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SYSTEMATIC REVIEW

Time until onset of action when treating psoriatic arthritis: meta-analysis and novel approach of generating confidence intervals

Phuong Anh Pham[1] · Corinna Dressler[1] · Lisa Eisert[1] · Alexander Nast[1] · Ricardo Niklas Werner[1]

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Abstract

Psoriatic arthritis (PsA) is associated with progressive joint destruction and reduced quality of life. The time until a drug treatment starts to show an effect (TOA) is important for preventing joint destruction. The objective was to assess the time until onset of action of drugs when treating PsA. A systematic review of PsA drug trials was performed. Outcomes were: time until 25% of patients (TOA) reached (1) ≥ 20%, (2) ≥ 50% improvement in modified American College of Rheumatology response criteria (ACR), (3) ≥ 75% reduction in Psoriasis Area and Severity Index (PASI75). 95% confidence intervals were calculated extracting data from graphs using a novel method. Meta-analysis was conducted. Two head-to-head trials show no difference between ixekizumab and adalimumab or adalimumab and tofacitinib for TOA-ACR outcomes. For PASI75, ixekizumab had a faster onset than adalimumab. Infliximab plus MTX was faster than MTX alone. Pooled results from 32 study arms for TOA-ACR20 (week [95% CI]) are: < 2 weeks: infliximab (1.18 [0.72–1.65]), ixekizumab (1.04 [0.80–1.28]), tofacitinib (10 mg 1.56 [1.14–1.98]); ≤ 4 weeks: adalimumab (1.95 [1.35–2.55]), secukinumab (75 mg 1.89 [0.16–3.62], 150 mg 2.13 [1.34–2.91], 300 mg 2.26 [1.75–2.76]), tofacitinib (5 mg 2.20 [1.41–2.99]); 4 + weeks: apremilast, ustekinumab. For TOA-ACR50, all pooled point estimates are > 4 weeks. For TOA-PASI75, the range is between 2.24 [1.65–2.84] for ixekizumab and 6.03 [3.76–8.29] for adalimumab. Indirect, mixed comparison suggest a faster onset of infliximab, ixekizumab and tofacitinib compared to apremilast, methotrexate and ustekinumab for ACR20, not ACR50. For PASI75, ixekizumab is faster than adalimumab.

Keywords Arthritis · Psoriatic [MeSH] · Anti-rheumatic agents* · Meta-analysis [MeSH] · Confidence intervals [MeSH]

Abbreviations

ACR	American College of Rheumatology
ACR20	≥ 20% improvement in modified American College of Rheumatology response criteria
ACR50	≥ 50% improvement in modified American College of Rheumatology response criteria
ADA	Adalimumab
APR	Apremilast
bDMARD	Biological disease-modifying anti-rheumatic drug
BID	Twice a day
BIW	Twice weekly
BW	Body weight
CASPAR	Classification criteria for the diagnosis of psoriatic arthritis
CI	Confidence intervals
CRP	C-reactive protein
CSA	Cyclosporine

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✉ Corinna Dressler
Corinna.dressler@charite.de

Phuong Anh Pham
Phuong-anh.pham-thi@charite.de

Lisa Eisert
Lisa.eisert@charite.de

Alexander Nast
Alexander.nast@charite.de

Ricardo Niklas Werner
Ricardo.werner@charite.de

[1] Division of Evidence-Based Medicine (dEBM), Department of Dermatology, Venerology und Allergy, Berlin Institute of Health, Charité-Universitätsmedizin Berlin, corporate member of Freie Universität Berlin, Humboldt-Universität zu Berlin, Charitéplatz 1, 10117 Berlin, Germany

csDMARD	Conventional synthetic disease-modifying anti-rheumatic drug
CZP	Certolizumab pegol
d	Day
EE	Early escape
ES	Point estimate
ESR	Erythrocyte sedimentation rate
ETA	Etanercept
EULAR	European League against Rheumatism
GOL	Golimumab
GRAPPA	Group for research and assessment of psoriasis and psoriatic arthritis
GUS	Guselkumab
Hx	History of
ICTRP	The International Clinical Trials Registry Platform
INF	Infliximab
IQR	Interquartile range
iv	Intravenous
IXE	Ixekizumab
LE	Lesion
LEF	Leflunomide
LES	Least squares
MTX	Methotrexate
NA	Not available
NI	No information
NR	Not restricted
NSAID	Non-steroidal anti-inflammatory drug
PASI	Psoriasis Area and Severity Index
PASI75	≥ 75% reduction in Psoriasis Area and Severity Index
PBO	Placebo
PGA	Physician's global assessment
PICOS	Participants, interventions, comparisons, outcomes, study design
PJC	Painful joint count
PRED	Prednisolone
PRISMA	Preferred reporting items for systematic reviews and meta-analyses
PsA	Psoriatic arthritis
PsARC	Psoriatic arthritis response criteria
Pso	Cutaneous psoriasis
pts	Patients
Q12W	Every 12 weeks
Q1W	Once per week
Q2W	Every 2 weeks
Q4W	Every 4 weeks
QD	Once per day
RA	Rheumatoid arthritis
RF	Rheuma factor
sc	Subcutaneous
SD	Standard deviation
SE	Standard error
SEC	Secukinumab
SJC	Swollen joint count
SSZ	Sulfasalazine
tbc	Tuberculosis
TJC	Tender joint count
TOF	Tofacitinib
tsDMARD	Targeted synthetic disease-modifying anti-rheumatic drug
TOA	Time until onset of action
TOA-ACR20	Time until 25% of patients reach a ≥ 20% improvement in ACR criteria
TOA-ACR50	Time until 25% of patients reach a ≥ 50% improvement in ACR criteria
TOA-PASI75	Time until 25% of patients reach a ≥ 75% improvement in PASI
UST	Ustekinumab
w	Week/weeks
y/yrs	Year/years

Introduction

Psoriatic arthritis (PsA) is a chronic systemic inflammatory disease of unknown etiology [1]. It is a clinically heterogeneous condition associated with progressive joint destruction and skin involvement that may cause functional impairment and a reduced quality of life [2–5]. The prevalence of PsA ranges from 0.06 to 0.25% in the general population, while 6 to 41% of patients with cutaneous psoriasis (Pso) are affected [6].

