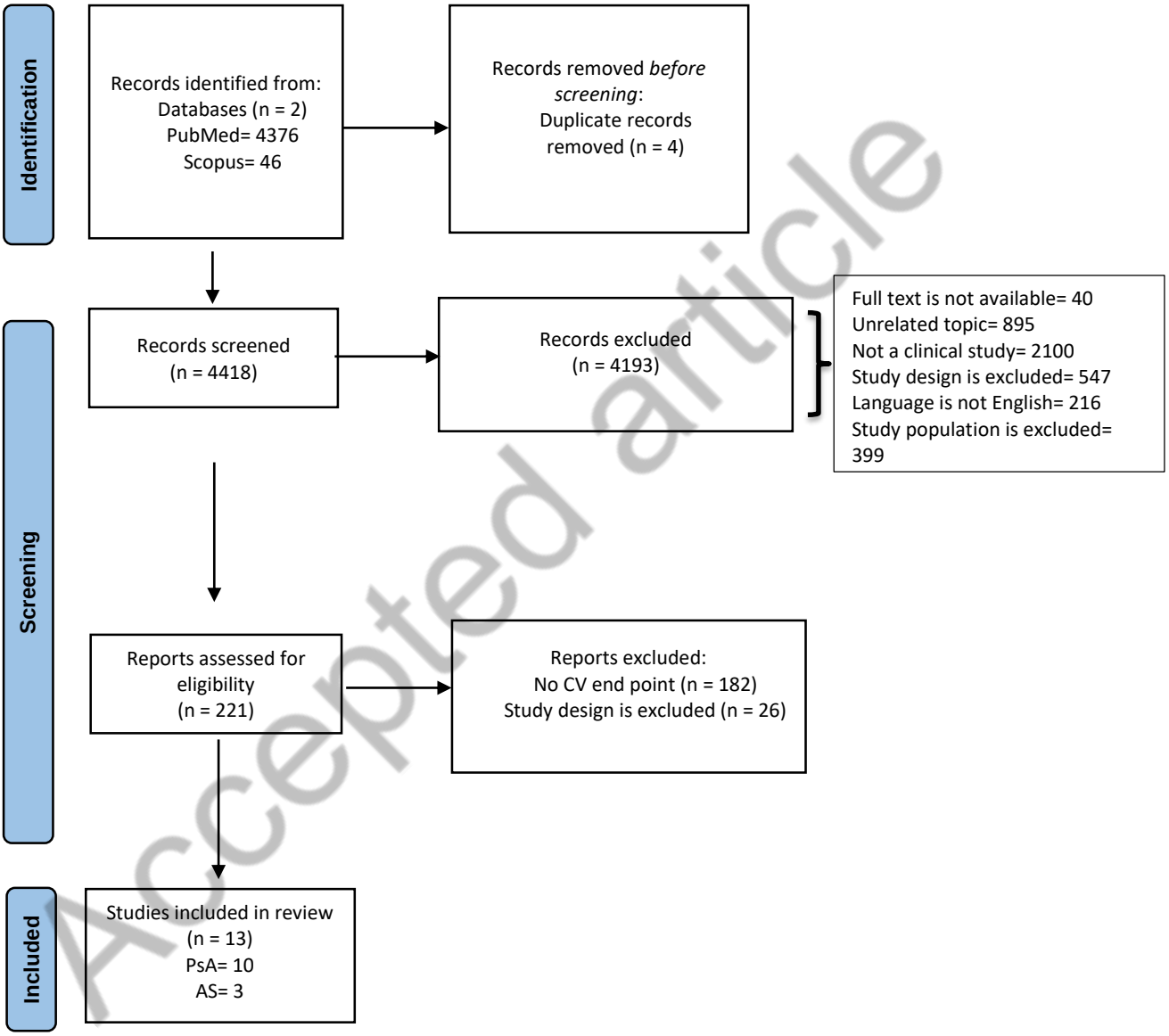

Figure 1: Flowchart of the systematic review.

Table I. Baseline characteristics in AS patients.

