



A Systematic Review With Network Meta-Analysis of the Available Biologic Therapies for Psoriatic Disease Domains

Tiago Torres^{1,2*}, Anabela Barcelos^{3,4,5†}, Paulo Filipe^{6,7,8} and João Eurico Fonseca^{9,10}

¹ Department of Dermatology, Centro Hospitalar Universitário do Porto, Porto, Portugal, ² Multidisciplinar Medical Research Unit, Instituto de Ciências Biomédicas Abel Salazar, University of Porto, Porto, Portugal, ³ Rheumatology Department, Centro Hospitalar do Baixo Vouga, Aveiro, Portugal, ⁴ NOVA National School of Public Health, Public Health Research Centre, Universidade NOVA de Lisboa – Portugal, Lisbon, Portugal, ⁵ Comprehensive Health Research Center (CHRC), Universidade NOVA de Lisboa – Portugal, Lisbon, Portugal, ⁶ Serviço de Dermatologia e Venereologia, Hospital de Santa Maria, Centro Hospitalar Universitário Lisboa Norte, Lisbon, Portugal, ⁷ Unidade de Investigação em Dermatologia, Instituto de Medicina Molecular João Lobo Antunes, Faculdade de Medicina, Universidade de Lisboa, Lisbon, Portugal, ⁸ Clínica Universitária de Dermatologia, Faculdade de Medicina da Universidade de Lisboa, Lisbon, Portugal, ⁹ Serviço de Reumatologia e Doenças Ósseas Metabólicas, Hospital de Santa Maria, Centro Hospitalar Universitário Lisboa Norte, Lisbon, Portugal, ¹⁰ Unidade de Investigação em Reumatologia, Instituto de Medicina Molecular João Lobo Antunes, Faculdade de Medicina, Universidade de Lisboa, Lisbon, Portugal

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*Correspondence:

Tiago Torres
torres.tiago@outlook.com

†These authors have contributed
equally to this work

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Introduction: Several new treatments have been developed for psoriatic disease, an inflammatory condition that involves skin and joints. Notwithstanding, few studies have made direct comparisons between treatments and therefore it is difficult to select the ideal treatment for an individual patient. The aim of this systematic review with network meta-analysis (NMA) was to analyze available and approved biologic therapies for each domain of psoriatic disease: skin, peripheral arthritis, axial arthritis, enthesitis, dactylitis, and nail involvement.

Methods: Data from randomized clinical trials (RCTs) were included. A systematic review was performed using the MEDLINE database (July 2020) using PICO criteria. Bayesian NMA was conducted to compare the clinical efficacy of biological therapy in terms of the American College of Rheumatology criteria (ACR, 24 weeks) and Psoriasis Area and Severity Index (PASI, 10–16 weeks).

Results: Fifty-four RCTs were included in the systematic review. Due to the design of the RCTs, namely, outcomes and time points, network meta-analysis was performed for skin and peripheral arthritis domains. For the skin domain, 30 studies reporting PASI100 were included. The peripheral arthritis domain was analyzed through ACR70 in 12 studies. From the therapies approved for both domains, secukinumab and ixekizumab were the ones with the highest probability of reaching the proposed outcomes. There is a lack of outcome uniformization in the dactylitis, enthesitis, and nail domains, and therefore, an objective comparison of the studies was not feasible. Nevertheless, secukinumab was the treatment with the best compromise between the number of studies in each domain and the results obtained in the different outcomes.

Conclusion: Secukinumab and ixekizumab were the treatments with the highest probability of reaching both PASI100 and ACR70 outcomes. Due to the lack of a standard evaluation of outcomes of the other psoriatic disease domains, a network meta-analysis for all the domains was not possible to perform.

Keywords: psoriasis, psoriatic arthritis, psoriatic disease, biologic therapy, systematic review, network meta-analysis

INTRODUCTION

Psoriasis (PsO) affects 1–3% of the world population. Psoriatic arthritis (PsA) occurs in a third of the patients with PsO. These two conditions share clinical, genetic, and pathogenic factors and can be considered a single entity—psoriatic disease (PsD) (1–3).

PsD involves chronic inflammation of the skin, nails, and joints (arthritis, enthesitis, dactylitis, and spondylitis) (4). Autoimmune mechanisms are involved in PsA pathogenesis, and this is ultimately related with the systemic nature of the disease and raised the concept of a Systemic Psoriatic Disease. This fact highlights the heterogeneity of the disease and the need for optimizing its management (5).

Optimal management of PsD requires early diagnosis, monitoring of the disease activity, and treatment with effective and safe therapies. Over the last 20 years, targeted therapies emerged in the treatment of PsD, namely, biologic agents such as tumor necrosis factor inhibitors (TNFi), IL-17 inhibitors (IL-17i), and IL-12/23 inhibitors (IL-12/23i), and small molecules, such as Janus Kinase (JAK) or phosphodiesterase 4 (PDE4) inhibitors (6).

The Group for Research and Assessment of Psoriasis and Psoriatic Arthritis (GRAPPA) is a global association of more than 500 rheumatologists, dermatologists, and patient research partners that publish treatment recommendations for PsD (2). The treatment of six domains—peripheral arthritis, axial disease, enthesitis, dactylitis, skin disease, and nail disease—are included in the recommendations directed to anyone involved in the treatment of patients with PsD (2). Based on these recommendations, we performed a systematic review and network meta-analyses assessing the main results of randomized clinical trials (RCT) including biologic therapies in the treatment of patients with PsD.

METHODS

Literature Search

A literature search according to the Population, Intervention, Comparator, Outcomes (PICO) framework was performed establishing criteria for study eligibility. The population was defined as adult (≥ 18 years) patients with the PsD (PsO and/or PsA) and the intervention as any biologic therapy: adalimumab (ADA), etanercept (ETN), infliximab (IFX), golimumab (GOL), certolizumab (CZP), ustekinumab (UST), secukinumab (SEC), ixekizumab (IXE), guselkumab (GUS), brodalumab (BRD), risankizumab (RIS), and tildrakizumab (TIL), in all formulations and treatment durations. The comparator was the same drug (different dose or regimen), any different drug, or placebo.

Outcomes considered were American College of Rheumatology (ACR) or Psoriasis Area Severity Index (PASI) or dactylitis assessment or enthesitis assessment or nail psoriasis assessment. The MEDLINE database search was performed on 1 July 2020, with the filters “Humans,” “Clinical Trials,” “Phase III,” and “English,” with no date limits. In line with the GRAPPA and EULAR recommendations, we did not include abatacept in this systematic review. In addition, as this systematic review was focused only on biologic treatments apremilast and tofacitinib were not analyzed.

Statistics and Network Meta-Analyses

Network meta-analyses (NMA) were carried out using the web application CINeMA 1.9.0 (Confidence in Network Meta-Analysis) from Cochrane (7). This application is based on a described methodological framework that considers six domains: within-study bias, reporting bias, indirectness, imprecision, heterogeneity, and incoherence (8). NMAs based on the Bayesian framework using the fixed-effects model were performed to pool all the direct and indirect evidence together. Odds ratio (OR) with 95% credible intervals (CrI) was used to evaluate comparisons. Only comparisons showing high confidence in the six domains were considered for the results.

Assessment of Bias

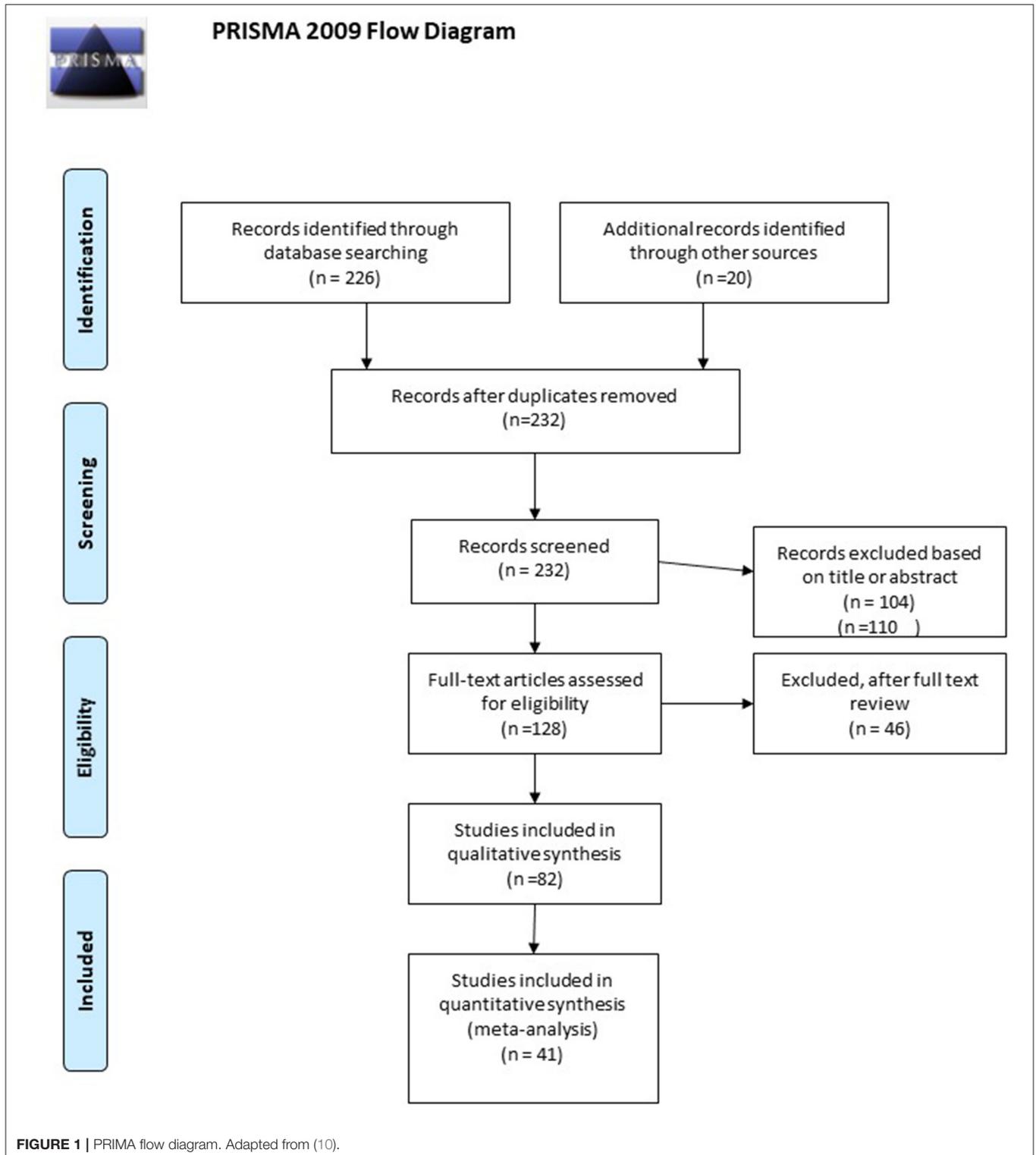
Assessment of bias was performed using the latest version of RoB2—Cochrane (9).

RESULTS

A detailed flowchart with the results of the literature review is shown in **Figure 1**. Out of the 232 references retrieved, 82 studies were selected for data (1, 11–57). For NMAs, only studies reporting ACR20, ACR50, ACR70 (peripheral arthritis domain), PASI75, PASI90, or PASI100 (skin domain) were included. For the peripheral arthritis domain, only 24 weeks were included. For the skin domain, results between 10 and 16 weeks were considered. Moreover, the doses of the drugs for the systematic review and NMAs, for the peripheral arthritis and skin domains, were the ones approved by the regulatory authorities. The studies included in the NMAs are identified in **Table 1**. Extension studies are specified in **Table 2** (48, 58–84). In **Figure 2** the drugs that have been studied specifically for each domain of PsD were included.

