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The changing face of clinical trials in psoriatic arthritis

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Abstract

Purpose of the review—We will address current treatment and unmet needs in psoriatic arthritis (PsA), examine existing randomized controlled trials (RCTs), and consider options for new trial designs and challenges in their implementation.

Recent Findings—While therapeutic options for PsA have rapidly increased, there continues to be a need for clinical trials to test new therapies and establish optimal treatment strategies in order to improve the care for patients with PsA. In addition, more data is needed on how to select the best therapy for a given patient in clinical practice. Consideration of alternative outcome measures is also needed.

Summary—Despite the rapid expansion in the number of therapy options available, there is still much to be learned about how to treat the individual patient with PsA.

Keywords

Psoriatic arthritis; Clinical Trials; Treatment

INTRODUCTION

Psoriatic arthritis (PsA) is a heterogeneous, chronic inflammatory arthritis affecting 10–30% of patients with psoriasis. Over the past 15 years, therapeutic options for PsA have increased tremendously with more targeted therapies developed as we continue to gain insight into the pathogenesis of the disease. However only approximately half of patients achieve a 20% improvement in most clinical trials. Thus, there continues to be a need for clinical trials to

Compliance with Ethics Guidelines

Conflict of Interest

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test new therapies and treatment strategies in order to improve the care for patients with PsA. In this paper, we will review current treatment and unmet needs in PsA, examine existing randomized controlled trials (RCTs), consider options for new trial designs and challenges in their implementation.

Overview of treatment of PsA and knowledge gaps in care optimization

Prior to 2004, treatments for PsA mainly consisted of non-steroidal anti-inflammatory drugs, corticosteroids, and oral agents used to treat rheumatoid arthritis (RA) such as methotrexate, sulfasalazine, and cyclosporine. Leflunomide was later added to the list of available oral agents.[1] In 2004, the first phase III trial examining the use of etanercept, tumor necrosis factor inhibitor (TNFi), was published.[2] Since then, four additional TNFi have been studied and approved in PsA.[3–7] In 2013, the first non-TNFi agent phase III trial was published for ustekinumab, an interleukin (IL)-12/23 inhibitor.[8, 9] This was followed apremilast (a phosphodiesterase inhibitor) in 2014[10] and secukinumab (an IL-17 inhibitor) in 2015.[11, 12] All eight medications are now approved for the treatment of PsA and more new therapies are in development. Phase III trials for three more medications (ixekizumab, tofacitinib, and abatacept) have been completed [13–16], and phase II trials have been completed or in progress for drugs with other new modes of action (e.g. IL-23 inhibitors guselkumab and tildrakizumab).[17, 18]

While the treatment options and expected response to therapy have advanced substantially since 2004, a significant unmet needs continue to exist. In RCTs, only half patients achieve ≥ 20% improvement and approximately 40% or less reach Minimal Disease Activity (MDA).[19] Whilst we need to continue to develop new, improved therapies for PsA, it is imperative to understand how to best use existing therapies to optimize patient care. There is sparse data comparing biologic medications, particularly among drug classes. Such studies would inform treatment recommendations. Second, data to support selection therapies for patients who have not responded to a first TNFi are needed. This population of patients tends to have more difficult to treat disease. Additionally, treatment strategy trials, such as the Tight Control of Psoriatic Arthritis (TiCoPA) study, are needed to inform management strategies that optimize care.[20] In conjunction with pharmacologic therapies, non-pharmacologic interventions may have promise; for example weight loss has been associated with achievement of MDA among patients with PsA and improvements in cutaneous psoriasis.[21–23] However, the role of non-pharmacologic therapies in PsA remains understudied. Finally, “personalized” therapy selection based on a patients disease manifestations, comorbidities, genetic factors or biomarkers could ultimately change how we deliver care for this disease but relatively little is known about predictors of treatment response.