Author Year of publication	Group/dose (number of patients)	Duration of the blinded controlled (in weeks)	Countries of conduct	Age-(Years)	Sex (Male%)	Method of diagnosis
A. Calin et al., 2004 (21)	Etanercept/25 mg sc/twice weekly (45) Matching Placebo (39)	12	14 sites in Belgium, Finland, France, Germany, I-taly, The Netherlands, Spain, and the United Kingdom	43.2	79	Modified New York Criteria (34)
Robert D. Inman et al., 2008 [1](22)	Golimumab/ 50 mg/two sc injections/every 4 weeks (138) Golimumab/ 100 mg/two sc injections/every 4 weeks (140) Matching Placebo (78)	24	57 sites in the US, Canada, Europe, and Asia	39.5	71.2	Modified New York Criteria (34)
Désirée van der Heijde et al., 2018 [2] (23)	Ixekizumab/80 mg sc/every two weeks (83) Ixekizumab/80 mg sc/every four weeks (81) Adalimumab/40 mg sc/every two weeks (90) Matching Placebo (87)	16	84 sites in the Czech Republic, Germany, Hungary, the Netherlands, Poland	41.7	81	Modified New York Criteria (34)

sc: subcutaneous, mg: milligram, cv: cardiovascular

Table II. Baseline characteristics in PsA patients.

Author Year of publication	Group/dose (number of patients)	Duration of the blinded controlled (in weeks)	Countries of conduct	Age-(Years)	Sex (Male%)	Method of diagnosis
Philip J. Mease et al., 2005 (24)	40 mg/Adalimumab sc/every other week (151) Matching Placebo (162)	24	50 sites in Austria, Belgium, Canada, France, Germany, I-taly, the United Kingdom, and the US	49	56	Not reported
Philip J. Mease et al., 2013[3] (26)	200 mg/Certolizumab pegol sc/ every 2 weeks (138)	24	104 sites in North America and South America, Europe, the	48	45	CASPAR group criteria (35)

[1] At week 16, patients who achieved 20% improvement from baseline in both the total back pain and morning stiffness measures entered early escape in a double-blinded manner: patients in the placebo group received golimumab 50 mg, patients in the golimumab 50-mg group had a dose escalation to 100 mg, and patients in the 100-mg group continued to receive 100 mg.

[2] At week 16, patients entered an ongoing extended treatment period (weeks 16 to 52), during which time patients in the ixekizumab treatment groups remained on their assigned treatment and patients in the placebo or adalimumab groups were randomly reassigned to receive one of the two ixekizumab dosing regimens, while maintaining masking of treatment allocation. All patients continued to receive masked treatment until week 52.

[3] Patients were randomized 1:1:1 to placebo (0.9% saline), or 400 mg CZP at week 0, 2 and 4 loading doses followed by either 200 mg CZP every 2 weeks (Q2W) or 400 mg CZP every 4 weeks (Q4W), administered subcutaneously by investigators using a blinded prefilled syringe (the cumulative monthly dose of CZP was the same for subjects randomized to CZP).

	400 mg/Certolizumab pegol sc/ every 4 weeks (135) Matching Placebo (136)		Middle East, Australia, and Asia			
Philip J. Mease et al., 2015 [4] (27)	iv Secukinumab (at a dose of 10 mg per kilogram) at weeks 0, 2, and 4, followed by sc/Secukinumab at a dose of 150 mg/every 4 weeks (202) iv Secukinumab (at a dose of 10 mg per kilogram) at weeks 0, 2, and 4, followed by Sc/Secukinumab at a dose of 75 mg/every 4 weeks (202) iv Secukinumab (at a dose of 10 mg per kilogram) at weeks 0, 2, and 4, followed by matching placebo (202)	16 or 24 (based on clinical response)	104 sites in North America and South America, Europe, the Middle East, Australia, and Asia	49	46	CASPAR group criteria (35)
Iain B McInnes et al.[5], 2015 (28)	sc Secukinumab/300 mg/once a week from baseline to week 4 and then every 4 weeks thereafter (100) sc Secukinumab/150 mg/once a week from baseline to week 4 and then every 4 weeks thereafter (100) sc Secukinumab/75 mg/once a week from baseline to week 4 and then every 4 weeks thereafter (99) Matching Placebo (98)	16 or 24 (based on clinical response)	76 sites in Asia, Australia, Canada, Europe, and the USA	48	48	CASPAR group criteria (35)
Philip J. Mease et al., 2016 (25)	sc injections of Placebo (106) sc/Adalimumab 40 mg/once every 2 weeks (101) sc/Ixekizumab 80 mg/once every 2 weeks (103)	24	114 sites in Belgium, Bulgaria, Canada, Czech Republic, Estonia, France, Japan, Mexico, Netherlands, Poland, Russia, Spain, Ukraine, United Kingdom, and USA	50	46	CASPAR group criteria (35)