Peripheral Arthritis

The peripheral arthritis domain is predominantly assessed by instruments, such as ACR20, ACR50, and ACR70 criteria, which



specify the improvement of 20, 50, or 70% in the number of tender and swollen joints, respectively, and a 20, 50, or 70% improvement in three of the following five criteria: patient global assessment, physician global assessment, functional ability measure (most often Health Assessment Questionnaire—HAQ),

visual analog pain scale, and erythrocyte sedimentation rate or C-reactive protein (85). The main results of the ACR response in RCTs, at 24 weeks, are included in **Table 3** (1, 11, 18, 24, 26, 28, 31, 32, 37, 38, 47, 51, 55). The head-to-head comparison of the ACR responses of SEC vs. ADA at week

TABLE 1 | RCT included in the systematic review and NMA, focusing on the outcomes of GRAPPA domains.

Study	Enrolled patients						NMA
	Author	Year	N	Drug	Dosage	Outcomes	
IMPACT 2 (1)	Antoni	2005	200	IFX PLB	5 mg/kg	①②③④ ⑤⑥⑦⑧	YES
ADEPT (11)	Mease	2005	313	ADA PLB	40 mg	①②③ ④⑤⑥	YES
(12)	Reich	2005	378	IFX PLB	5 mg/kg	④⑤ ⑥⑩	YES
(13)	Genovese	2007	100	ADA PLB	40 mg	①②③ ⑦⑨	NO
(14)	Tyring	2007	618	ETN PLB	50 mg	④⑤⑥	YES
PHOENIX 1 (15)	Leonardi	2008	766	UST UST PLB	45 mg 90 mg	④⑤⑥	YES
PHOENIX 1 (16)	Papp	2008	1,230	UST UST PLB	45 mg 90 mg	④⑤⑥	YES
(17)	Rich	2008	378	IFX PLB	5 mg/kg	⑩	NO
(18)	Kavanaugh	2009	405	GOL GOL PLB	50 mg 100 mg	①②③ ④⑤⑥ ⑧⑨⑩	YES
(19)	Barker	2011	868	IFX MTX	5 mg/kg 15 mg	④⑤⑥	YES
(20)	Gottlieb	2011	347	BRK ETN PLB	200 mg 50 mg	⑤⑥⑦	YES
(21)	Strober	2011	350	BRK ETN PLB	200 mg 50 mg	⑤⑥⑦	YES
RESPOND (22)	Baranaukaite	2012	115	IFX + MTX MTX	5 mg/kg 15 mg	①②③ ⑤⑧⑨	NO
(23)	Gottlieb	2012	478	MTX + ETN	15 mg + 50 mg	④⑤⑥	NO
PSUMMIT 1 (24)	McInnes	2013	615	UST UST PLB	45 mg 90 mg	①②③ ⑥⑧⑨	YES
ERASURE (25)	Langley	2014	738	SEC SEC PLB	150 mg 300 mg	⑤⑥⑦	YES
FIXTURE (25)	Langley	2014	1,306	SEC SEC ETN PLB	150 mg 300 mg 50 mg	⑤⑥⑦	YES
RAPID-PsA (26)	Mease	2014	409	CZP CZP PLB	200 mg 400 mg	①②③ ④⑤⑥ ⑧⑨⑩	YES
PHOENIX 1 (27)	Rich	2014	766	UST UST PLB	45 mg 90 mg	④⑤ ⑥⑩	YES

(Continued)

TABLE 1 | Continued

Study	Enrolled patients						NMA
	Author	Year	N	Drug	Dosage	Outcomes	
PSUMMIT 2 (28)	Ritchlin	2014	312	UST UST PLB	45 mg 90 mg	①②③ ⑤⑧⑨	YES
UNOCOVERT 2 (29)	Griffiths	2015	1,224	IXE IXE ETN PLB	80 mg 2 w 80 mg 4 w 50 mg	⑤⑥⑦	YES
UNOCOVERT 3 (29)	Griffiths	2015	1,346	IXE IXE ETN PLB	80 mg 2 w 80 mg 4 w 50 mg	⑤⑥⑦	YES
AMAGINE-2 (30)	Lebwohl	2015	1,831	BRD BRD UST PLB	140 mg 210 mg 45/95 mg	⑤⑦	YES
AMAGINE-3 (30)	Lebwohl	2015	1,881	BRD BRD UST PLB	140 mg 210 mg 45/95 mg	⑤⑦	YES
FUTURE 2 (31)	McInnes	2015	397	SEC SEC SEC PLB	75 mg 150 mg 300 mg	①②③ ⑤⑥⑧	YES
(32)	Mease	2015	606	SEC SEC SEC PLB	10 mg/kg 75 mg 150 mg	①②⑤ ⑥⑧⑨	YES
CLEAR (33)	Thaçi	2015	676	SEC UST	300 mg 45/90 mg	⑤⑥⑦	YES
BELIEVE (34)	Thaçi	2015	730	ADA PLB	40 mg	⑩	NO
AMAGINE-1 (35)	Papp	2016	661	BRD BRD PLB	140 mg 210 mg	⑤⑥⑦	YES
VOYAGE 1 (36)	Blauvelt	2017	837	GUS ADA PLB	100 mg 40 mg	⑤⑥⑦⑩	YES
SPIRIT-P1 (37)	Mease	2017	417	IXE IXE ADA PLB	80 mg 2 w 80 mg 4 w 40 mg	①②⑤ ⑥⑦⑧ ⑨⑩	YES
SPIRIP-P2 (38)	Nash	2017	363	IXE IXE PLB	80 mg 2 w 80 mg 4 w	①②③ ⑤⑥⑦ ⑧⑨⑩	YES
reSURFACE 1 (39)	Reich	2017	772	TIL TIL PLB	100 mg 200 mg	⑤⑥⑦	YES

(Continued)

TABLE 1 | Continued

Study	Enrolled patients						NMA
	Author	Year	N	Drug	Dosage	Outcomes	
reSURFACE 2 (39)	Reich	2017	1,090	TIL TIL ETN PLB	100 mg 200 mg 50 mg	567	YES
IXORA-S (40)	Reich	2017	302	IXE UST	80 mg 45/90 mg	567	YES
CLARITY (41)	Bagel	2018	1102	SEC UST	300 mg 45/90 mg	567	YES
(42)	Elewski	2018	217	ADA PLB	40 mg	11	NO
UltiMMa-1 (43)	Gordon	2018	506	RIS UST PLB	150 mg 45/90 mg	567	YES
UltiMMa-2 (43)	Gordon	2018	491	RIS UST PLB	150 mg 45/90 mg	567	YES
CIMPASI-1 (44)	Gottlieb	2018	234	CZP CZP PLB	200 mg 400 mg	67	YES
CIMPASI-2 (44)	Gottlieb	2018	227	CZP CZP PLB	200 mg 400 mg	67	YES
CIMPACT (45)	Lebwohl	2018	559	CZP CZP ETN PLB	200 mg 400 mg 50 mg	56	YES
TRANSFIGURE (46)	Reich	2018	198	SEC SEC PLB	150 mg 300 mg	56 711	YES
FUTURE 5 (47)	Mease	2018	774	SEC SEC PLB	150 mg 300 mg	123 578	YES
SustalMM (48)	Ohtsuki	2019	171	RIS RIS PLB	75 mg 150 mg	567	YES
ECLIPSA (50)	Araujo	2019	47	UST TNFi	45/90 mg	9	NO
IMMvent (52)	Reich	2019	605	RIS ADA	150 mg 40 mg	567	YES
ECLIPSE (53)	Reich	2019	1048	GUS SEC	100 mg 300 mg	567	YES
DISCOVER-2 (49)	Mease	2020	741	GUS PLB	100 mg	1235 6789	NO
SPIRIT H2H (51)	Mease	2020	566	ADA IXE	40 mg 80 mg	1235 68910	YES
DISCOVER-1 (54)	Deodhar	2020	624	GUS PLB	100 mg	1235 6789	NO
EXCEED (55)	McInnes	2020	853	SEC ADA	300 mg 40 mg	1235 6789	NO

(Continued)

TABLE 1 | Continued

Study	Enrolled patients						NMA
	Author	Year	N	Drug	Dosage	Outcomes	
ORION (56)	Ferris	2020	78	GUS PLB	100 mg	⑤⑥⑦	YES
IMMerge (57)	Warren	2020	327	RIS SEC	150 mg 300 mg	⑤⑥⑦	YES

N, number; *NMA*, network meta-analysis; *GRAPPA*, Group for Research and Assessment of Psoriasis and Psoriatic Arthritis; *RCT*, randomized clinical trial; *ADA*, adalimumab; *ETN*, etanercept; *INF*, infliximab; *GOL*, golimumab; *CZP*, certolizumab; *UST*, ustekinumab; *SEC*, secukinumab; *IXE*, ixekizumab; *GUS*, guselkumab; *BRD*, brodalumab; *RIS*, risankizumab; *TIL*, tildrakizumab; *BRK*, briakinumab; *MTX*, methotrexate; *PLB*, placebo.

① ACR20, ② ACR50, ③ ACR70, ④ PASI50, ⑤ PASI75, ⑥ PASI90, ⑦ PASI100, ⑧ dactylitis assessment, ⑨ enthesitis assessment, ⑩ nail assessment.

YES—the study was in *NMA*; NO—the study was not included in *NMA*.

TABLE 2 | Extension studies from RCT focusing on outcomes of GRAPPA domains.

Study	Enrolled patients						NMA
	Author	Year	N	Time of outcome (weeks)	Drug	Dosage	
IMPACT 2 (58)	Kavanaugh	2007	200	52	IFX PLB	5 mg/kg	①②③④ ⑤⑥⑧⑨
(59)	Menter	2008	1,212	52	ADA PLB	40 mg	⑥⑦
REVEAL (60)	Gordon	2012	522	156	ADA PLB	40 mg	PASI improvement
GO-REVEAL (61)	Kavanaugh	2012	405	52	GOL GOL PLB	50 mg 100 mg	①②③④ ⑤⑧⑨⑩
PHOENIX 1 (62)	Kimball	2012	766	156	UST UST PLB	45 mg 90 mg	④⑤⑥
GO-REVEAL (63)	Kavanaugh	2013	405	104	GOL GOL PLB	50 mg 100 mg	①②③④ ⑤⑧⑨⑩
PHOENIX 1 (64)	Kimball	2013	766	260	UST UST PLB	45 mg 90 mg	④⑤⑥
GO-REVEAL (65)	Kavanaugh	2014	405	268	GOL GOL PLB	50 mg 100 mg	①②③④ ⑤⑧⑨⑩
PSUMMIT 1 PSUMMIT 2 (66)	Kavanaugh	2014	927	52	UST UST PLB	45 mg 90 mg	Radiographic progression
PSUMMIT 1 (67)	Kavanaugh	2015	615	100	UST UST PLB	45 mg 90 mg	①②③⑤ ⑥⑧⑨
PHOENIX 2 (68)	Langley	2015	1,212	260	UST UST PLB	45 mg 90 mg	⑤⑥
UNCOVER 3 (69)	Dennehy	2016	491	60	IXE IXE ETN PLB	80 mg 2 w 80 mg 4 w 50 mg	⑩