Recent advances in understanding the pathology of PsA lead to the development of novel treatment options such as targeted biologic drugs. These have been shown to slow down joint damage and radiographic progression and to improve the quality of life [7]. The treatment of PsA usually follows a "step-up" approach [8]: mild forms of PsA are treated with non-steroidal anti-inflammatory drugs (NSAIDs) and intra-articular glucocorticoids injections. For patients suffering from moderate-to-severe PsA, the European League Against Rheumatism (EULAR) and the Group for Research and Assessment of Psoriasis and Psoriatic Arthritis (GRAPPA) recommend the use of conventional synthetic disease-modifying anti-rheumatic drugs (csDMARDs), preferably methotrexate (MTX). For patients, who are intolerant or fail to achieve sufficient improvement of symptoms under csDMARD mono- or combination therapy, treatment with biological DMARDs (bDMARDs) is recommended [9].

The rapidity of improvement under drug therapy may play an important role, especially regarding the prevention of progressive joint destruction. A shorter onset of action relieves joint and skin symptoms sooner. This influences adherence positively, which may reduce health care costs

[10]. However, despite of its importance, data on the onset of action have rarely been assessed in PsA. Therefore, the aim of this paper was to assess the time until onset of action of different drugs when treating PsA.

Methods

We followed the methods for conducting systematic reviews as recommended by Cochrane [11] and the preferred reporting items for systematic reviews and meta-analyses (PRISMA) guideline [12]. A protocol was published (International prospective register of systematic reviews CRD42017058782).

Search strategy

We searched in four electronic databases, namely MEDLINE Ovid (1946 to February week 3, 2017), MEDLINE In-Process and Other Non-Indexed Citations Ovid (February 28, 2017), Embase Ovid (1974 to February 28, 2017), and Cochrane Central Register of Controlled Trials (CENTRAL; Wiley), the International Clinical Trials Registry Platform (ICTRP) and checked references lists of included studies. An example search strategy for Embase is shown in Supplementary (S) Table S1 (see Appendix A).

We pre-specified PICOs (participants, interventions, comparisons, outcomes, study design), see Table 1. Additionally, studies were only eligible if data on ACR20 was reported for at least two time points within 16 weeks after initiation of treatment.

Main outcome variables

We were primarily interested in the time at which 25% of patients achieved a ≥ 20% and ≥ 50% improvement in the modified American College of Rheumatology Response Criteria (ACR) [13]; and the time at which 25% of patients achieved a 75% improvement in the Psoriasis Area Severity Index (PASI).

Study selection and data extraction

Title, abstract and full-text screening was performed by two reviewers independently (PAP, LE). Data extraction and evaluation of risk of bias were performed by one reviewer (PAP) and checked by another (CD). Extracted data include general study information, population, patients' demographics, baseline characteristics, details of the interventions, and outcome data with times of assessment. Discrepancies were resolved by discussion with AN. Missing or incomplete data regarding primary outcomes were requested from the corresponding author or the trial sponsor via email.

Table 1 An overview of population, interventions, comparators, outcomes and study design (PICOs)

PICOs	Description
Population	Adults with a diagnosis of psoriatic arthritis
Intervention	PsA induction therapy with at least one of the following drugs[a] csDMARDs: methotrexate (MTX), sulfasalazine (SSZ), cyclosporine (CSA) or leflunomide (LEF) bDMARDs: adalimumab (ADA), etanercept (ETA), golimumab (GOL), infliximab (INF), ustekinumab (UST), secukinumab (SEC), guselkumab, ixekizumab (IXE), certolizumab pegol (CZP) tsDMARDs: apremilast (APR) or tofacitinib (TOF) Concomitant use of topical drugs as part of the study was allowed (e.g. mild to moderate topical steroids)
Comparison	With another included drug, placebo, combination of included drugs and/or dose comparison of the same drug
Outcome	Primary outcomes: time until onset of action (TOA), defined as Time until 25% of patients reach a ≥ 20% improvement in ACR criteria (TOA-ACR20) Time until 25% of patients reach a ≥ 50% improvement in ACR criteria (TOA-ACR50) Time until 25% of patients reach a ≥ 75% improvement in PASI (TOA-PASI75) Secondary outcomes for induction therapy (12–24 weeks) Mean change from baseline in swollen joint count (SJC), tender joint count (TJC) and health assessment questionnaire disability index (HAQ-DI) Rate of patients achieving an ACR50 response Rate of patients achieving a 75% reduction in Psoriasis Area and Severity Index (PASI 75) Rate of patients with ≥1 adverse event (AE) Rate of withdrawals due to AE
Study design	Randomized controlled trials only as these are the most rigorous methods for assessing efficacy

ACR modified American College of Rheumatology Response Criteria, *bDMARDS* biological disease-modifying anti-rheumatic drugs, *csDMARDs* conventional synthetic disease-modifying anti-rheumatic drugs, *PASI* Psoriasis Area Severity Index, *PsA* psoriatic arthritis, *tsDMARDs* targeted synthetic disease-modifying anti-rheumatic drugs

[a]The choice of included drugs was based on the 2015 updated EULAR recommendations for the management of PsA with drug therapy [8]. Included agents had to be approved for treating PsA or mentioned in the recommendation as being currently under investigation

Time until onset of action (TOA)

The time until onset of action (TOA) was extracted from graphs, as done previously [14]. We assumed a linear relationship between two neighboring data points. While this method provides us with a point estimate of the duration of time until efficacy onsets, we have no measure of precision precluding further analysis. To determine 95% confidence intervals (CI), we developed a new approach that generates estimates from aggregated data reported in graphs. It is possible to determine 95% CI for any given rate. For instance, let us assume that $n = 55$ out of $N = 220$ participants in a trial—or 25% of the participants—reach the outcome ACR20 at time X. This is the time until onset of action (TOA), see Fig. 1a. It is possible to calculate the 95% CI for the rate of participants reaching ACR20 at time X using regular statistical software, such as Open Epi [15]. The CI for our rate would be 19.74–31.12% of participants.