RCTs and Pragmatic Trials: Background

The randomized control trial (RCTs) is the gold standard study design for defining whether an intervention is efficacious or not. In RCTs, a patient population is selected by employing pre-defined inclusion criteria. Patients most often represent a relatively homogenous population; this increases specificity of the diagnosis (to avoid treating patients without the disease) and may affect the range of the expected treatment responses. Patients are then

randomized to receive the intervention or a comparator (e.g., placebo) and followed over a pre-specified period of time for pre-specified primary and secondary outcomes defined by a series of outcome measures. There are often many follow up visits required, particularly for new agents, to monitor disease activity and adverse events. Benefits of RCTs over cohort studies or other observational designs include the process of randomization. Randomization equally distributes confounders (both measured and unmeasured) among the exposed and unexposed whereas confounders must be measured and accounted for in cohort studies. Investigators may choose to "stratify" randomization in order to purposefully balance certain patient characteristics (e.g., previous failure of TNFi) among the groups. This allows for analyses of these subsets (if the study is powered for such analyses). Another advantage of RCTs is reduction in systematic bias. RCTs generally have highly standardized protocols for data collection with rigorous monitoring of data collection and data entry. This minimizes information bias (i.e., data collected differently for the exposed than the unexposed). In fact, RCTs were primarily designed in the mid-twentieth century specifically to reduce bias.[24–26] Methods used in RCTs have developed significantly since they were first used. The New England Journal of Medicine (NEJM) recently launched a new series titled "The changing face of clinical trials." [27] This series of review articles and perspectives addresses methods, designs, and other important issues in RCTs.

While RCTs can address efficacy, or whether a drug *can* work, the homogenous population selected for inclusion in RCTs is not generalizable to the broader population of patients with PsA (a highly heterogeneous disease). By contrast, pragmatic trials test the effectiveness of management strategies in "real-world" clinical practice as opposed to the highly controlled settings in RCTs (Table 1). Pragmatic trials, as defined by Ford et al, "inform a clinical or policy decision by providing evidence for adoption of the intervention into real-world clinical practice."[28] These trials are embedded within clinical practice with subjects representative of the population of patients with the disease so that the outcomes are relevant to patients and physicians making treatment decisions. Such designs can be used to address comparative effectiveness, management strategies, and non-pharmacologic therapies. It is important to note that while we have categorized these as separate study designs, there is fluidity between them and, depending on the specific design, aspects of both types of trials may be present. For example, some industry-sponsored RCTs have examined comparative effectiveness of therapies in RA in a more representative population of patients.[29–32] While there have not been "pure" pragmatic trials in PsA, the TiCoPA and Methotrexate in Psoriatic Arthritis (MIPA) trials were more pragmatic-like in their inclusion of a more heterogeneous and broadly representative group of patients.

Pragmatic trials provide "pragmatic" data for clinicians and patients, however, there are obstacles for the design of pragmatic PsA trials as well. For example, because of the inclusion and exclusion criteria applied in RCTs, disease activity tends to be lower in pragmatic trials than traditional RCTs. Some outcome measures are potentially better suited for higher disease activity levels and are not always directly transferable to patients with lower baseline disease activity who may have "lower to fall," thus not reaching cut-offs such as the ACR20. On the other hand, because these trials are usually not designed to gain drug approval, there is more liberty to select alterative primary outcome measures (e.g., functional

improvement as measured by the Routine Assessment of Patient Index Data was recently used as the primary outcome in a pragmatic trial in rheumatoid arthritis).