(Continued)

TABLE 2 | Continued

Study	Enrolled patients						NMA
	Author	Year	N	Time of outcome (weeks)	Drug	Dosage	Outcomes
UNCOVER 2 (70)	Gordon	2016	1,224	60	IXE IXE ETN PLB	80 mg 2 w 80 mg 4 w 50 mg	⑤⑥⑦
UNCOVER 3 (70)	Gordon	2016	1,346	60	IXE IXE ETN PLB	80 mg 2 w 80 mg 4 w 50 mg	⑤⑥⑦
(71)	van der Heijde	2016	606	52	SEC SEC SEC	10 mg/kg 75 mg 150 mg	Radiographic progression
PSTELLAR (72)	Blauvelt	2017	325	112	UST UST	q12 wk q24 wk	⑤⑥⑦
UNCOVER 3 (73)	Blauvelt	2017	1,346	108	IXE IXE ETN PLB	80 mg 2 w 80 mg 4 w 50 mg	⑤⑥⑦
CLEAR (74)	Blauvelt	2017	676	52	SEC UST	300 mg 45/90 mg	⑤⑥⑦
FUTURE 2 (75)	McInnes	2017	397	104	SEC SEC SEC PLB	75 mg 150 mg 300 mg	①②③ ⑥⑧⑨
(76)	Mease	2017	422	54	TOF TOF ADA PLB	5 mg 10 mg 40 mg	①②③ ⑤⑧⑨
LIBERATE (77)	Reich	2017	250	52	APR ETN PLB	30 mg 50 mg	④⑤ ⑥⑩
UNCOVER 3 (78)	van der Kerkhof	2017	809	60	IXE IXE ETN PLB	80 mg 2 w 80 mg 4 w 50 mg	⑩
(79)	Griffiths	2018		100	GUS ADA PLB	100 mg 40 mg	⑤⑥⑦
UNCOVER 3 (80)	Leonardi	2018	1,346	156	IXE IXE ETN PLB	80 mg 2 w 80 mg 4 w 50 mg	⑤⑥⑦
(81)	Ohtsuki	2018	191	52	GUS GUS PLB	50 mg 100 mg	④⑤⑥ ⑦⑩
LIBERATE (82)	Reich	2018	250	104	APR ETN PLB	30 mg 50 mg	⑤⑩

(Continued)

TABLE 2 | Continued

Study	Enrolled patients						NMA
	Author	Year	N	Time of outcome (weeks)	Drug	Dosage	Outcomes
UNCOVER 2/3 (83)	Kemény	2019	2570	156	IXE	80 mg 2 w	⑤⑥⑦
					IXE	80 mg 4 w	
					ETN	50 mg	
					PLB		
IXORA-S (84)	Paul	2019	302	52	IXE	80 mg	⑤⑥⑦
					UST	45/90 mg	
SUSTalMM (48)	Ohtsuki	2019	171	52	RIS	75 mg	⑤⑥⑦
					RIS	150 mg	
					PLB		

N, number; NMA, network meta-analysis; GRAPPA, Group for Research and Assessment of Psoriasis and Psoriatic Arthritis; RCT, randomized clinical trial; ADA, adalimumab; ETN, etanercept; IFX, infliximab; GOL, golimumab; UST, ustekinumab; SEC, secukinumab; IXE, ixekizumab; GUS, guselkumab; RIS, risankizumab; APR, apremilast; TOF, tofacitinib; PLB, placebo.

① ACR20, ② ACR50, ③ ACR70, ④ PASI50, ⑤ PASI75, ⑥ PASI90, ⑦ PASI100, ⑧ dactylitis assessment, ⑨ enthesitis assessment, ⑩ nail assessment.

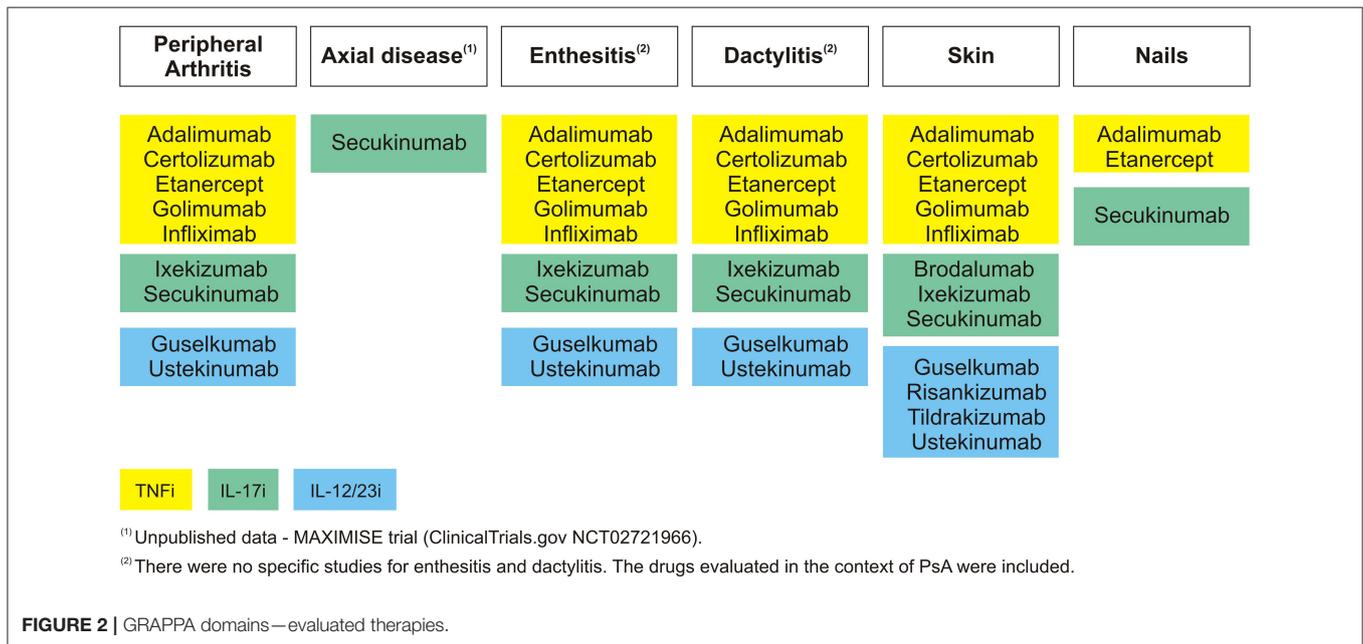


FIGURE 2 | GRAPPA domains—evaluated therapies.

52 in the EXCEED study is also listed but not included on the NMA (55).

An NMA was performed for the three outcomes (ACR20, ACR50, and ACR70). The included studies are identified in **Table 1**. A network plot for ACR70 is included in **Figure 3**, as an example of the network plots of these three NMAs.

The NMA results from the network of biologic therapies for the outcome ACR70 response are included in **Table 4**.

Axial Disease

Data including biologic therapies for axial disease, in the context of PsD, are scarce, possibly because there is no validated instrument to assess this domain. Nowadays, the only trial

addressing specifically PsD patients with the axial disease is still ongoing and this data is not yet published. This trial—MAXIMIZE—evaluates the efficacy and safety of SEC 300 or 150 mg in managing axial manifestations in patients with PsA, who have failed to respond to at least 2 non-steroidal anti-inflammatory drugs (NSAIDs) over 4 weeks, according to Assessment of Spondyloarthritis International Society (ASAS) recommendations for the treatment of axial spondyloarthritis (ClinicalTrials.gov NCT02721966) (86).

Enthesitis

There are at least 6 indices to evaluate enthesitis outcomes (4-point enthesitis measure, Leeds Enthesis Index (LEI),

TABLE 3 | ACR improvements in patients with psoriatic arthritis—peripheral disease.

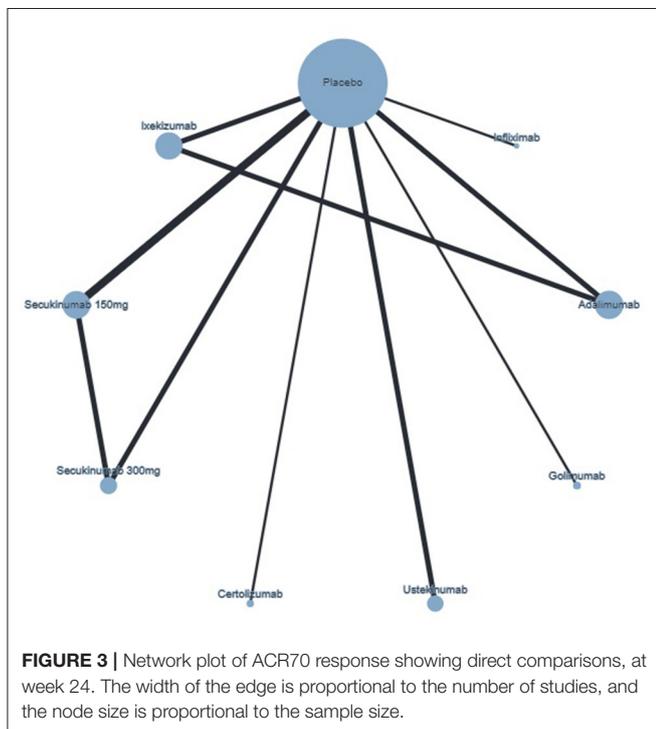
Study	Weeks	Treatment	Improvement		
			ACR20 n/total (%)	ACR50 n/total (%)	ACR70 n/total (%)
Antoni 2005 IMPACT 2 (1)	24	PLB	16/100 (16.0)	4/100 (4.0)	2/100 (2.0)
	24	IFX	54/100 (54.0)	41/100 (41.0)	27/100 (27.0)
	<i>p</i> -value		<0.001	<0.001	<0.001
Mease 2005 ADEPT (11)	24	PLB	15/162 (9.3)	6/162 (3.7)	1/162 (0.6)
	24	ADA	57/151 (37.7)	39/151 (25.8)	23/151 (15.2)
	<i>p</i> -value		<0.001	<0.001	<0.001
Kavanaugh 2009 (18)	24	PLB	12/113 (10.6)	1/113 (0.9)	0/113 (0)
	24	GOL	75/146 (51.3)	39/146 (26.7)	25/146 (17.1)
	<i>p</i> -value		<0.001	<0.001	<0.001
McInnes 2013 PSUMMIT 1 (24)	24	PLB	47/206 (22.8)	18/206 (8.7)	5/206 (2.4)
	24	UST	87/205 (42.4)	51/205 (24.8)	25/205 (12.2)
	<i>p</i> -value		<0.0001	<0.0001	0.0001
Mease 2014 RAPID-PsA (26)	24	PLB	32/136 (23.5)	17/136 (12.5)	6/136 (4.4)
	24	CZP	88/138 (63.8)	60.1/138 (44.2)	39/138 (28.3)
	<i>p</i> -value		<0.001	<0.001	<0.001
Ritchlin 2014 PSUMMIT 2 (28)	24	PLB	21/104 (20.2)	7/104 (6.7)	3/104 (2.9)
	24	UST	45/103 (43.7)	18/103 (17.4)	7/103 (6.8)
	<i>p</i> -value		<0.001	<0.05	n.s.
Mease 2015 FUTURE 1 (32)	24	PLB	35/202 (17.3)	15/202 (7.4)	4/202 (2.0)
	24	SEC 150 mg	101/202 (50.0)	70/202 (34.7)	38/202 (18.8)
	<i>p</i> -value		<0.001	<0.001	<0.001
McInnes 2015 FUTURE 2 (31)	24	PLB	15/98 (15.3)	7/98(7.1)	1/98 (1.0)
	24	SEC 300 mg*	54/100 (54.0)	35/100 (35.0)	20/100 (20.0)
	24	SEC 150 mg**	51/100 (51.0)	35/100 (35.0)	21/100 (21.0)
<i>p</i> -value		*,**<0.0001	*,**<0.0001	*0.0003; **<0.0001	
Mease 2017 SPIRIT P1 (37)	24	PLB	32/106 (30.2)	16/106 (15.1)	6/106 (5.7)
	24	IXE Q4W*	62/107 (57.9)	43/107 (40.2)	25/107 (23.4)
	24	ADA	58/101 (57.4)	39/101 (38.6)	26/101 (25.7)
<i>p</i> -value		*≤0.001	*≤0.001	*≤0.001	
Nash 2017 SPIRIT P2 (38)	24	PLB	23/118 (19.5)	6/118 (5.1)	0/118 (5.7)
	24	IXE Q4W	65/122 (53.3)	43/122 (35.2)	27/122 (22.1)
	<i>p</i> -value		<0.0001	<0.0001	<0.0001
Mease 2018 FUTURE 5 (47)	24	PLB	78/332 (23.5)	29/332 (8.7)	13/332 (3.9)
	24	SEC 300 mg	141/222 (63.5)	97/222 (43.7)	56/222 (25.7)
	24	SEC 150 mg	117/220 (53.2)	86/220 (39.1)	53/220 (24.1)
<i>p</i> -value		<0.0001	<0.0001	<0.0001	
Mease 2020 SPIRIT H2H (51)	24	ADA	204/283 (72.1)	132/283 (46.6)	73/283 (25.8)
	24	IXE	195/283 (68.9)	143/283 (50.5)	90/283 (31.8)
	<i>p</i> -value		0.403	0.338	0.111