We now suggest that to determine the 95% CI of the TOA for which 25% of participants reached ACR20, we assume that the lower 95% CI limit for TOA would be equal to time X at which the upper 95% CI limit for a given rate equals approximately 25%, see Fig. 1b. In our example, 19.09% (closest value in OpenEpi to 19.74%) is equal to $n = 42$ out of the $N = 220$ participants with ACR20 response, for which the 95% CI would be 14.45–24.80%. Theoretically, this was calculated backwards by transpositioning the Wilson Score interval equation whereby Z alpha was set for 95% (1.96), n is the denominator—in this case 220 patients, and we are looking for a (see formula). This, a, is the rate of patients for which the upper confidence interval limit is equal to 25%.

$$p_{\mathrm{LB}} = \frac{n}{n + Z^2_{1-\alpha/2}}\left[\frac{a}{n} + \frac{Z^2_{1-\alpha/2}}{2n} - Z^2_{1-\alpha/2}\sqrt{\frac{a(n-a)}{n^3} + \frac{Z^2_{1-\alpha/2}}{4n^2}}\right]$$

In other words, the point in time at which 19.09% of participants reached ACR20, corresponds to the point in time that barely excludes the rate of 25% of participants in its upper 95% CI and therefore determines the lower 95% CI limit for the point in time.

Likewise, we assume that the upper 95% CI limit of TOA corresponds to the point in time at which the lower 95% CI limit for a given rate equals 25%, see Fig. 1c. Using the same example with 220 participants, if 68 (or 30.91%) of the 220 participants reached ACR20, the 95% CI would be 25.17–37.30%. Again, we used the above-mentioned formula to calculate a. In other words, the point in time at which 30.91% of participants reached ACR20, corresponds to the point in time that barely excludes the rate of 25% of participants in its lower 95% CI and therefore determines the upper 95% CI limit for the point in time.

Lastly, we extracted the time at which 19.09% and 30.91% of participants achieved ACR20 from the graph, see Fig. 1d. In our example, TOA-ACR20 would be 5 weeks with a 95% CI from 3 to 7 weeks.

Risk of bias assessment

We used the Risk of Bias 2.0 tool to evaluate the risk of bias [16]. The tool evaluates bias arising from the randomization process, deviations from intended interventions, missing outcome data, measurement of the outcome and selection of the reported result. We focused on the result TOA-ACR20.

Analysis

We pooled TOA data where two or more study arms on the same intervention were available and disease severity at baseline was comparable. Stata SE14 was used to analyze data using a random-effects model (metan command package). Heterogeneity was assessed using the I^2 statistic following Cochrane guidance [17]. Sensitivity analyses were performed where necessary.

When comparing TOA data from head-to-head trials, we followed Greenland and colleagues [18]:

1. If the 95% CI fail to overlap, we assume $p < 0.05$.
2. If one 95% CI contains the points estimate of the other drug, we assume $p > 0.05$.

Results

The search was conducted on March 1st 2017 (Auto-alerts until April 26th 2018). In total, 5073 articles were identified. After removing duplicates, title/abstract screening lead to the exclusion of 3782 abstracts. A total of 31 articles involving 26 trials were included. The detailed record selection process is shown in Figure S2 (Appendix B). Excluded full-text records with reasons are listed in Table S7 (see Appendix F).

ICTRP was screened on April 25th 2018 yielding no further RCTs. We requested missing TOA data from 23 first authors (response rate 52%). Four authors (17%) provided data.

Study characteristics

We included 26 RCTs. Study characteristics are summarized in Table S3 (Appendix C). The overall study population consists of 5808 patients. Of the included studies, 6 study arms investigated adalimumab, 3 apremilast, 2 certolizumab pegol, 1 etanercept, 3 golimumab, 3 infliximab, 1 infliximab plus methotrexate, 4 ixekizumab, 1 methotrexate, 8 secukinumab, 6 tofacitinib, and 5 ustekinumab. Three