The Changing Face of PsA Clinical Trials

In Table 2, we present the phase III clinical trials published between 2004 (year of first TNFi Phase III trial publication) and 2016 based on a literature search for "clinical trials" and "psoriatic arthritis." It becomes clear that clinical trials have been mostly the same over the past 12 years, although evolving with our knowledge of PsA. Most patients in trials to date have polyarticular disease (mean swollen and tender joint counts among these trials are 12 and 21 joints respectively). The mean disease duration is 6–7 years. Most trials compared to placebo therapy, generally around 40–50% of patients were on concomitant methotrexate (or other oral DMARDs), many trials have more patients with moderate-to-severe psoriasis than we see in clinical practice, and relatively few studies included patients who had previously failed TNF inhibitors. However, over time, changes have emerged. First, recognition of the importance of individual disease manifestations of PsA (e.g., psoriasis, nail disease, enthesitis, dactylitis) and life impact (physical function, fatigue, participation, emotional wellbeing) has led to additional outcome measures included to measure these features in PsA RCTs.[33, 34] The newest trials are incorporating a proportion of patients who have previously used or failed a TNF inhibitor by either stratifying randomization for optimal stratified analysis, or in the case of tofacitinib, devoting a full trial to these patients.[14] These patient have blunted responses compared to biologic naïve patients and thus are a "risk" in some sense for trials. However these studies are highly clinically relevant because these patients are most likely to receive new therapies, at least initially. Moreover, the population of patients with PsA is changing – many more patients have been exposed to these agents and finding sufficient numbers of patients who have not been exposed to TNFi is increasingly difficult. Finally, the most recent trials have included an "active comparator." [14, 13] In registration placebo-controlled studies of new therapies, the absolute and relative differences from the placebo response are examined to understand their benefit. However, we never treat patients with placebo in clinical practice so this is not an intuitive comparison. Comparisons with effective and widely used therapies such as TNFis as an active comparator helps physicians better understand the clinical relevance of the results.

How could trials be modified or optimized?

PsA clinical trials could be optimized through the use of different primary outcomes and overall, better outcome measures, use of active comparators, and more pragmatic designs to complement information obtained from traditional RCTs. In addition, more data on the heterogeneity of response is needed; data sharing may be one avenue to allow for independent investigators to address such questions. We address each of these elements below.

Primary outcome of clinical trials

The American College of Rheumatology 20% response criteria (ACR20) is the primary outcome required by the FDA for approval of a new therapy for PsA (Box 1). These criteria were initially developed for rheumatoid arthritis and are used in PsA trials although the diseases differ significantly. This composite measure does not include many important

domains of PsA that are not seen in RA (e.g., dactylitis, enthesitis, and axial involvement). In addition, the CRP is less meaningful in patients with PsA than in RA; CRP is normal in at least half of PsA patients and elevated CRP values are difficult to interpret in obese patients (nearly 50% of PsA patients are obese).[42, 43] Next, reductions in tender and swollen joint counts are required items so if these aspects are not achieved, the patient cannot fulfill the criteria for response. Thus, patients with low joint counts may struggle to achieve higher response levels (floor effect).[44] For this reason, the ACR20 may not be well suited for pragmatic trials (e.g., MIPA) where patients entering the study have lower joint counts than those enrolled in traditional RCTs. This has not been adequately examined, particularly in PsA. Finally, the ACR20 is not a clinically meaningful threshold. The proportion "responding" to minimum proportion of change (20%) doesn't provide any further information about the magnitude of response. Furthermore, a patient may meet ACR20 criteria (e.g., joint counts, pain, physician global and CRP decrease by 20%) but have severely impaired and practically unchanged functional and patient global assessments. Whilst patients may notice this improvement with a decrease in swollen joints from 12 to 9 joints, the impact of disease on their daily life may not change significantly.

Box 1

ACR20

The ACR20 is defined as 20% improvement in tender and swollen joint counts as well as 20% improvement in 3 of the following:

- Health Assessment Questionnaire
- Patient pain assessment
- Patient global assessment
- Physician global assessment
- Acute Phase Response: C-reactive protein (CRP)

A great deal of work has been performed to identify new composite measures that take into account the varied features of PsA and patient reported outcomes.[45–47] More work is needed better define what the alternative primary outcome measures should be. Many of the existing composite measures have been included in the data collection for recent clinical trials. Analysis of these datasets may help identify optimal outcomes. It should also be noted that outcomes for traditional RCTs and pragmatic or treatment strategy trials may be different.