(Continued)

TABLE 3 | Continued

Study	Weeks	Treatment	Improvement		
			ACR20 n/total (%)	ACR50 n/total (%)	ACR70 n/total (%)
McInnes 2020 EXCEED (55)	52	SEC	285/426 (67)	209/426 (49)	141/426 (33)
	52	ADA	252/427 (43)	192/427 (45)	124/427 (29)
p-value			0.0239	0.2251	0.2950

ACR, American College of Rheumatology; n, number; ADA, adalimumab; IFX, infliximab; GOL, golimumab; CZP, certolizumab; UST, ustekinumab; SEC, secukinumab; IXE, ixekizumab; MTX, methotrexate; PLB, placebo **vs. placebo.



Maastricht Ankylosing Spondylitis Enthesitis Score (MASES), Spondyloarthritis Research Consortium of Canada (SPARCC) Enthesitis Index, 12-point Berlin Index, and the 17-point University of California, San Francisco (UCSF) Index) with no consensus on which is the most adequate (85). Moreover, some studies, instead of using a score, only discriminate the percentage of patients with complete enthesitis resolution. Since different instruments were used in different studies, it is impossible to compare results across studies. As such, we were not able to perform an NMA regarding this domain. A summary of the results of the different studies is included in **Table 5** (1, 13, 18, 22, 24, 26, 28, 31, 32, 37, 38, 47, 50, 51, 55, 61, 65).

Dactylitis

As enthesitis, dactylitis is also evaluated through different approaches. It can be assessed by counting dactylitis digits—a simple counting and scoring method or Leeds Dactylitis Index

(LDI) (85). Moreover, there is also no consensus regarding the better method to assess dactylitis, and therefore it was not possible to perform an NMA due to the heterogeneity found in the different RCTs (85). Also, some studies only evaluate the percentage of patients with complete resolution of dactylitis. A summary of the results of the different studies is included in **Table 6** (1, 18, 24, 26, 28, 31, 32, 37, 38, 47, 51, 55, 61, 65).

Skin

Psoriasis severity was evaluated by the most used tool in dermatology trials—PASI. PASI combines the assessment of the severity of psoriasis lesions (average redness, thickness, and scaliness of the lesions) and the area affected into a single score (87). PASI is commonly reported as the percentage of improvement from baseline, PASI75, PASI90, and PASI100, meaning 75, 90, and 100% of improvement, respectively.

The results of the systematic review including RCTs reporting PASI in patients with PsD, at weeks 10–16 of treatment, are included in **Table 7** (1, 11, 12, 14–16, 18–22, 25, 26, 29, 30, 33, 35–37, 39–41, 43–48, 51–53, 55–57, 59, 70).

An NMA was performed for the three outcomes: PASI75, PASI90, and PASI100. The included studies are identified in **Table 1**. A network plot for PASI100 is included in **Figure 4**, as an example of the network plots of these three NMAs.

Nails

As described for enthesitis and dactylitis, the assessment of nail psoriasis is not consensual at this time, with Nail Psoriasis Severity Index (NAPSI) and modified NAPSI being the most commonly used indices. Due to the low number of studies evaluating nail psoriasis and inconsistent use of these indices, we were not able to perform an NMA (85). A summary of the results of the different studies is included in **Table 9** (12, 18, 27, 32, 34, 36–38, 42, 46, 51, 61, 65, 69, 77, 78, 81, 88, 89).

DISCUSSION

The use of biologic therapies in the treatment of PsD is recommended across the six domains of the disease (2). A complete, effective, and safe treatment for all the manifestations of PsD is the main goal in the management of this condition. However, the heterogeneity of the manifestations challenges the achievement of this goal.

TABLE 4 | NMA results from the network of biologic therapies in the outcome ACR70.

	ADA	CZP	GOL	IFX	IXE	PLB	SEC 150 mg	SEC 300 mg	UST
ADA		0.907 (0.274–3.002)	0.163 (0.009–3.013)	0.427 (0.081–2.264)	0.832 (0.607–1.139)	7.745 (3.514–17.071)	0.832 (0.323–2.144)	0.821 (0.314–2.148)	1.827 (0.594–5.625)
CZP	1.102 (0.333–3.646)		0.179 (0.009–3.425)	0.471 (0.084–2.633)	0.916 (0.276–3.041)	8.535 (3.476–20.960)	0.917 (0.324–2.590)	0.905 (0.316–2.592)	2.014 (0.605–6.705)
GOL	6.151 (0.332–114.000)	5.582 (0.292–106.708)		2.629 (0.110–62.633)	5.115 (0.276–94.907)	47.641 (2.867–791.714)	5.117 (0.294–89.211)	5.052 (0.288–88.517)	11.240 (0.605–208.847)
IFX	2.340 (0.442–12.395)	2.123 (0.380–11.870)	0.380 (0.016–9.064)		1.946 (0.366–10.329)	18.123 (4.176–78.657)	1.947 (0.410–9.241)	1.922 (0.401–9.207)	4.276 (0.804–22.753)
IXE	1.203 (0.878–1.648)	1.091 (0.329–3.622)	0.196 (0.011–3.628)	0.514 (0.097–2.729)		9.315 (4.206–20.627)	1.000 (0.387–2.588)	0.988 (0.376–2.593)	2.198 (0.712–6.788)
PLB	0.129 (0.059–0.285)	0.117 (0.048–0.288)	0.021 (0.001–0.349)	0.055 (0.013–0.239)	0.107 (0.048–0.238)		0.107 (0.064–0.181)	0.106 (0.061–0.183)	0.236 (0.106–0.525)
SEC 150 mg	1.202 (0.466–3.098)	1.091 (0.386–3.082)	0.195 (0.011–3.407)	0.514 (0.108–2.439)	1.000 (0.386–2.586)	9.310 (5.529–15.679)		0.987 (0.688–1.418)	2.197 (0.846–5.706)
SEC 300 mg	1.218 (0.466–3.184)	1.105 (0.386–3.164)	0.198 (0.011–3.468)	0.520 (0.109–2.493)	1.012 (0.386–2.658)	9.430 (5.455–16.302)	1.013 (0.705–1.454)		2.225 (0.844–5.864)
UST	0.547 (0.178–1.685)	0.497 (0.149–1.653)	0.089 (0.005–1.653)	0.234 (0.044–1.244)	0.455 (0.147–1.405)	4.238 (1.905–9.431)	0.455 (0.175–1.182)	0.449 (0.171–1.185)	

OR and CrI are presented. Comparisons with high confidence rating based on CiNEMA evaluation are identified in bold and OR higher than 1 favor the intervention specified in the row.

NMA, network meta-analysis; CiNEMA, Confidence in Network Meta-Analysis; OR, odds ratio; CrI, credible interval; ADA, adalimumab; IFX, infliximab; GOL, golimumab; CZP, certolizumab; UST, ustekinumab; SEC, secukinumab; IXE, ixekizumab; PLB, placebo.

TABLE 5 | Enthesitis assessment in patients with psoriatic arthritis.

Study	Author	Year	Drug	Outcome	Time of outcome (weeks)	Result
IMPACT 2 (1)	Antoni	2005	IFX vs. PLB	Patients with enthesitis	14	22% vs. 34% ($p = 0.016$)
					24	20% vs. 37% ($p = 0.002$)
(13)	Genovese	2007	ADA vs. PLB	Reduction of enthesitis	12	-0.5 vs. -0.2 ($p > 0.05$)
GO-REVEAL (18)	Kavanaugh	2009	GOL 50 mg vs. PLB	Patients with enthesitis	14	55% vs. 71% ($p = 0.008$)
			GOL 100 mg vs. PLB			61% vs. 71% ($p = 0.10$)
			GOL 50 mg vs. PLB		24	49% vs. 69% ($p = 0.002$)
			GOL 100 mg vs. PLB			50% vs. 69% ($p = 0.003$)
GO-REVEAL (61)	Kavanaugh	2012	GOL 50 mg vs. PLB	Modified MASES index (change from baseline)	Week 52	56.3 ± 62.4 vs. 39.1 ± 76.1
			GOL 100 mg vs. PLB			51.9 ± 64.2 vs. 39.1 ± 76.1
RESPOND (22)	Baranaukaite	2012	IFX+MTX vs. MTX	Reduction of enthesitis	16	2 vs. 1 ($p = 0.082$)
PSUMMIT 1 (24)	McInnes	2013	UST vs. PLB	Patients with enthesitis	24	64.6% vs. 81% ($p = 0.006$)
GO-REVEAL (64)	Kavanaugh	2014	GOL 50 mg vs. PLB	Modified MASES index	Week 256	1.9 ± 3.3 vs. 2.4 ± 4.0
			GOL 100 mg vs. PLB			2.0 ± 3.4 vs. 2.4 ± 4.0
PSUMMIT 2 (28)	Ritchlin	2014	UST 45 mg vs. PLB	MASES	24	-33.33% vs. 0% ($p > 0.05$)
			UST 90 mg vs. PLB			-48.33% vs. 0% ($p < 0.01$)
			UST 45 mg vs. PLB		52	-36.67% vs. -33.33% ($p > 0.05$)
			UST 90 mg vs. PLB			-60% vs. -33.33% ($p > 0.05$)
RAPID-PsA (26)	Mease	2014	CZP 200 mg Q2W vs. PLB	LEI	24	-2.0 vs. -1.1 ($p < 0.001$)
			CZP 400 mg Q4W vs. PLB			-1.8 vs. -1.1 ($p = 0.003$)
(32)	Mease	2015	SEC (pooled data) vs. PLB	Resolution of enthesitis	24	47.5% vs. 12.8% ($p < 0.05$)
FUTURE 2 (31)	McInnes	2015	SEC (pooled data) vs. PLB	Resolution of enthesitis	24	22% vs. 40% ($p = 0.919$)
SPIRIT-P1 (37)	Mease	2017	IXE Q2W vs. PLB vs. ADA	LEI (responders)	Week 12	47.4 vs. 28.1 vs. 35.2 ($p < 0.05$)*
			IXE Q4W vs. PLB vs. ADA			27.9 vs. 28.1 vs. 35.2
			IXE Q2W vs. PLB vs. ADA		Week 24	38.6 vs. 19.3 vs. 33.3 ($p \leq 0.025$)*
			IXE Q4W vs. PLB vs. ADA			42.6 vs. 19.3 vs. 35.2 ($p \leq 0.01$)*
SPITIT-P2 (38)	Nash	2017	IXE Q2W vs. PLB	LEI (proportion of patients with a response)	Week 24	31% vs. 22% ($p = 0.27$)
			IXE Q4W vs. PLB			35% vs. 22% ($p = 0.08$)
FUTURE 5 (47)	Mease	2018	SEC 150 mg vs. PLB	Resolution of enthesitis	Week 16	54.6% vs. 35.4% ($p < 0.05$)
			SEC 300 mg vs. PLB			55.7% vs. 35.4% ($p < 0.05$)
ECLIPSA (50)	Araujo	2019	UST vs. TNFi	SPARCC = 0	Week 12	74% vs. 42% ($p = 0.018$)
			MASES = 0	82% vs. 50% ($p = 0.032$)		
			LEI = 0	78% vs. 50% ($p = 0.005$)		
SPIRIT H2H (51)	Mease	2020	IXE vs. ADA	SPARCC = 0	Week 24	45.0% vs. 56.6% ($p = 0.019$)
				LEI = 0		55.1% vs. 59.7% ($p = 0.432$)
EXCEED (55)	McInnes	2020	SEC vs. ADA	resolution of enthesitis	Week 52	53% vs. 50% ($p = 0.5117$)