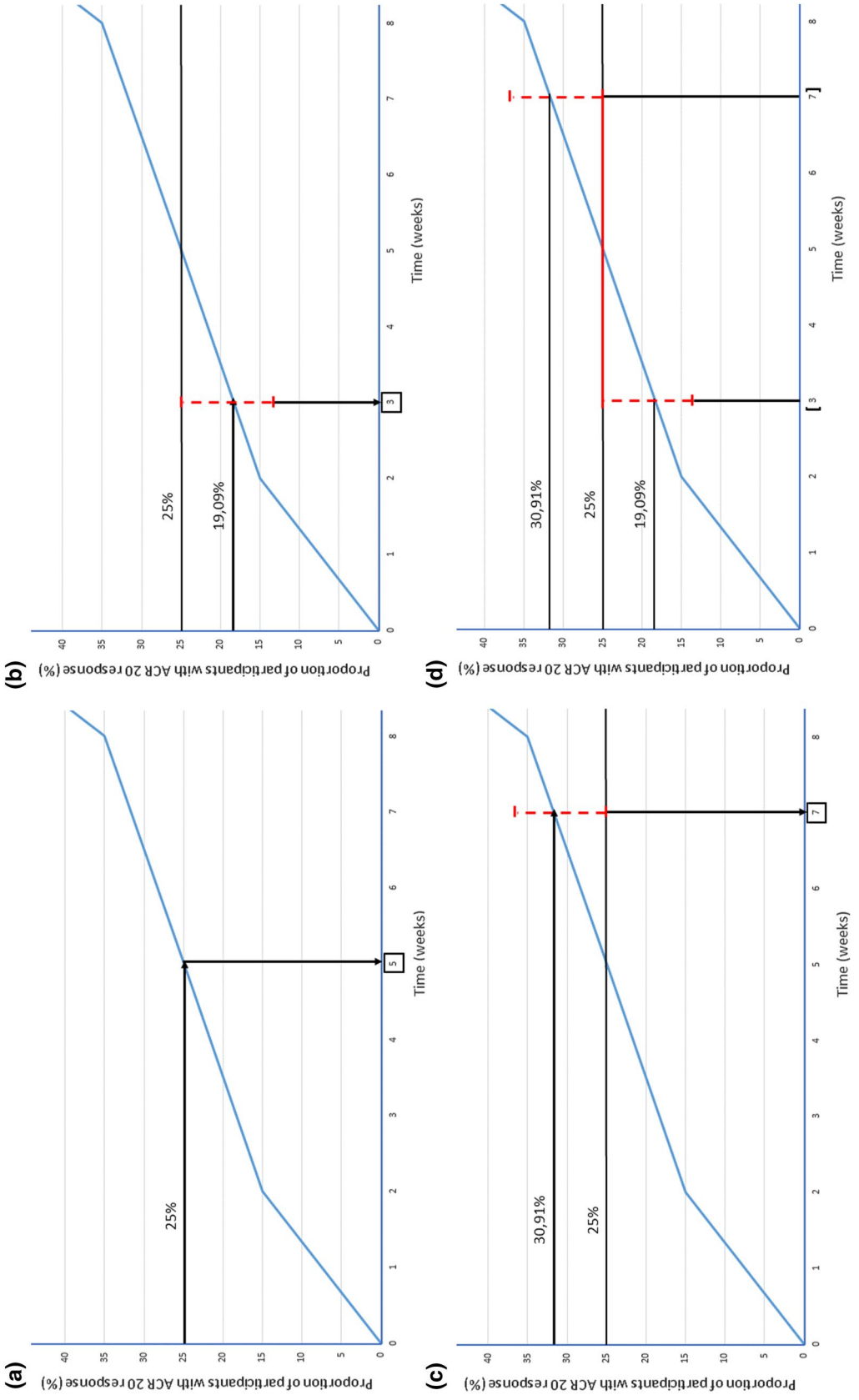

Fig. 1 Explanation of generating confidence intervals

studies included head-to-head comparisons of active treatments. No suitable TOA-data could be identified for CSA, GUS, LEF and SSZ.

TOA-ACR20

For forty-three study arms, the time until 25% of patients achieved ACR20 was reported. Table 2 shows all TOA-ACR20 results with their 95% confidence intervals (95% CI). For pooled TOA-ACR20 data, see Fig. 2.

Head-to-head comparison

The number of direct comparisons was limited to 14 trials (Table 2). Only three trials reported different drug comparisons (B, I, J): the TOA-ACR20 was shorter in the infliximab plus MTX arm (0.95 w [95% CI 0.56–1.39] than in the MTX monotherapy arm (3.81 w [95% CI 2.38–5.25]) in study B [19]. In another study (J) comparing TOF 5 mg and TOF 10 mg with ADA 40 mg, no differences were seen (2.42 w [95% CI 1.49–3.88] vs 1.58 w [95% CL 1.02–2.26] vs 2.98 w [95% CI 1.58–4.62], respectively) [20]. An equally rapid TOA-ACR20 was measured for ADA 40 mg, IXE Q2W and IXE Q4W (study I: 0.98 w [95% CI 0.65–2.29], 0.98 w [95% CI 0.74–1.47], 1.14 w [95% CI 0.82–1.71], respectively) [21].

Thirteen studies compared different dosing regimens of each of the following treatments: APR, CZP, GOL, IXE, SEC, TOF and UST. No differences were seen between APR 40 mg once daily and APR 20 mg taken twice daily (N) [22], CZP 200 mg Q2W and 400 mg Q4W (G) [23], or comparing low-dose and high-dose GOL (D) [24, 25], see Table 2. The results for TOA-ACR20 were similar for SEC 75 mg, 150 mg and 300 mg (pooled F, H, L. see Fig. 2) [26–28]. Pooled ACR-20 results comparing low and high-dose tofacitinib showed no differences for low-dose and high-dose regimens (pooled A, C, J, see Fig. 2) [20, 29, 30]. Similarly, no differences were seen for UST 45 mg compared to UST 90 mg (pooled E, M, see Fig. 2) [31, 32].

Single study arms

TOA-ACR20 results for different treatment regimens of CZP and IXE were pooled since the outcome was reached within the time of loading dose administration in all study arms before alterations in treatment applied. APR was pooled due to the same daily dose in both arms, see Fig. 2.

Overall, 20 study arms showed an onset within less than 2 weeks, 17 study arms between 2 and 4 weeks and 6 study arms after more than 4 weeks (for details, see Table 2).

TOA-ACR50

Twenty-six studies reported on ACR50 but in six studies the TOA-ACR50 could not be measured because ACR50 was evaluated < 2 times within 16 weeks after initiation of treatment, see Table 3. Pooled results are presented in Fig. 3.

Head-to-head comparisons

A study (B) comparing the efficacy of INF plus MTX vs MTX monotherapy showed a faster TOA-ACR50 in the INF plus MTX group than the MTX monotherapy group (3.64 w [95% CL 2.49–4.76] vs 10.04 w [95% CL 7.20–12.84]) [19]. One study (I) compared adalimumab and ixekizumab. The TOA-ACR50 showed no difference between ADA 40 mg, IXE 80 mg Q2W and Q4W (5.97 w [95% CI 3.56–14.30] vs 3.39 w [95% CL 2.31–5.73] vs 8.07 w [95% CI 5.29–18.58]) [21]. In another head-to-head trial (J), the TOA-ACR50 for ADA 40 mg was similar compared to TOF 5 mg or 10 mg (8.87 w [95% CI 6.10–12.00] vs 10.09 w [95% CL 6.04–15.05] vs 5.68 w [95% CL 3.55–8.60]) [20].

Different dosing regimens were compared for CZP, GOL, IXE, SEC and TOF. No difference was seen between CZP 200 mg Q2W and 400 mg Q4W (G) [23, 33] and GOL 50 mg and 100 mg (D) [24, 25]. IXE Q2W was similar to IXE Q4W in time until onset of action (pooled I, K, see Fig. 3) [21, 34]. Pooled TOA-ACR50 results showed no differences between SEC 150 mg and SEC 300 mg (pooled F, H, L, see Fig. 3) [26–28]. The additional SEC 75 mg arm in one SEC trial (F) did not reach the outcome within the observed time [27]. No differences were found between low and high-dose TOF (pooled A, C, J) [20, 29, 30].

Single study arms

Additionally, we were able to pool 6 study arms evaluating ADA; see Fig. 3.

Generally, the TOA-ACR50-results extracted from individual study arms ranged from 2.29 weeks [95% CI 0.00–5.93] for TOF 10 mg [30] as the shortest and 27.28 weeks [95% CI 11.47–NA[a]] for SEC 150 mg as the longest TOA-ACR50 [28]. Overall, 6 study arms showed an TOA-ACR50 within less than 4 weeks, 12 study arms between 4 and 8 weeks and 15 study arms after more than 8 weeks (for details; see Table 3).