[4] Patients in the placebo group were switched to subcutaneous secukinumab at a dose of 150 mg or 75 mg at week 16 or 24, depending on clinical response. In the safety analyses, the placebo-controlled period included data only through week 16, when patients received the originally assigned study medication.
[5] At week 16, patients were classified as responders (≥20% improvement from baseline in tender and swollen joint counts) or non-responders. Placebo-treated patients were randomly assigned again in a 1:1 ratio to receive subcutaneous secukinumab 300 mg or 150 mg every 4 weeks from week 16 (non-responders) or week 24 (responders).

	sc/Ixekizumab 80 mg/once every 4 weeks (107)					
Peter Nash et al., 2017 [6] (29)	sc injection of Placebo (118) sc/80 mg Ixekizumab/every 4 weeks (122) sc/80 mg Ixekizumab/every 2 weeks (123)	24	109 sites across Asia, Australia, Europe, and North America	52	47	CASPAR group criteria (35)
Arthur Kavanaugh et al., 2017 (30)	iv infusions of Placebo at 2 mg/kg at weeks 0 and 4 and every 8 weeks (239) iv infusions of golimumab at 2 mg/kg at weeks 0 and 4 and every 8 weeks (240)	24	90 sites in Belarus, Canada, Germany, Hungary, Lithuania, Poland, Romania, Russia, Spain, Ukraine, and the US	46	52	CASPAR group criteria (35)
Atul Deodhar et al., 2018 [7] (31)	sc/Guselkumab 100 mg at week 0, week 4, and every 8 weeks thereafter for 24 weeks (100) sc/Placebo at week 0, week 4, and every 8 weeks thereafter for 24 weeks (49)	24	34 sites in Canada, Germany, Poland, Romania, Russia, Spain, and the USA	46	51	CASPAR group criteria (35)
Atul Deodhar et al., 2020 (32)	sc/Guselkumab 100 mg every 4 weeks (128) sc/Guselkumab 100 mg at weeks 0, 4, then every 8 weeks (127) Matching placebo (126)	24	86 sites in Asia, Australasia, Europe, and North America	48	51	Not reported
Philip J. Mease et al., 2020 (33)	Guselkumab was administered as a 100-mg sc injection at week 0, week 4, and every 4 weeks (245) Guselkumab was administered as a 100-mg sc injection at week 0, week 4, and then every 8 weeks (248) Matching Placebo (246)	24	118 sites in Bulgaria, Czech Republic, Estonia, Latvia, Lithuania, Malaysia, Poland, Russia, Spain, Taiwan, Turkey, Ukraine, and the USA	46	53	CASPAR group criteria (35)

[6] Patients randomized to ixekizumab every 4 weeks or every 2 weeks were administered a starting dose of 160 mg given as two injections at week 0.

[7] At week 16, patients with less than 5% improvement in swollen and tender joint counts were eligible for early escape to ustekinumab. At week 24, the remaining placebo-treated patients crossed over to receive guselkumab 100 mg at weeks 24, 28, 36, and 44 and guselkumab-treated patients received a placebo injection at week 24, followed by guselkumab injections at weeks 28, 36, and 44.

Table III. Effects on CV events in AS patients.

Author Year of publication	Group/dose (number of patients)	Number of CV events
A Calin et al., 2004 (21)	Etanercept/25 mg sc/twice weekly (45)	1
	Matching Placebo (39)	0
Robert D. Inman et al., 2008 (22)	Golimumab/50 mg/two sc injections/every 4 weeks (138)	1
	Golimumab/100 mg/two sc injections/every 4 weeks (140)	0
	Matching Placebo (78)	0
Désirée van der Heijde et al., 2018 (23)	Ixekizumab/80 mg sc/every two weeks (83)	0
	Ixekizumab/80 mg sc/every four weeks (81)	1
	Adalimumab/40 mg sc/every two weeks (90)	0
	Matching Placebo (87)	0