ADA, adalimumab; IFX, infliximab; GOL, golimumab; CZP, certolizumab; UST, ustekinumab; SEC, secukinumab; IXE, ixekizumab; BRD, brodalumab; MTX, methotrexate; PLB, placebo; MASES, Maastricht Ankylosing Spondylitis Enthesitis Score; LEI, Leeds Enthesitis Index; SPARCC, Spondyloarthritis Research Consortium of Canada Enthesitis Index; TNFi, tumor necrosis factor inhibitor; *IXE vs. placebo.

Recent advances in the knowledge of the pathophysiology of the disease led to the extensive study and approval of different mechanisms of action, including TNFi such as IFX, ETN, GOL, CZP, and ADA; IL-17i such as SEC, IXE, and BRD; and IL-12 and/or IL-23i such as UST, GUS, RIS, and TIL. Nevertheless, direct comparisons between them are scarce and therefore NMA is the preferred method to indirectly compare drugs, aiming to help clinicians in the choice of the best treatment.

The report of the outcomes of each GRAPPA domain is not standardized (Tables 5, 6, 9) except for the peripheral arthritis

and skin domains, which use mainly ACR and PASI responses, respectively (Tables 3, 7). Thus, we were only able to perform NMAs based on ACR and PASI responses, evaluated at weeks 24 or 10–16, respectively. Although we also performed NMAs for ACR20, ACR50, PASI75, and PASI90, based on the current expectations on the efficacy of new biologic treatments and on the confidence in the results, we decided to present the efficacy of the different biologic therapy using ACR70 (Table 4) and PASI100 (Table 8), the most challenging outcomes. The confidence rating on direct and indirect estimates was calculated using CINeMA to

TABLE 6 | Dactylitis assessment in patients with psoriatic arthritis.

Study	Author	Year	Intervention	Outcome	Time of outcome	Result
IMPACT 2 (1)	Antoni	2005	IFX vs. placebo	At least 1 dactylitis digit	Week 14 Week 24	22% vs. 34% ($p = 0.025$) 12% vs. 34% ($p < 0.001$)
GO-REVEAL (18)	Kavanaugh	2009	GOL 50 mg vs. placebo GOL 100 mg vs. placebo GOL 50 mg vs. placebo GOL 100 mg vs. placebo	Patients with dactylitis	Week 14 Week 24	22% vs. 26% ($p = 0.46$) 17% vs. 26% ($p = 0.10$) 16% vs. 22% ($p = 0.21$) 14% vs. 22% ($p = 0.09$)
GO-REVEAL (61)	Kavanaugh	2012	GOL 50 mg vs. placebo GOL 100 mg vs. placebo	Dactylitis score change from baseline	Week 52	-4.20 ± 4.81 vs. -1.68 ± 2.79 -4.55 ± 6.60 vs. -1.68 ± 2.79
PSUMMIT 1 (24)	McInnes	2013	UST vs. placebo	Patients with dactylitis	Week 24	56.2% vs. 76.1% ($p = 0.0013$)
PSUMMIT 2 (28)	Ritchlin	2014	UST 45 mg vs. placebo UST 90 mg vs. placebo UST 45 mg vs. placebo	Percent change in dactylitis score	Week 24 Week 52	0.0 vs. 0.0 -64.58 vs. 0.0 -95.00 vs. -100
RAPID-PsA (26)	Mease	2014	CZP 200 mg Q2W vs. placebo CZP 400 mg Q4W vs. placebo	LDI change from baseline	Week 24	-40.7 vs. -22.0 ($p = 0.002$) -53.5 vs. -22.0 ($p < 0.001$)
GO-REVEAL (65)	Kavanaugh	2014	GOL 50 mg vs. placebo GOL 100 mg vs. placebo UST 90 mg vs. placebo	Dactylitis score	Week 260	6.3 ± 6.1 vs. 3.1 ± 2.1 5.4 ± 6.7 vs. 3.1 ± 2.1 -90.91 vs. -100
(30)	Mease	2015	SEC (pooled data) vs. placebo	Resolution of dactylitis	Week 24	52.4% vs. 15.5 ($p < 0.05$)
FUTURE 2 (31)	McInnes	2015	SEC (pooled data) vs. placebo	Resolution of dactylitis	Week 24	47% vs. 15% ($p = 0.919$)
SPIRIT-P1 (37)	Mease	2017	IXE Q2W vs. placebo vs. ADA IXE Q4W vs. placebo vs. ADA IXE Q2W vs. placebo vs. ADA IXE Q4W vs. placebo vs. ADA	LDI-B (change from baseline)	Week 12 Week 24	-63.9 (10.6) vs. -36.3 (10.3) vs. -62.1 (11.9) ($p \leq 0.05$)* -72.8 (8.8) vs. -36.3 (10.3) -62.1 (11.9) ($p \leq 0.001$)* -66.1 (9.8) vs. -33.7 (9.7) vs. -76.0 (10.9) ($p \leq 0.01$)* -75.4 (8.1) vs. -33.7 (9.7) -76.0 (10.9) ($p \leq 0.001$)*
SPIRIT-P2 (38)	Nash	2017	IXE Q2W vs. placebo IXE Q4W vs. placebo	LDI-B (change from baseline)	Week 24	-32.1 (6.7) vs. -36.2 (8.4) $p = 0.65$ -34.7 (6.7) vs. -36.2 (8.4) $p = 0.85$
FUTURE 5 (47)	Mease	2018	SEC 150 mg vs. placebo SEC 300 mg vs. placebo	Resolution of dactylitis	Week 16	57.5% vs. 32.3% ($p < 0.05$) 65.9% vs. 32.3% ($p < 0.05$)
SPIRIT H2H (51)	Mease	2020	IXE vs. ADA	LDI-B = 0	Week 24	88.1 vs. 93.1 ($p = 0.658$)
EXCEED (55)	McInnes	2020	SEC vs. ADA	Resolution of dactylitis	Week 52	75% vs. 70% ($p = 0.3560$)

ADA, adalimumab; IFX, infliximab; GOL, golimumab; CZP, certolizumab; UST, ustekinumab; SEC, secukinumab; IXE, ixekizumab; BRD, brodalumab; PLB, placebo; LDI, Leeds Dactylitis Index; *IXE vs. placebo.

improve the transparency and limit the subjectivity of the process (90–92). Comparisons with a high confidence rating, based on the CINeMA evaluation (91), are represented in bold. The level of confidence of the other comparisons is either low or very low, and consequently, the surface under the cumulative rating (SUCRA) will result in misleading inferences (90, 93). Thus, a SUCRA was not done and, therefore, it was impossible to rank the available biologic treatments.

In the ACR70 NMA (Table 4), the results of the comparisons between drugs are not reliable, except when compared with the placebo. From the 12 RCTs reporting ACR70 responses at week 24 (Table 3) (1, 11, 18, 24, 26, 28, 31, 32, 37, 38, 49, 51), only one performed head-to-head comparisons, at week 24, and there was no superiority regarding this specific

endpoint (51). The other head-to-head study is EXCEED, with a primary endpoint at 52 weeks, showing also no superiority regarding ACR70. Nevertheless, and as expected, compared with the placebo, all drugs were significantly better in achieving ACR20/50/70.

In the PASI100 response NMA (Table 8), as for ACR70, the comparisons with high confidence levels were few and therefore it was not possible to rank the drugs regarding their probability to achieve differences in PASI100 between weeks 10 and 16. The comparisons with placebo were reliable, and the drugs that lead to a higher probability in achieving PASI100 were BRD, RIS, IXE, and GUS. Although based on CINeMA analysis we were not able to have high confidence in all of our comparisons, the results from placebo comparison were partially following

TABLE 7 | PASI Improvements in patients with psoriasis skin.