TOA-PASI75

PASI75 was assessed in 19 studies of which 11 yielded data for the TOA-PASI75 calculations. For the remaining

Table 2 Time until 25% of the patients achieved at least an ACR20 response: individual results (in weeks) of included study arms

Study	Treatment	TOA-ACR20 in weeks	95% CI	Risk of Bias 2.0	
2.1 Data from studies with placebo as comparator					
Antoni 2005 [36]	*INF 5 mg/kg/BW*	*1.18*	*0.60–1.70*	Low	
Antoni 2005 [35]	*INF 5 mg/kg/BW*	*1.65*	*1.14–2.66*	Low	
Genovese 2007 [37]	*ADA 40 mg Q2W*	*3.05*	*1.97–10.64*	Low	
Gottlieb 2009 [38, 56]	UST 90 mg Q1W	2.41	1.63–3.56	Low	
Kavanaugh 2017 [39]	GOL 2 mg/kg/BW Q8W	1.11	0.86–1.32	Low	
McInnes 2014 [41]	SEC 10 mg at d1 + d22	1.99	0.63–22.83	Some concerns	
Mease 2004 [43]	ETN 25 mg BIW	2.50	1.61–3.49	Some concerns	
Mease 2005 [42]	*ADA 40 mg Q2W*	*1.84*	*1.33–2.38*	Some concerns	
Mease 2017 [46]	*ADA 40 mg Q2W*	*2.43*	*1.53–3.19*	Some concerns	
Nash 2018 [48]	APR 30 mg BID	4.09	2.36–5.09	High	
Torii 2010 [44]	*INF 5 mg/kg/BW*	*0.74*	*0.00–1.49*	Some concerns	
van Kuijk 2009 [45]	*ADA 40 mg at d1 + d15, then Q2W*	*2.42*	*0.00–5.52*	Some concerns	
					Study ID
2.2 Head-to-head comparisons					
Asahina 2016 [30]	*TOF 10 mg BID*	*0.89*	*0.00–2.09*	Low	A
	TOF 5 mg BID	*2.68*	*0.00–6.56*		
Baranauskaite 2012 [19]	**INF 5 mg/kg/BW + MTX 15 mg/w**	**0.95**	**0.56–1.39**	High	B
	MTX 15 mg/w	**3.81**	**2.38–5.25**		
Gladmann 2017 [29, 47]	*TOF 10 mg BID*	*1.79*	*1.24–2.52*	High	C
	TOF 5 mg BID	*1.96*	*1.36–3.58*		
Kavanaugh 2009 [24, 25]	GOL 100 mg Q4W	2.80	2.00–3.51	Low	D
	GOL 50 mg Q4W	3.26	2.34–4.23		
McInnes 2013 [31]	*UST 45 mg Q12W*	*5.74*	*4.21–7.16*	Low	E
	UST 90 mg Q12W	*5.19*	*3.85–6.54*		
McInnes 2015 [27]	*SEC 150 mg Q4W*	*2.06*	*1.52–2.52*	Low	F
	SEC 300 mg Q4W	*2.35*	*1.74–3.04*		
	SEC 75 mg Q4W	*3.17*	*2.11–6.62*		
Mease 2014 [23, 33]	CZP 200 mg Q2W	1.30	0.86–1.90	Low	G
	CZP 400 mg Q4W	1.10	0.77–1.93		
Mease 2015 [26]	*SEC 150 mg Q4W*	*1.42*	*0.86–2.14*	Low	H
	SEC 75 mg Q4W	*1.28*	*0.86–1.71*		
Mease 2016 [21]	***ADA 40 mg Q2W***	***0.98***	**0.65–*2.29***	Low	I
	IXE 80 mg Q2W	***0.98***	***0.74*–1.47**		
	IXE 80 mg Q4W	***1.14***	**0.82–*1.71***		
Mease 2017 [20, 40]	***ADA 40 mg Q2W***	***2.98***	**1.58–*4.62***	Low	J
	TOF 10 mg BID	***1.58***	**1.02–*2.26***		
	TOF 5 mg BID	***2.42***	**1.49–*3.88***		
Nash 2017 [34]	*IXE 80 mg Q2W*	*1.68*	*0.70–3.57*	Low	K
	IXE 80 mg Q4W	*0.97*	*0.65–1.57*		
Nash 2018 [28]	*SEC 150 mg Q4W*	*2.98*	*2.11–3.65*	Low	L
	SEC 300 mg Q4W	*2.11*	*1.06–2.69*		
Ritchlin 2014 [32]	*UST 45 mg Q12W*	*6.19*	*4.07–7.30*	Some concerns	M
	UST 90 mg Q12W	*6.07*	*4.00–8.71*		
Schett 2012 [22]	*APR 20 mg BID*	*3.58*	*1.95–5.79*	High	N
	APR 40 mg QD	*4.79*	*1.98–8.59*		

Italics—pooled in meta-analysis, see Fig. 2. Bold text—different drugs/combinations are compared

BW body weight, *BID* twice a day, *BIW* twice weekly, *CI* confidence interval, *d* day, *ES* point estimate, *PBO* placebo, *QD* once per day, *Q1W* once per week, *Q2W* every 2 weeks, *Q4W* every 4 weeks, *TOA* time until onset of action