sc: subcutaneous, mg: milligram, cv: cardiovascular

Table IV. Effects on CV events in PsA patients

Author Year of publication	Group/dose (number of patients)	Number of CV events
Philip J. Mease et al., 2005 (24)	40 mg/Adalimumab sc/every other week (151)	0
	Matching Placebo (162)	2
Philip J. Mease et al., 2013 (26)	200 mg/Certolizumab pegol sc/ every 2 weeks (138)	1
	400 mg/Certolizumab pegol sc/ every 4 weeks (135)	0
	Matching Placebo (136)	0
Philip J. Mease et al., 2015 (27)	iv Secukinumab (at a dose of 10 mg per kilogram) at weeks 0, 2, and 4, followed by sc/secukinumab at a dose of 150 mg/every 4 weeks (202)	0
	iv Secukinumab (at a dose of 10 mg per kilogram) at weeks 0, 2, and 4, followed by sc/Secukinumab at a dose of 75 mg/every 4 weeks (202)	1
	iv Secukinumab (at a dose of 10 mg per kilogram) at weeks 0, 2, and 4, followed by matching placebo (202)	0
Iain B McInnes et al., 2015 (28)	sc Secukinumab/300 mg/once a week from baseline to week 4 and then every 4 weeks thereafter (100)	0
	sc Secukinumab/150 mg/once a week from baseline to week 4 and then every 4 weeks thereafter (100)	0
	sc Secukinumab/75 mg/once a week from baseline to week 4 and then every 4 weeks thereafter (99)	1
	Matching Placebo (98)	0
Philip J. Mease et al., 2017 (25)	sc injections of placebo (106)	0
	sc Adalimumab 40 mg/once every 2 weeks (101)	3
	sc Ixekizumab 80 mg/once every 2 weeks (103)	0
	sc Ixekizumab 80 mg/once every 4 weeks (107)	0
Peter Nash et al., 2017 (29)	sc injection of Placebo (118)	2
	sc/80 mg Ixekizumab/every 4 weeks (122)	0
	sc/80 mg Ixekizumab/every 2 weeks (123)	0

Arthur Kavanaugh et al., 2017 (30)	iv infusions of Placebo at 2 mg/kg at weeks 0 and 4 and every 8 weeks (239)	1
	iv infusions of Golimumab at 2 mg/kg at weeks 0 and 4 and every 8 weeks (240)	1
Atul Deodhar et al., 2018 (31)	sc Guselkumab 100 mg at week 0, week 4, and every 8 weeks thereafter for 24 weeks (100)	1
	sc placebo at week 0, week 4, and every 8 weeks thereafter for 24 weeks (49)	0
Atul Deodhar et al., 2020 (32)	sc Guselkumab 100 mg every 4 weeks (128)	0
	sc Guselkumab 100 mg at weeks 0, 4, then every 8 weeks (127)	0
	Matching Placebo (126)	1
Philip J. Mease et al., 2020 (33)	Guselkumab was administered as a 100-mg sc injection at week 0, week 4, and every 4 weeks (245)	1
	Guselkumab was administered as a 100-mg sc injection at week 0, week 4, and then every 8 weeks (248)	0
	Matching Placebo (246)	0

sc: subcutaneous, iv: intravenous, mg: milligram, cv: cardiovascular

Table V. Quality assessment of studies.

Studies included	Did the study address a clearly focused research question?	Was the assignment of participants to interventions rando-mised?	Were all participants who entered the study accounted for at its conclusion?	• Were the participants 'blind' to intervention they were given? • Were the investigators 'blind' to the intervention they were giving to participants? • Were the people assessing/analyzing outcome/s 'blinded'?	Were the study groups similar at the start of the randomized controlled trial?	Apart from the experimental intervention, did each study group receive the same level of care (that is, were they treated equally)?	Were the effects of intervention reported comprehensively?	Was the precision of the estimate of the intervention or treatment effect reported?	Do the benefits of the experimental intervention outweigh the harms and costs?	Can the results be applied to your local population/in your context?	Would the experimental intervention provide greater value to the people in your care than any of the existing interventions?
(21)	Yes	Yes	Yes	Yes	Can't tell	Yes	Yes	Yes	Can't tell	Yes	Can't tell
(22)	Yes	Yes	Yes	Yes	Can't tell	Yes	Yes	No	Can't tell	Yes	Can't tell
(23)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Can't tell	Can't tell	Can't tell
(24)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Can't tell	Yes	Can't tell
(26)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Can't tell	Yes	Can't tell
(27)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Can't tell	Yes	Can't tell
(28)	Yes	Yes	Yes	Yes	Can't tell	Yes	Yes	Yes	Can't tell	Yes	Can't tell
(25)	Yes	Yes	Yes	Yes	Can't tell	Yes	Yes	No	Can't tell	Yes	Can't tell
(29)	Yes	Yes	Yes	Yes	Can't tell	Yes	Yes	Yes	Can't tell	Yes	Can't tell
(30)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Can't tell	Yes	Can't tell
(31)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Can't tell	Yes	Can't tell
(32)	Yes	Yes	Yes	Yes	Can't tell	Yes	Yes	Yes	Can't tell	Yes	Can't tell
(33)	Yes	Yes	Yes	Yes	Can't tell	Yes	Yes	Yes	Can't tell	Yes	Can't tell

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