Need to better understand measurement of disease activity in PsA

PsA is a heterogeneous condition and this creates challenges in how best to measure the disease in a meaningful way for all patients. In addition to changes in the primary outcome of trials, key secondary outcomes also need to reflect the diversity of disease activity and impact in PsA. With the increasing understanding of the complexity of PsA, we have also begun to understand that measuring PsA requires measuring the many aspects of the disease. In 2016, the Group for Research and Assessment of Psoriasis and Psoriatic Arthritis

(GRAPPA) in conjunction with the Outcome Measures in Rheumatology Clinical Trials (OMERACT) working group developed a new core set of domains that were important to both physicians and patients and should be measured in all future research studies.[34] However, we don't necessarily know how to best measure all of these domains. When considering disease activity, there are often disconnects between clinical assessments of activity and imaging assessments. Clinical assessment of enthesitis is rather non-specific for true inflammatory change on imaging and conversely the clinical significance of ultrasound evidence for asymptomatic enthesitis is unclear.[48] There is no gold standard for this as histological evidence is impractical. Should asymptomatic imaging evidence of enthesitis be counted as "active disease" and if yes, how much active disease is missed with current clinical enthesitis scores? Dactylitis seems relatively straight forward to measure clinically but a study presented at the ACR Annual Meeting suggested that dactylitis active on ultrasound wasn't always tender on examination.[49] Finally, axial disease, present in 20–50% of PsA can have substantial effects on mobility and function, but aside from imaging (which may not correlate with function),[50] we have no clinical or patient-reported measures that can differentiate between peripheral and axial symptoms.[51]

Following the 2016 updating of the GRAPPA/OMERACT core domain set for PsA, the working group is now addressing which instruments should be used to measure the included domains. The establishment of a core instrument set will start the standardization of instruments and allow easier comparison across populations. This process is also likely to identify that we need new instruments to accurately assess some domains. In addition, related to the discussion above about inclusion of more heterogeneous populations and different subgroups in trials, we need to better understand factors that affect how well an instrument works (e.g., baseline disease activity)[44] so that the outcome measures selected for a trials are appropriate to identify a response.

Need for active comparators

Trials testing efficacy of new therapies must fulfil regulatory requirements for subsequent registration and labelling. In nearly all cases, this requires a placebo-controlled RCT to establish efficacy. However given the number of drugs already on the market, regulators and researchers are now considering whether placebo for up to 16 weeks is really an ethical option for a comparator in RCTs. We know that joint inflammation predicts subsequent irreversible joint damage and that such erosive disease can happen rapidly.[52, 53] In order to really understand the value of a new medication, we need to understand how that therapy works when compared to other active therapies (e.g., methotrexate or TNFi). Such studies, along with comparative effectiveness studies, will also help inform treatment recommendations.

Need for pragmatic trials in PsA

When developing new therapies, traditional RCTs will continue to play an important role in establishing their efficacy but pragmatic trials are also needed to help us understand how to use these therapies in routine practice. In clinical practice, only 50–60% of patients have polyarticular arthritis limiting the generalizability of RCTs where polyarthritis is the dominant phenotype. It is also likely that many others patients are also excluded by rigorous

inclusion/exclusion criteria but the impact of this has not been measured in PsA.[54] In a recent study within the Corrona Registry, over half of patients initiating a TNFi would be excluded from a clinical trial based on joint counts alone.[55] Because drug approvals and reimbursement is based on these phase III RCTs, in the UK only patients with at least three tender and 3 swollen joints are eligible for biologics because there are no data to support their use in other groups. Effectiveness studies are needed to inform treatment decisions across the broad spectrum of patients with diverse phenotypes of PsA. Such pragmatic trials are highly relevant for understanding therapy effectiveness in diverse, real-world PsA populations to inform clinical practice.

Examining and utilizing heterogenity of response: the road to personalized therapy

Reliance on data from RCTs in highly selected popuulations offers little chance to understand treatment outcomes in many other subtypes of disease. Establishing effectiveness in other subgroups of patients defined by their phenotype could provide important insight into the disease pathophysiology and would allow accurate targeting of therapies to improve long term outcomes.