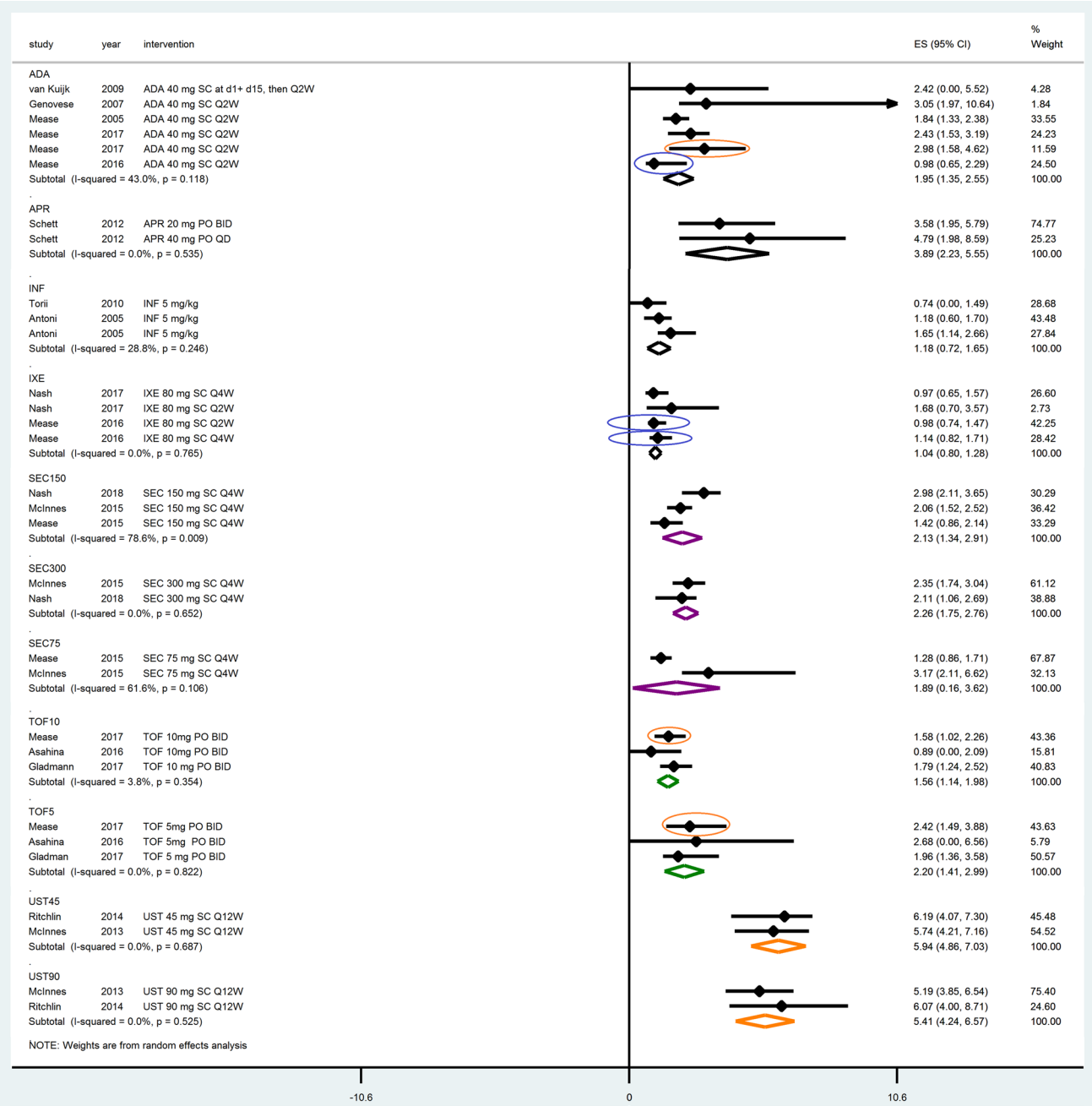

Fig. 2 Time until 25% of patients achieved an ACR20 response (in weeks): pooled results. Same colored diamonds (purple, green and orange) can be compared directly as pooled data originated from head-to-head trials; same colored circle indicate that study arms come from the same study

eight studies, the TOA-PASI75 could not be measured because the PASI75 was evaluated < 2 times within 16 weeks.

Head-to-head comparisons

No differences between INF plus MTX compared to MTX monotherapy were seen (B; 3.66 w [95% CI 2.53–4.72] vs 8.47 w [95% CI 3.29–14.34]) [19]. In one study (I), the TOA-PASI75 was slower for ADA than IXE administered Q2W and Q4W (8.76 w [95% CI 5.91–13.05] vs 2.48 w [95% CI 1.71–3.33] and 2.00 w [95% CI 1.43–2.76]) [21]. In another trial (J), the TOA-PASI75 was comparable for ADA 40 mg, TOF 5 mg and TOF 10 mg (7.50 w [95% CI 4.29–10.62] vs 4.82 w [95% CI 2.71–8.51] vs 3.70 w [95% CI 2.07–7.98]) [20].

Table 3 Time until 25% of the patients achieved at least an ACR50 response: individual results (in weeks) of included study arms (for RoB 2.0 see Table 2)

Study	Treatment	TOA-ACR50 in weeks	95% CI	
3.1 Data from studies with PBO as comparator				
Antoni 2005 [35]	INF 5 mg/kg/BW	7.50	4.50–12.16	
Genovese 2007 [37]	*ADA 40 mg Q2W*	*11.60*	*3.68–14.30*	
Gottlieb 2009 [38, 56]	UST 90 mg Q1W	12.00	3.99–NA[a]	
Kavanaugh 2017 [39]	GOL 2 mg/kg/BW Q8W	4.31	3.15–6.34	
McInnes 2014 [41]	SEC 10 mg at d11 + 22	7.35	1.84–NA[a]	
Mease 2004 [43]	ETN 25 mg BIW	8.12	5.58–10.57	
Mease 2005 [42]	*ADA 40 mg Q2W*	*3.87*	*3.07–8.79*	
Mease 2017 [46]	*ADA 40 mg Q2W*	*6.69*	*4.37–10.43*	
van Kuijk 2009 [45]	*ADA 40 mg d1 + d15, then Q2W*	*3.05*	*0.00–9.34*	
				Study ID
3.2 Data from head-to-head studies				
Asahina 2016 [30]	*TOF 10 mg BID*	*2.29*	*0.00–5.93*	A
	TOF 5 mg BID	*3.78*	*0.00–10.47*	
Baranauskaite 2012 [19]	**INF 5 mg/kg/BW + MTX 15 mg Q1W**	**3.64**	**2.49–4.76**	B
	MTX 15 mg/w Q1W	**10.04**	**7.20–12.84**	
Gladmann 2017 [29, 47]	*TOF 10 mg BID*	*8.00*	*4.01–13.10*	C
	TOF 5 mg BID	9.78	6.32–NA[a]	
Kavanaugh 2009 [24, 25]	GOL 100 mg Q4W	10.02	5.42–17.27	D
	GOL 50 mg Q4W	9.30	6.35–16.52	
McInnes 2015 [27]	*SEC 150 mg Q4W*	*6.32*	*4.99–11.46*	F
	SEC 300 mg Q4W	*7.36*	*3.72–14.66*	
	SEC 75 mg Q4W	Not reached[a]	NA[a]	
Mease 2014 [23, 33]	CZP 200 mg Q2W	6.61	3.74–9.27	G
	CZP 400 mg Q4W	9.03	3.80–12.05	
Mease 2015 [26]	*SEC 150 mg Q4W*	*8.29*	*4.99–11.46*	H
	SEC 75 mg Q4W	8.06	5.74–14.69	
Mease 2016 [21]	***ADA 40 mg Q2W***	***5.97***	**3.56–*14.30***	I
	IXE 80 mg Q2W	***3.39***	**2.31–*5.73***	
	IXE 80 mg Q4W	***8.07***	**5.29–*18.58***	
Mease 2017 [20, 40]	***ADA 40 mg Q2W***	***8.87***	**6.10–*12.00***	J
	TOF 10 mg BID	***5.68***	**3.55–*8.60***	
	TOF 5 mg BID	***10.09***	**6.04–*15.05***	
Nash 2017 [34]	*IXE 80 mg Q2W*	*10.16*	*8.43–11.89*	K
	IXE 80 mg Q4W	*7.57*	*4.65–22.09*	
Nash 2018 [28]	SEC 150 mg Q4W	27.28	11.47–NA[a]	L
	SEC 300 mg Q4W	*8.00*	*4.05–16.77*	