Study	Weeks	Drug	Improvement		
			PASI75 n/total (%)	PASI90 n/total (%)	PASI100 n/total (%)
Antoni 2005	14	PLB	1/87 (1.0)	0/87 (0.0)	–
IMPACT 2 (1)	14	IFX	55/87 (64.0)	34/87 (41.0)	–
<i>p</i> -value			<0.001	<0.001	
Mease 2005	12	PLB	4/69 (5.8)	0/69 (0.0)	–
ADEPT (11)	12	ADA	49/69 (71.0)	30/69 (43.5)	–
<i>p</i> -value			<0.001	<0.001	
Reich 2005	10	PLB	2/77 (3.0)	1/77 (1.0)	–
(12)	10	IFX	242/301 (80.0)	172/301 (57.0)	–
<i>p</i> -value			<0.0001	<0.0001	
Tyring 2007	12	PLB	5/292 (1.7)	1/292 (0.3)	–
(13)	12	ETA	47/305 (15.4)	21/305 (6.9)	–
<i>p</i> -value			<0.001	<0.001	
Leonardi 2008	12	PLB	5/255 (2.0)	5/255 (2.0)	0/255 (0.0)
PHOENIX 1 (15)	12	UST 45 mg	171/255 (67.0)	106/255 (41.6)	32/255 (12.5)
<i>p</i> -value			<0.0001	<0.0001	<0.0001
Menter 2008	12	PLB	20/398 (5.0)	8/398 (2.0)	4/398 (1.0)
(59)	12	ADA	554/814 (68.1)	301/814 (37.0)	114/814 (14.0)
<i>p</i> -value			<0.001	<0.001	<0.001
Papp 2008	12	PLB	15/410 (3.7)	3/410 (0.7)	0/410 (0.0)
PHOENIX 2 (16)	12	UST 45 mg	273/409 (66.5)	173/409 (42.3)	74/409 (18.1)
<i>p</i> -value			<0.0001	<0.0001	<0.0001
Kavanaugh 2009	14	PLB	2/79 (2.5)	0/73 (0.0)	–
(18)	14	GOL 50 mg	44/109 (40.3)	22/106 (20.8)	–
<i>p</i> -value			<0.001	<0.001	
Barker 2011	16	MTX	90/216 (41.7)	41/216 (19.0)	–
RESTORE1 (19)	16	IFX	508/656 (77.4)	356/656 (54.2)	–
<i>p</i> -value			n.s.	<0.001	
Gottlieb 2011	12	PLB	5/68 (7.4)	1/68 (1.5)	0/68 (0.0)
(20)	12	BRK*	112/138 (81.0)	83/138 (60.0)	39/138 (28.3)
	12	ETA	78/141 (55.0)	18/141 (12.7)	5/141 (3.6)
<i>p</i> -value			<0.001	<0.001	<0.001
Strober 2011	12	PLB	5/72 (6.9)	3/72 (4.2)	0/72 (0.0)
(20)	12	BRK*	111/139 (80.0)	83/139 (60)	30/139 (21.9)
	12	ETA	40/139 (28.8)	18/139 (13.0)	5/139 (3.6)
<i>p</i> -value			<0.001	<0.001	<0.001
Baranauskaite 2012	16	MTX	19/35 (54.3%)	–	–
RESPOND (22)	16	MTX+IFX	33/34 (97.1%)	–	–
<i>p</i> -value			<0.0001	–	–
Langley 2014	12	PLB	11/246 (4.5)	3/246 (1.2)	2/246 (0.8)
ERASURE (25)	12	SEC 300 mg	200/245 (81.6)	145/245 (59.2)	70/245 (26.6)
<i>p</i> -value			<0.001	<0.001	<0.001
Langley 2014	12	PLB	16/324 (4.9)	5/324 (1.5)	0/324 (0.0)
FIXTURE (25)	12	SEC 300 mg*	249/323 (77.0)	175/323 (54.1)	78/323 (24.1)
	12	ETA	142/323 (44.0)	67/323 (20.7)	14/323 (4.3)
<i>p</i> -value			<0.001	<0.001	<0.001
Mease 2014	12	PLB	12/86 (13.9)	4/86 (4.7)	–
RAPID-PsA (26)	12	CZP 200 mg	42/90 (46.7)	20/90 (22.2)	–
<i>p</i> -value			<0.001	<0.001	

(Continued)

TABLE 7 | Continued

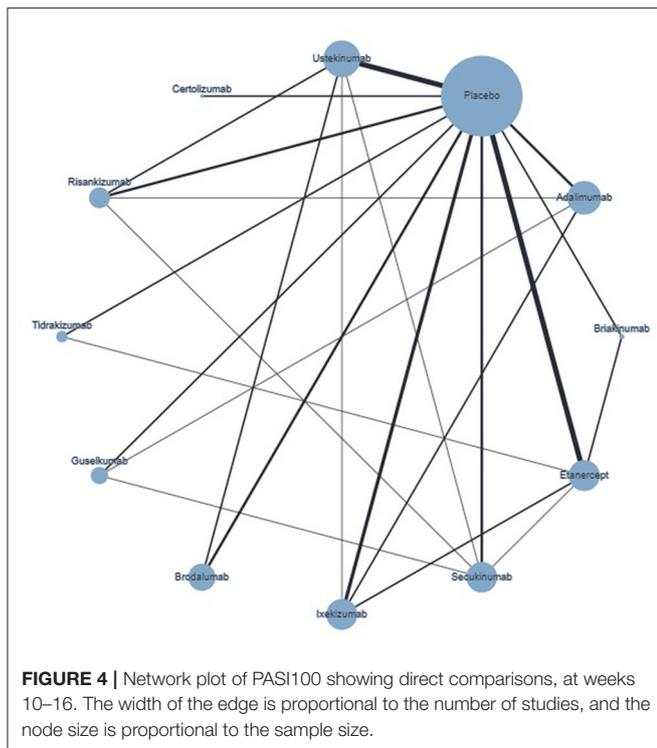
Study	Weeks	Drug	Improvement		
			PASI75 n/total (%)	PASI90 n/total (%)	PASI100 n/total (%)
Griffiths 2015 UNCOVER 2 (29)	12	PLB	4/168 (2.4)	1/168 (0.6)	1/168 (0.6)
	12	IXE Q4W*	269/347 (77.5)	267/347 (76.9)	107/347 (30.8)
	12	ETA	149/358 (41.6)	67/358 (18.7)	19/358 (5.3)
<i>p</i> -value			<0.0001	<0.0001	<0.0001
Griffiths 2015 UNCOVER 3 (29)	12	PLB	14/193 (7.2)	6/193 (3.1)	0/193 (0.0)
	12	IXE*	325/386 (84.2)	352/386 (91.2)	135/386 (35.0)
	12	ETA	201/382 (52.6)	98/382 (25.6)	19/358 (5.3)
<i>p</i> -value			<0.0001	<0.0001	<0.0001
Lebwohl 2015 AMAGINE 2 (30)	12	PLB	25/309 (8.1)	12/309 (3.9)	2/309 (0.6)
	12	UST	210/300 (70.0)	141/300 (47.0)	65/300 (21.7)
	12	BRD 210 mg*	528/612 (86.3)	428/612 (69.9)	272/612 (44.4)
<i>p</i> -value			<0.001	<0.001	<0.001
Lebwohl 2015 AMAGINE 3 (30)	12	PLB	19/315 (6.0)	6/315 (1.9)	1/315 (0.3)
	12	UST	217/313 (69.3)	141/313 (45.0)	58/313 (18.5)
	12	BRD*	531/624 (85.1)	430/624 (68.9)	229/624 (36.7)
<i>p</i> -value			<0.001	<0.001	<0.001
Thaci 2015 CLEAR (33)	12	SEC	311/334 (93.1)	264/334 (79.0)	148/334 (44.3)
	12	UST	277/334 (82.9)	277/334 (82.9)	130/334 (38.9)
<i>p</i> -value			<0.0001	<0.0001	=0.003
Gordon 2016 UNCOVER 1 (70)	12	PLB	17/431 (3.9)	7/431 (1.7)	0/431 (0.0)
	12	IXE Q4W	357/432 (82.6)	279/432 (64.6)	145/432 (33.6)
<i>p</i> -value			<0.001	<0.001	<0.001
Papp 2016 (35)	12	PLB	6/220 (2.7)	2/220 (0.9)	1/220 (0.5)
	12	BRD	185/222 (83.3)	156/220 (70.9)	93/222 (41.9)
<i>p</i> -value			<0.001	<0.001	<0.001
Blauvelt 2017 VOYAGE 1 (36)	16	PLB	10/174 (5.7)	5/174 (2.9)	1/174(0.6)
	16	GUS*	300/329 (91.2)	241/329 (73, 3)	123/329 (37.4)
	16	ADA	244/334 (73.1)	166/334 (49.7)	57/334 (17.4)
<i>p</i> -value			<0.001	<0.001	<0.001
Mease 2017 SPIRIT 1 (37)	12	PLB	5/67 (7.5)	1/67 (1.5)	1/67 (1.5)
	12	IXE Q4W*	55/73 (75.3)	38/73 (52.0)	23/73 (31.5)
	12	ADA	23/68 (33.8)	15/68 (22.1)	10/68 (14.7)
<i>p</i> -value			≤0.01	≤0.01	≤0.01
Reich 2017 reSURFACE 1 (39)	12	PLB	9/154 (5.8)	4/154 (3.0)	2/154 (1.3)
	12	TIL 100 mg	197/309 (63.8)	107/309 (35.0)	43/309 (13.9)
<i>p</i> -value			<0.0001	<0.0001	<0.0001
Reich 2017 reSURFACE 2 (39)	12	PLB	9/156 (5.8)	2/156 (1.3)	0/156 (0.0)
	12	TIL 100 mg*	188/307 (61.2)	119/307 (38.8)	38/307 (12.4)
	12	ETA	151/313 (48.2)	67/313 (21.4)	15/313 (4.8)
<i>p</i> -value			0.0001	0.0001	0.0001
Reich 2017 IXORA-S (40)	12	IXE	120/136 (88.2)	99/136 (72.8)	49/136 (36.0)
	12	UST	114/166 (68.7)	70/166 (42, 2)	24/166 (14.5)
<i>p</i> -value			0.001	0.001	0.001
Bagel 2018 CLARITY (41)	16	SEC	504/550 (91.7)	421/550 (76.6)	249/550 (45.3)
	16	UST	440/552 (79.8)	299/552 (54.1)	147/552 (26.7)
<i>p</i> -value			<0.0001	<0.0001	<0.0001
Gordon 2018	12	PLB	10/102 (9.8)	2/102 (2.0)	0/102 (0.0)

(Continued)

TABLE 7 | Continued

Study	Weeks	Drug	Improvement		
			PASI75 n/total (%)	PASI90 n/total (%)	PASI100 n/total (%)
UltiMMa 1 (43)	12	UST*	70/100 (70)	42/100 (42.0)	12/100 (12.0)
	12	RIS*	264/304 (86.8)	229/304 (75.3)	109/304 (35.9)
<i>p</i> -value			<0.0001	<0.0001	<0.0001
Gordon 2018	12	PLB	8/98 (8.1)	2/98 (2.0)	2/98 (2.0)
UltiMMa 2 (43)	12	UST	69/99 (69.7)	47/99 (47.5)	24/99 (24.2)
	12	RIS	261/294 (88.8)	220/294 (74.9)	149/294 (50.7)
<i>p</i> -value			<0.0001	<0.0001	<0.0001
Gottlieb 2018	16	PLB	3/51 (6.5)	0/51 (0.0)	0/51 (0.0)
CIMPASI 1 (44)	16	CZP 200 mg	63/95 (66.3)	34/95 (35.8)	13/95 (13.7)
	<i>p</i> -value			<0.0001	<0.0001
Gottlieb 2018	16	PLB	6/49 (11.6)	2/49 (2.2)	1/49 (1.8)
CIMPASI 2 (44)	16	CZP 200 mg	74/92 (81.4)	48/91 (52.6)	14/91 (15.4)
	<i>p</i> -value			<0.0001	<0.0001
Lebwohl 2018	16	PLB	3/57 (5.3)	5/57 (0.0)	–
CIMPACT (45)	16	CZP 200 mg	113/165 (68.5)	66/165 (40.0)	–
	<i>p</i> -value			<0.0001	<0.0001
Reich 2018	16	PLB	3/65 (4.6)	1/65 (1.5)	0/65 (0.0)
TRANSFIGURE (46)	16	SEC 300 mg	56/66 (84.8)	48/66 (72.7)	22/66 (33.3)
	<i>p</i> -value			<0.001	<0.001
Mease 2018	16	PLB	40/332 (12.3)	31/332 (9.3)	–
FUTURE 5 (47)	16	SEC 150 mg	132/220 (60.0)	81/220 (36.8)	–
	16	SEC 300 mg	155/222 (70.0)	119/222 (53.6)	–
<i>p</i> -value			<0.05	<0.05	
Reich 2019	16	RIS 150 mg	237/301 (91)	218/301 (72)	120/301 (40)
IMMvent (52)	16	ADA	218/304 (72)	144/304 (47)	70/304 (23)
	<i>p</i> -value			<0.0001	<0.0001
Reich 2019	12	GUS	477/534 (89)	369/534 (69)	311/534 (58)
ECLIPSE (53)	12	SEC	471/514 (92)	391/514 (76)	249/514 (48)
	<i>p</i> -value			NA	NA
Ohtsuki 2019 SustalMM (48)	16	RIS 75 mg*	52/58 (89.8)	–	13/58 (22.4)
	16	RIS 150 mg*	52/55 (94.5)	–	18/55 (32.7)
<i>p</i> -value	16	PLB	5/58 (8.6)	–	0/0
	<i>p</i> -value			<0.001	
Mease 2020	16	ADA	195/238 (88.9)	158/283 (55.8)	132/283 (46.6)
SPIRIT H2H (51)	16	IXE	227/283 (80.2)	203/283 (71.7)	170/283 (60.1)
	<i>p</i> -value			<i>p</i> = 0.002	<0.001
McInnes 2020	52	SEC	170/215 (79)	140/215 (54)	99/215 (46)
EXCEED (55)	52	ADA	123/202 (61)	87/202 (43)	61/202 (30)
	<i>p</i> -value			0.0002	<0.0001
Ferris 2020	16	GUS	55/62 (88.7)	47/62 (75.8)	31/62 (50.0)
ORION (56)	16	PLB	0/16 (0)	0/16 (0)	0/16 (0)
	<i>p</i> -value			<0.001	<0.001
Warren 2020	16	RIS	92/164 (56.1)	74/164 (45.1)	44/164 (26.9)
IMMerge (57)	16	SEC	80/163 (49.1)	66/163 (40.5)	34/163 (20.9)