Trials could ultimately be designed to address response among subgroups of patients with PsA (e.g., patients with axial disease in addition to peripheral arthritis). Important subgroups would be considered as stratification variables. Inclusion of multiple subgroups, however, requires an increase in the sample size and complexity of trials and may pose a risk for industry sponsors if a particular group of patients with PsA do not respond as well to a particular drug. However, understanding the efficacy of therapy for the different phenotypes is critical to developing “personalized” treatment strategies and improving long-term outcomes. Current treatment recommendations for PsA use a patient’s active disease features to select a therapy but there is still little evidence supporting many recommendations.[56–58]

Genetic studies have suggested that the phenotypic heterogeneity of PsA may be linked to differing genotypes.[59] Including pharmacogenomics and biomarker studies embedded within clinical trials, while it increases the expense, may have significant scientific value. Similar biomarker studies may also provide additional value in pragmatic trials but obtaining samples in pragmatic trials will increase the complexity of the study. Finally, several studies have now found that women tend to have less robust responses than men and also have lower persistence on therapy.[60–63, 55] Little is known about why this occurs; biologic differences or potentially difference in pain perception or reporting of disease activity? More studies are needed to understand this differential response.

Data Sharing to better understand clinical trial results

The knowledge to be gained from existing trials is tremendous, particularly across trials using individual patient level data. Few datasets have such rich clinical information with known treatment allocation that occurred in a randomized (and most often blinded) fashion. However, sharing of individual patient level data from RCTs has been a topic of debate for the past 5–10 years. To this end, the Institute of Medicine in the United States published its standing on this issue in a report in 2015, “Sharing Clinical Trial Data: Maximizing

Benefits, Minimizing Risk."[64] In this report, the group highlights the challenges of data sharing (e.g., risk for loss of patient confidentiality, inappropriate analyses by different investigators) but noted that the benefits of the knowledge that can be gained from such datasets substantially outweighs these risks.[65] While there has been resistance to data sharing, mechanisms for data sharing are becoming more common place to help ensure secure access to the data and that appropriate hypotheses are being tested (e.g., the Yale Open Data Access platform).[66–68] Hopefully such platforms will make data sharing more widely achievable.

Conclusion

In summary, despite the rapid expansion in the number of therapy options available, there is still much to be learned about how to treat the individual patient with PsA. RCTs are able to address efficacy of new therapies and are designed to have high internal validity (and thus low systematic bias). However, we also need pragmatic trials more reflective of the population of patients with PsA to address effectiveness of therapies in the real world and to inform treatment selection. For both trial types, we need to reconsider whether the outcomes we're measuring in trials are the ideal outcomes and whether primary outcome measures that are more specific to PsA and more relevance to patients (e.g., a "higher bar" to achieve than a 20% improvement) should be used instead of the ACR20. Before outcomes can change, there needs to be consensus around the ideal outcomes and evidence suggesting that they are sensitive to change in a diverse group of patients with PsA. Finally, more data is needed to better understand how the heterogeneity of this disease impacts therapy response. Clinical trials are enormous endeavors both in cost and effort on the part of sponsors, physicians and patients. Optimizing trial design to make the most of these studies is critical to maximizing the knowledge obtained.

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Table 1

Differences between randomized controlled trials and pragmatic trials.

	RCTs	**Pragmatic Trials**
Purpose	Test efficacy of new therapies	Test effectiveness of therapies (in the 'real world'), comparative effectiveness, management strategies, and non-pharmacologic therapies
Randomization	Yes	Yes
Patients	Homogenous population	More heterogeneous population representative of clinical practice
Inclusion/Exclusion Criteria	More strict and specific for the target population	More relaxed to be more representative
Intervention	Tightly controlled, usually double-blinded	Delivered as it would be in clinical practice, more likely to be open label.
Data collection	Regular study visits, higher complexity of data collection	More unobtrusive data collection (e.g., through electronic medical record), fewer study visits
Outcomes	Often large number of outcomes	Smaller, more limited number of outcomes that are simple to measure
Cost	Higher	Lower
Patient and Provider Burden	Higher	Lower