Italics text—pooled in meta-analysis, see Fig. 3. Bold text—different drugs/combinations are compared

NA not available

[a]Value was not reached within study period

Different dosing regimens were compared for CZP, GOL, IXE, and TOF. In one study (G) CZP 200 mg Q2W and CZP 400 mg Q1W were comparable [23, 33]. The TOA-PASI75 for low-dose and high-dose GOL was similar (D) [24, 25]. No differences between IXE 80 mg Q2W and IXE 80 mg Q4W (pooled I, K; see Figure S5) [21, 34] and between low-dose and high-dose TOF were found (pooled C, J; see Figure S5 (Appendix D)) [20, 29].

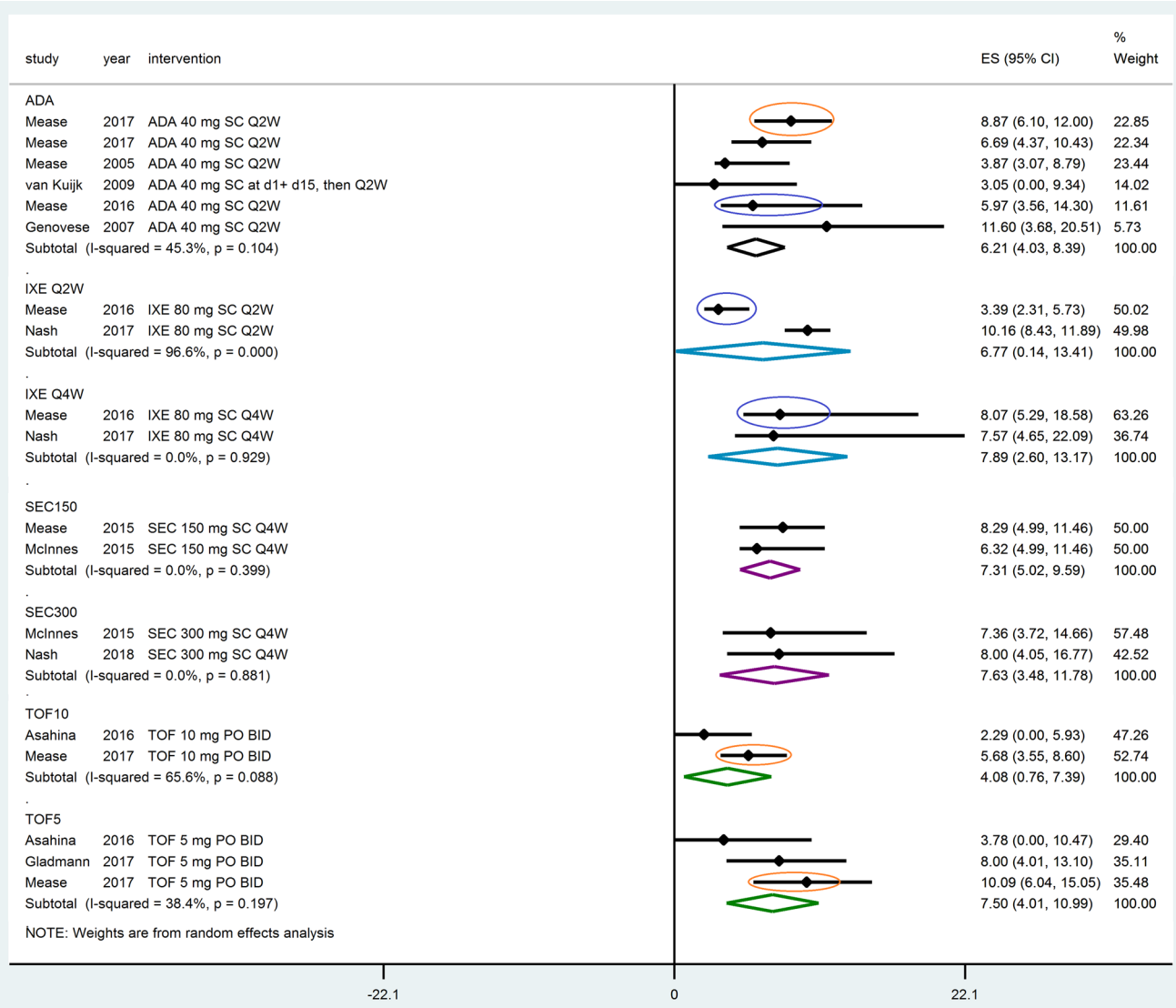

Fig. 3 Time until 25% of patients achieved an ACR50 response (in weeks): pooled results. Same colored diamonds (blue, purple, green) can be compared directly as pooled data originated from head-to-head trials; same colored circle indicates that study arms come from the same study

Single study arms

Furthermore, we were able to pool 4 study arms evaluating ADA; see Figure S5.

Largely, the TOA-PASI75 results extracted from individual study arms ranged from 1.96 weeks [95% CI 1.41–3.17] for ixekizumab Q2W as study arm (K) with the shortest and 15.63 weeks [95% CI 4.00–NA[a]] for tofacitinib (C) with the longest TOA-PASI75. In all, 8 study arms showed an TOA-PASI75 within less than 4 weeks, 7 study arms between 4 and 8 weeks and 5 study arms after more than 8 weeks [for details, see Table S4 (Appendix D)].

Secondary outcomes

Results of secondary outcomes for individual studies are summarized in Table S6 (Appendix E) but are not the focus here.

Heterogeneity

Considerable heterogeneity was seen for the outcome ACR50, IXE Q2W ($I^2 = 96.6\%$; 2 studies) and ACR20, SEC150 ($I^2 = 78.6\%$; 3 studies) as well as substantial heterogeneity for ACR20 SEC75 ($I^2 = 61.1\%$; 2 studies), ACR50 TOF10 ($I^2 = 65.5\%$; 2 studies) and PASI75 ADA 40 mg

($I^2 = 67.1\%$; 4 studies). We investigated the influence of risk of bias and clinical differences (see Appendix G). Sensitivity analysis were performed for the latter which yielded a similar result (see Appendix G). In all other cases, either sensitivity analyses could not be performed since only two studies reported the outcome, or we were unable to identify plausible reasons to justify the exclusion of data (in case of ACR20, SEC 150 mg). Lastly, we considered the impact of studies evaluated as high risk of bias, which was only the case once. Sensitivity analyses yielded a similar result (ACR20, TOF 10 mg).