PASI, Psoriasis Area Severity Index; ADA, adalimumab; ETN, etanercept; IFX, infliximab; GOL, golimumab; CZP, certolizumab; UST, ustekinumab; SEC, secukinumab; IXE, ixekizumab; GUS, guselkumab; BRD, brodalumab; RIS, risankizumab; TIL, tildrakizumab; BRK, briakinumab; MTX, methotrexate; PLB, placebo; *vs. placebo.



recently published network meta-analysis (94–96). Although the number of RCTs reporting PASI100 response (**Table 7**) (15, 16, 20, 21, 25, 29, 30, 33, 35–37, 39–41, 43, 44, 46, 48, 51–53, 56, 57, 59, 70) as an outcome was superior to the ones reporting ACR70 response, the confidence in the NMA was not superior. Since 2015 some head-to-head trials were designed to evaluate the efficacy of specific drugs in the PASI response outcome (33, 40, 41, 51–53, 55, 57), and significant differences were found (**Table 7**).

A complete treatment of a patient with PsD should be ideally based on a single drug that is effective in all the manifestations. Currently, from the therapies included in the PASI100 NMAs, only ADA, CZP, IXE, SEC, and UST were approved for PSO and PsA. Thus, in integrative analysis of NMA results, and based only on comparisons of the drugs with placebo, those with the highest probability of reaching the proposed outcome for skin and joint domains are SEC and IXE. For SEC, OR (95% CrI) are 9.430 (5.455, 16.302) and 42.897 (26.848, 68.539) versus placebo for ACR70 and PASI100, respectively. For IXE, OR are 9.315 (4.206, 20.627) and 64.027 (39.805, 102.997) versus placebo for ACR70 and PASI100, respectively. Even though a few previous NMAs analyzed treatment options in PsD including ACR and PASI outcomes, most of them did not find significant differences in the efficacy and safety between the drugs, only detecting that treatments were more efficacious than placebo (97–101).

As reported in **Table 5**, data regarding the enthesitis domain were not so consistent as skin and peripheral arthritis results (1, 13, 18, 22, 24, 26, 28, 31, 32, 37, 38, 47, 50, 51, 55, 61, 65, 76).

In addition to the outcome not being standardized, there were studies reporting more than one outcome without consistent results (50, 51). There were drugs that even in comparison with the placebo did not show a consistent significant benefit (22, 28, 31, 38, 76). Long-term evaluation of enthesitis showed that the benefit was maintained with IFX at week 54 (58). Although the benefit of UST was not consistent at weeks 24 and 52 (28), at week 100 there was a 100% improvement of MASES from baseline (67) and the same was true for SEC results, which showed inconsistent data at week 24 (31, 32), but at week 104 there was 100% resolution of enthesitis in 70% of the patients who had enthesitis at baseline (75). Enthesopathy affects 35–50% of patients with PsA and should be managed carefully since it can affect the quality of life and work productivity even in the early stages of the disease (102). A recent study showed that enthesitis is the phenotypes of PsD that contribute most to Quality of Life Scores and that this domain should be evaluated, bilaterally, in all PsD patients, particularly in those referring joint pain (103). Nevertheless, the clinical evaluation of enthesitis is not standardized and lacks accuracy and the reliability is highly dependent on the observer (104). A recent study compared MASES, SPARCC, and LEI, the three enthesitis index, and showed that MASES had a better correlation with disease activity and functional measures (105). On the other hand, another study has reported a better performance in LEI and SPARCC indices, which showed a higher discriminatory ability and treatment responses suggested to be related to the fact that MASES evaluates fewer peripheral sites, which may be clinically relevant in the context of PsA, a predominantly peripheral disease (106).

Similarly to enthesitis, the outcomes measured in the dactylitis domain were not standardized as is explicit in **Table 6** (1, 18, 24, 26, 28, 31, 32, 37, 38, 47, 51, 55, 61, 76). Moreover, there were data with the same drug in different studies that were not consistent (31, 32, 37, 38). Long-term data showed that the benefit with IFX was maintained at week 54 (58). For UST, the median percent improvement in the enthesitis score at week 100 was 100% (67) whereas for SEC treatment 90% of the patients presented complete dactylitis resolution at week 104 (75). A major limitation in dactylitis evaluation is that physical examination is the basis for the clinical assessment of dactylitis and imaging tools have been used only to complement the clinical examination. Nevertheless, the criteria for image resolution are not uniform and therefore data from different studies are not comparable (107, 108). Like enthesitis, dactylitis also has a huge impact on the quality of life and in the structural impact of PsD, and data from enthesitis and dactylitis highlight the difficulty in treating these manifestations and the long period of treatment that is needed to achieve remission. Recently, a real-world PsA population multinational study has shown that enthesitis, dactylitis, inflammatory back pain, and sacroiliitis are significantly associated with the worsening of the patient's quality of life and/or work productivity, through evaluation of an extensive patient-reported outcomes (PROs) list—namely EQ-5D, HAQ-DI, Psoriatic Arthritis Impact of Disease (PsAID)12, and Work Productivity and Activity Impairment (WPAI) (109).

TABLE 8 | NMA results from the network of biologic therapies in the outcome PASI100.

	ADA	BRK	BRD	CZP	ETN	GUS	IXE	PLB	RIS	SEC	TIL	UST
ADA		0.511 (0.247–1.057)	0.412 (0.279–0.610)	3.005 (0.531–16.998)	4.078 (2.825–5.887)	0.518 (0.363–0.738)	0.514 (0.393–0.671)	32.891 (20.602–52.505)	0.426 (0.320–0.567)	0.767 (0.556–1.058)	1.590 (0.830–3.047)	1.152 (0.831–1.597)
BRK	1.956 (0.946–4.046)		0.807 (0.374–1.740)	5.877 (0.929–37.192)	7.977 (4.211–15.111)	1.013 (0.476–2.155)	1.005 (0.501–2.017)	64.335 (29.280–141.359)	0.833 (0.395–1.758)	1.500 (0.722–3.116)	3.110 (1.332–7.263)	2.253 (1.076–4.717)
BRD	2.424 (1.640–3.548)	1.239 (0.575–2.673)		7.285 (1.276–41.571)	9.887 (6.322–15.462)	1.256 (0.847–1.862)	1.245 (0.837–1.854)	79.742 (48.415–131.341)	1.033 (0.718–1.486)	1.859 (1.329–2.601)	3.855 (1.925–7.718)	2.793 (2.230–3.498)
CZP	0.333 (0.059–1.883)	0.170 (0.027–1.077)	0.137 (0.024–0.783)		1.357 (0.237–7.759)	0.172 (0.030–0.984)	0.171 (0.030–0.969)	10.946 (2.063–58.067)	0.142 (0.025–0.805)	0.255 (0.045–1.444)	0.529 (0.087–3.225)	0.383 (0.068–2.168)
ETN	0.245 (0.170–0.354)	0.125 (0.066–0.237)	0.101 (0.065–0.158)	0.737 (0.129–4.212)		0.127 (0.083–0.193)	0.126 (0.094–0.169)	8.066 (4.866–13.368)	0.104 (0.070–0.157)	0.188 (0.129–0.274)	0.390 (0.222–0.686)	0.282 (0.191–0.418)
GUS	1.931 (1.355–2.752)	0.987 (0.464–2.100)	0.796 (0.537–1.181)	5.801 (1.016–33.129)	7.873 (5.169–11.994)		0.992 (0.678–1.452)	63.510 (38.479–104.815)	0.823 (0.576–1.175)	1.481 (1.177–1.862)	3.070 (1.554–6.065)	2.224 (1.602–3.087)
IXE	1.947 (1.490–2.544)	0.995 (0.496–1.998)	0.803 (0.539–1.195)	5.849 (1.032–33.159)	7.938 (5.908–10.667)	1.008 (0.689–1.476)		64.027 (39.805–102.997)	0.829 (0.589–1.168)	1.493 (1.063–2.095)	3.095 (1.664–5.758)	2.243 (1.605–3.134)
PLB	0.030 (0.019–0.049)	0.016 (0.007–0.034)	0.013 (0.008–0.021)	0.091 (0.017–0.485)	0.124 (0.075–0.206)	0.016 (0.010–0.026)	0.016 (0.010–0.025)		0.013 (0.008–0.021)	0.023 (0.015–0.037)	0.048 (0.024–0.097)	0.035 (0.022–0.056)
RIS	2.347 (1.763–3.125)	1.200 (0.569–2.531)	0.968 (0.673–1.393)	7.052 (1.242–40.037)	9.571 (6.376–14.368)	1.216 (0.851–1.736)	1.206 (0.856–1.698)	77.192 (47.727–124.861)		1.800 (1.330–2.436)	3.732 (1.908–7.299)	2.704 (2.022–3.616)
SEC	1.304 (0.945–1.800)	0.667 (0.321–1.385)	0.538 (0.385–0.753)	3.919 (0.693–22.174)	5.319 (3.650–7.749)	0.675 (0.537–0.850)	0.670 (0.477–0.940)	42.897 (26.848–68.539)	0.556 (0.411–0.752)		2.074 (1.077–3.992)	1.502 (1.165–1.938)
TIL	0.629 (0.328–1.205)	0.322 (0.138–0.751)	0.259 (0.130–0.519)	1.890 (0.310–11.518)	2.565 (1.458–4.511)	0.326 (0.165–0.643)	0.323 (0.174–0.601)	20.687 (10.326–41.438)	0.268 (0.137–0.524)	0.482 (0.251–0.928)		0.724 (0.374–1.405)
UST	0.868 (0.626–1.203)	0.444 (0.212–0.929)	0.358 (0.286–0.448)	2.608 (0.461–14.746)	3.540 (2.390–5.242)	0.450 (0.324–0.624)	0.446 (0.319–0.623)	28.551 (17.930–45.468)	0.370 (0.277–0.495)	0.666 (0.516–0.858)	1.380 (0.712–2.676)	

OR and CrI are presented. Comparisons with high confidence rating based on CINeMA evaluation are identified in bold. OR higher than 1 favor the intervention specified in the row.