Bias Assessments

RoB varied among studies. Fifteen RCTs had an overall low risk [21, 23, 25–28, 30, 31, 34–40], seven study reports raised some concerns [32, 41–46]. Four had a high risk RoB [19, 22, 47, 48]. The latter was considered in the analyses but none of those study arms had been eligible for pooling. The overall risk of bias assessments for TOA-ACR20 is shown in Table 2. Details are available upon request.

Publication bias did not become apparent but cannot be pre-cluded [49], even though trial registers were searched and authors/companies contacted.

Discussion

We conducted a systematic review on the time until onset of action for different PsA treatments and developed a new method of generating confidence intervals from graphical data.

Infliximab plus MTX is faster than MTX alone. No difference was seen between ixekizumab and adalimumab or adalimumab and tofacitinib in the onset of action for the psoriatic arthritis outcomes (ACR) but ixekizumab had a faster onset than adalimumab concerning skin improvement (PASI75). When results from head-to-head trials are pooled with data from the other eligible placebo-controlled trials, we see a similar trend but now, ixekizumab and tofacitinib 10 mg are faster than adalimumab for ACR20, too. Confidence intervals no longer overlap due to the larger sample sizes. However, the compared results originate from head-to-head and between-study comparisons. That said, only the results obtained from one study [47] present with a high risk of bias.

When comparing across studies, a fast onset of action (< 2 weeks) for certolizumab pegol, golimumab 2 mg/kg bodyweight, infliximab, infliximab plus methotrexate, ixekizumab, and tofacitinib (10 mg) was seen. An onset of action later than 2 weeks was seen for adalimumab, secukinumab (75 mg, 150 mg and 300 mg), tofacitinib (5 mg) and etanercept. A comparably delayed onset was indicated for apremilast, methotrexate and ustekinumab (90 mg and 45 mg) with onsets of action after more than 5 weeks. For ACR50 pooled results indicate an onset of action between 6 and 8 weeks for most drugs. Fewer studies reported data suitable for generating time until onset of action data for the outcomes ACR50 and even fewer for PASI75. However, assessing skin activity is a core outcome for PsA and should be evaluated in studies more regularly [50]. A recent review reported an onset time for ixekizumab of 2.4 weeks considering PASI75 which is very similar to our results [51]. The results are also very similar to those identified by our previous review about the time until onset of action of drugs in psoriasis vulgaris [14].

Furthermore, ustekinumab has been reported to have a slower onset of action than adalimumab elsewhere too [52]. The delayed onset of MTX compared to all other drugs except for apremilast and ustekinumab is not surprising since a large RCT found no difference between methotrexate and placebo [53]. Though evidence remains scarce [54].

Dose comparison trials do not show clear results in favor of lower or higher doses/treatment intervals for onset of action outcomes.

To provide a precision estimate, we developed the novel approach to provide a 95% confidence interval for time until onset of action data and pooled results for comparable interventions. When making indirect comparison, results from individual study arms across studies should be treated as if they were derived from observational studies and thus are susceptible to bias, such as confounding bias.

The data extraction approach assumes a linear relationship between assessment times. Thus, the accuracy of data depends greatly on the frequency of assessments. We reduced this source of bias by excluding studies not reporting at least two data points. Another drawback to our method of generating confidence intervals is that the data cannot be verified. Onset of action data is not usually measured in trials and to our knowledge, no other method to generate this data exists.

Overall, few head-to-head trials exist. No trials on csDMARDs with exception of MTX could be included due to the absence of a comparable outcome. This evidence gap may lead to bias underestimating the effect of csDMARDs. Furthermore, the cut-off point of 25% was chosen, as a higher percentage is not reached under some interventions, which mean we would not have been able to compare drugs. Few studies were available for each drug, which may limit the reliability of the findings. To add, on several occasions we were only able to pool data from two studies and in same cases heterogeneity was high—uncertainty remains when drawing conclusions.

Assessing time until onset of action becomes even more relevant when comparing different drugs that have a comparable efficacy. Patients, physicians and other healthcare

professionals may use results when discussing the nature of treatment responses. Future trials should collect data on the main efficacy outcomes early on and more frequently.

Conclusion

We developed a new method of generating confidence intervals from graphs to meta-analyze time until onset of action of different drugs. This review is the first to investigate the onset of action in the treatment of PsA. Comparisons suggest a more rapid onset of certolizumab pegol, infliximab, infliximab plus methotrexate, ixekizumab and tofacitinib compared to apremilast, methotrexate and ustekinumab for ACR20 but almost never for ACR50. However, general conclusions on the drug with the fastest onset of action cannot be drawn due to limited evidence and variation in study quality. Future trials should consider incorporating time until onsets as an outcome measure.

Author contributions PAP: design, data acquisition, analysis and interpretation, and drafting the manuscript. CD: design, data acquisition, analysis and interpretation. LE: design, data acquisition. AN: conception, design. RNW: conception, design and data interpretation. All authors have revised the manuscript critically for important intellectual content and approved the final manuscript. Furthermore, all authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. No external writing or editing support was involved.

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Compliance with ethical standards

Conflict of interest Authors Phuong Anh Pham (PAP), Dr. Corinna Dressler (CD), Ricardo N. Werner, MD (RNW) declare that they have no conflicts of interest. Author Lisa Eisert, MD (LE) has received seminar participation fees from Pfizer (Enbrel), Leo Pharma (Daivobet, Protopic, Enstilar). Author Prof. Alexander Nast, MD (AN) has received institutional research grants/participated as an investigator (without personal honoraria) in research projects, advisory activities or trials from the following companies with an interest in psoriatic arthritis: Lilly, Novartis, Dermira. AN has received personal honoraria for lectures/educational activities from the following companies which—to his knowledge—currently have no interest in psoriatic arthritis: Bayer Healthcare, Pierre Fabre, Boehringer Ingelheim.

Ethical approval This article does not contain any studies with human participants or animals performed by any of the authors.

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