NMA, network meta-analysis; PASI, Psoriasis Area Severity Index; CINeMA, Confidence in Network Meta-Analysis; OR, odds ratio; CrI, credible interval; ADA, adalimumab; ETN, etanercept; IFX, infliximab; GOL, golimumab; CZP, certolizumab; UST, ustekinumab; SEC, secukinumab; IXE, ixekizumab; GUS, guselkumab; BRD, brodalumab; RIS, risankizumab; TIL, tildrakizumab; BRK, briakinumab; MTX, methotrexate; PLB, placebo.

TABLE 9 | Nail psoriasis assessment in patients with psoriasis.

Study	Author	Year	Intervention	Outcome	Time of outcome	Result	
(12)	Reich	2005	IFX vs. placebo	Percentage of improvement NAPSI	Week 10	26.0 (42.3) vs. -5.9 (54.3) ($p < 0.0001$)	
					Week 24	56.3 (43.3) vs. -3.2 (62.3) ($p < 0.0001$)	
(18)	Kavanaugh	2009	GOL 50 mg vs. placebo	Percentage of change NAPSI	Week 14	25% vs. 0% ($p = 0.015$)	
			GOL 100 mg vs. placebo			53% vs. 0% ($p < 0.001$)	
			GOL 50 mg vs. placebo			33% vs. 0% ($p < 0.001$)	
			GOL 100 mg vs. placebo			54% vs. 0% ($p < 0.001$)	
GO-REVEAL (61)	Kavanaugh	2012	GOL 50 mg vs. placebo	NAPSI (percentage change from baseline)	Week 52	51.6 ± 46.8 vs. 56.2 ± 48.1	
			GOL 100 mg vs. placebo			65.8 ± 51.9 vs. 56.2 ± 48.1	
PHOENIX 1 (27)	Rich	2014	ETN 50 mg BIW	NAPSI	Week 12	-13.6 (-16.7 to -10.5)	
			ETN 50 mg QW			-15.7 (-19.0 to -12.5)	
			UST 45 mg vs. placebo			26.7% vs. 11.8% ($p < 0.001$)	
(65)	Kavanaugh	2014	UST 90 mg vs. placebo	NAPSI baseline score	Week 12	24.9% vs. 11.8% ($p < 0.001$)	
			UST 45 mg vs. placebo			Week 24	46.5% vs. 29.1%
			GOL 50 mg vs. placebo			Week 256	1.7 ± 2.5 vs. 1.1 ± 1.9
BELIEVE (33)	Thaci	2015	ADA	NAPSI baseline reduction	Week 8	15.1%	
					Week 16	39.5%	
(26)	Mease	2015	CZP 200 mg Q2W vs. placebo	mNAPSI change from baseline	Week 24	-1.6 VS. -1.1 ($p = 0.003$)	
			CZP 400 mg Q4W vs. placebo			-2.0 vs. -1.1 ($p < 0.001$)	
UNCOVER 3 (69)	Dennehy	2016	IXE Q2W vs. placebo vs. ETN	Improvement in nail psoriasis	Week 12	38% vs. 28% vs. -4.7%	
			IXE Q4W vs. placebo vs. ETN			40% vs. 48% vs. -4.7%	
SPIRIT-P1 (37)	Mease	2017	IXE Q2W vs. placebo vs. ADA	NAPSI	Week 12	-7.7 (1.4) vs. -1.1 (1.4) vs. -6.8 (1.4) $p < 0.05^*$	
			IXE Q4W vs. placebo vs. ADA			-15.5 (1.5) vs. -2.4 (1.7) vs. -10.7 (1.5) $p < 0.05^*$	
			IXE Q2W vs. placebo vs. ADA			Week 24	-8.4 (1.5) vs. -1.1 (1.4) vs. -6.8 (1.4) $p < 0.05^*$
			IXE Q4W vs. placebo vs. ADA			-14.0 (1.5) 2.4 (1.7) vs. -10.7 (1.5) $p < 0.05^*$	
SPIRIT-P2 (38)	Nash	2017	IXE Q2W vs. placebo	Proportion of patients who had a response	Week 24	34.8% vs. 11.0% ($p < 0.0005$)	
			IXE Q4W vs. placebo			20% vs. 7.0% ($p < 0.0001$)	
UNCOVER 3 (78)	van der Kerkhof	2017	IXE Q2W vs. placebo	NAPSI from baseline	Week 12	35.2% vs. -34.3% $p < 0.001$	
			IXE Q4W vs. placebo			36.7% vs. -34.3% $p < 0.001$	
			IXE Q2W vs. ETN			35.2 (6.9) vs. 20.0 (5.9) $p > 0.005$	
			IXE Q4W vs. ETN			36.7% vs. 20% $p = 0.048$	
			IXE Q2W vs. placebo			Week 12	17.5% vs. 4.3% $p < 0.001$
			IXE Q4W vs. placebo			19.7% vs. 4.3% $p < 0.001$	
			IXE Q2W vs. ETN			17.5% vs. 10.2% $p < 0.05$	
			IXE Q4W vs. ETN			19.7% vs. 10.2% $p < 0.05$	
(36)	Blauvelt	2017	GUS vs. placebo vs. ADA	NAPSI percent improvement	Week 16	34.4 ± 42.46 vs. -0.9 ± 57.89 vs. 38.0 ± 53.87 $p < 0.001^{**}$	
			GUS vs. ADA		Week 24	49.8 ± 44.16 vs. 49.4 ± 60.04	
			GUS vs. ADA		Week 48	68.1 ± 43.00 vs. 61.4 ± 49.20	

(Continued)

TABLE 9 | Continued

Study	Author	Year	Intervention	Outcome	Time of outcome	Result
LIBERATE (77)	Reich	2017	APR vs. placebo	NAPSI (percentage of change)	Week 16	−18.7 (40.2) vs. −17.0 (25.0) $p = 0.4959$
			ETN vs. placebo			
(42)	Elewski	2018	ADA vs. placebo	mNAPSI75	Week 26	46.6% vs. 3.4% ($p < 0.001$)
			UST 90 mg vs. placebo	Improvement NAPSI	Week 26	56.2% vs. 11.5% ($p < 0.01$)
						48.7% vs. 29.1%
(81)	Ohtsuki	2018	GUS 50 mg vs. placebo	Change in NAPSI	Week 16	−1.2 (1.61) vs. −0.2 (1.13) $p < 0.001$
			GUS 100 mg vs. placebo			
TRANSFIGURE (46)	Reich	2018	SEC 150 mg vs. placebo	NAPSI (percentage of change)	Week 16	−37.9% vs. −10.8% ($p < 0.001$)
			SEC 300 mg vs. placebo			
(88)	Elewski	2019	ADA	Percentage of achievement mNAPSI75	Week 16	27.3
					Week 26	53.4
					Week 52	65.0
SPIRIT H2H (51)	Mease	2020	IXE vs. ADA	Fingernails NAPSI = 0	Week 24	58.1% vs. 71.7% ($p < 0.001$)

ADA, adalimumab; ETN, etanercept; IFX, infliximab; GOL, golimumab; CZP, certolizumab; UST, ustekinumab; SEC, secukinumab; IXE, ixekizumab; GUS, guselkumab; RIS, risankizumab; PLB, placebo; NAPSI, Nail Psoriasis Severity Index; mNAPSI, modified Nail Psoriasis Index. *IXE vs. placebo, **GUS vs. placebo.

Inflammatory back pain and sacroiliitis are common axial manifestations in PsA patients and can arise in 30 to 70% of patients (110, 111). There is an ongoing discussion on whether axial manifestations in PsA are equivalent to those seen in axial spondyloarthritis and consequently if they may be treated in the same way (112). In fact, the evidence of the efficacy of biologic therapies in the PsA axial domain is still scarce. However, some studies and case reports have suggested a positive impact of TNFi, IL-17i, and IL-12/23i in axial involvement-related outcomes in PsD patients, namely, BASDAI and ASAS-PR, showing that it could be possible to achieve remission and minimal disease activity (113–115). To our knowledge, the only randomized clinical trial addressing treatment efficacy in this specific domain patient profile is the MAXIMIZE trial (ClinicalTrials.gov NCT02721966) (86)—a study evaluating SEC efficacy in axial manifestations improvement in PsA patients. In fact, from the data released in the latest international congresses, results suggest that IL-17 inhibition, namely, with SEC, is effective in axial PsA treatment, evaluated by ASAS response and Berlin MRI score (116).

Nail psoriasis is common among patients with moderate-to-severe PsO and more prevalent in patients with PsA (117). Different studies assessed the efficacy of biologic agents in the treatment and resolution of nail psoriasis (Table 9) (12, 18, 26, 27, 34, 37, 38, 42, 46, 51, 61, 65, 69, 73, 77, 78, 81, 88). All of them showed the benefit of the tested drug compared to the placebo. The head-to-head comparison between IXE and ADA showed superiority at week 24 of IXE (51). The response is sustained in long-term studies (46, 69, 81). Of

note, most studies reporting NAPSI represent subgroup analysis including recruited patients who had manifestations of nail psoriasis. However, from the data described there are only drugs with studies designed specifically to evaluate nail Psoriasis: ETN (89), ADA (42), and SEC (46). Importantly, these studies were specifically designed to evaluate nail outcomes and have demanding recruitment criteria, with NAPSI scores more severe and, therefore, much more difficult to treat. Therefore, the results obtained with these 3 drugs may be considered more robust and significant concerning their impact on nail treatment. Of note, all studies demonstrated an improvement in the evaluated scores. However, scores and time points were not the same, making comparisons impossible.

Taking all the results from the systematic review and network meta-analysis together in Figure 2, IL-17i are the drugs tested in more manifestations, namely, SEC that had specific studies for all the domains, even though axial domain data were not yet published.

This result is in line with what was recently published in two NMA (98, 118). The first one concluded that SEC demonstrated good efficacy across the evaluated outcomes (ACR, PASI, and PsARC at 12–16 weeks) and all the treatments demonstrated superiority to placebo (98). The other study demonstrated that SEC may be the most efficacious and the safest biologic for short-term treatment of PsA (118).

Limitations

One of the main limitations of this study is the high variability of study designs, inclusion and exclusion criteria, and patients' characteristics. It is important to

note that for enthesitis, dactylitis, and nail psoriasis the evaluated outcomes are heterogeneous and do not allow the performance of a network meta-analysis. The results of the NMAs highlight the limitations of this method, and caution is needed in the interpretation of these results to avoid misleading inferences.

CONCLUSIONS

PsD is a very complex disease in which the same patient may present several manifestations with a great impact on functional and quality of life. Nowadays, we should be more demanding in the analysis of therapeutic outcomes, focusing on achieving remission in all PsD manifestations.

Although there are several effective therapies, this study showed that the concept of a holistic and efficacious treatment for patients with PsD is achievable and that IL-17i are the drugs most extensively tested in this context. Specifically, SEC demonstrated good efficacy in all the evaluated GRAPPA domains, allowing a complete short-term treatment for patients with multiple manifestations of the disease.

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DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/supplementary materials, further inquiries can be directed to the corresponding author/s.

AUTHOR CONTRIBUTIONS

TT and AB conceptualized the study, designed PICO criteria, managed the literature search, and wrote the first draft of the manuscript. PF and JF interpreted the data and critically revised the manuscript. All the authors approved the final manuscript.

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The remaining author declares that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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