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Table 2

Psoriatic Arthritis Clinical Trials

Study	Comparison	PsA duration (yrs)	Swollen joints	Tender Joints	Mean PASI	CRP	TNFi IR	MTX use	Primary Outcome	Primary Endpoint (weeks)
Mease PJ Arth Rheum 2004[2] Double-blinded	Etanercept vs Placebo (N=205)	9.1	NR	NR	Mean BSA 10.5%	NR	0%	41%	ACR20	24
Fraser AD Ann Rheum Dis 2005[35] Double-blinded	Cyclosporin +MTX vs Placebo +MTX (N=72)	3.5	11.7	25.3	2.1	16.5 mg/L	0%	All	Ritchie Index	52
Antoni C Arth Rheum 2005 (IMPACT) [36] Double-blinded	Infliximab vs placebo (N=104)	11.4	14.7	22.1	4.7	26.4 mg/L	0%	NR	ACR20	16
Mease PJ Arth Rheum 2005 (ADEPT) [3] Double-blinded	Adalimumab vs Placebo (N=313)	9.5	14.3	24.9	7.9	1.4 mg/dL	0%	51%;	ACR20	12
Nash P Dermatology 2006 (LOPAS) [1] Double-blinded	Leflunomide vs Placebo (N=186)	NR	NR	NR	9.1	NR	0%	None	PsARC	24
Mease PJ Arth Rheum 2006[37]	Alefacept vs Placebo (N=185)	NR	12.5	22	10	14.8 mg/dL	0%	Mean dose 14.0 mg	ACR20	24
Antoni C Ann Rheum Dis 2007 (IMPACT2) [4] Double-blinded	Infliximab vs Placebo (N=200)	8	14.2	24.9	10.8	21 mg/L	0%	46%;	ACR20	24 *
Kivitz AJ Semin Arth Rheum 2007[38]	Celecoxib (2 doses) vs Placebo (N=609)	8.3	18.3	29.7	6.3		N/A	44% DMARDs 1% biologics	ACR20	12

Study	Comparison	PsA duration (yrs)	Swollen joints	Tender Joints	Mean PASI	CRP	TNFi IR	MTX use	Primary Outcome	Primary Endpoint (weeks)
Double-blinded										
Kavanaugh A Arth Rheum 2009 (GO-REVEAL) [6] Double-blinded	Golimumab (2 doses) vs Placebo (N=405)	7.5	13.1	22.9	9.8	1.34 mg/dL	0%	48%	ACR20	14
Sterry W BMJ 2010 (BRESTA) [39] Double-blinded	Etanercept 50 mg twice weekly vs once weekly (N=752)	7	12.5	19.0	19.5	15.7 mg/L	0%	25%	PGA -clear/almost clear; ACR20 (secondary)	12
Braanauskaite A. Ann Rheum Dis 2012 (RESPOND) [40] Open Label	Infliximab plus MTX vs MTX alone (N=110)	3.2	14.7	20.6	9.9	NR	0%	Mean 14.6mg and 15.4 mg respectively	ACR20	16
Kingsley GH Rheumatol 2012 (MIPA) [41] Double-blinded	Methotrexate vs Placebo (N=221)	1	6.0	10.0	3.8	8.0 mg/L	0%	N/A	ACR20	24
McInnes IB Lancet 2013 (PSUMMIT 1)[8] Double-blinded	Ustekinumab (2 doses) vs Placebo (N=615)	4.0	10.7	20.0	8.1	10.6 mg/L	0%	48%;	ACR20, EULAR response PASI75	24*
Mease PJ Ann Rheum Dis 2014 (RAPID-PsA)[7] Double-blinded	Certolizumab pegol vs Placebo (N=406)	8.6	10.7	20.5	7.4†	8.3 mg/L	19.1%	64.1%;	ACR20, EULAR response	12
Di Minno Ann Rheum Dis 2014[22] Open-label	Hypocaloric diet + TNFi vs Self-managed diet + TNFi (N=126)	4.9	3.1	14.5	0.8	6.0 mg/L	0%	29.4%;	MDA	24

Study	Comparison	PsA duration (yrs)	Swollen joints	Tender Joints	Mean PASI	CRP	TNFi IR	MTX use	Primary Outcome	Primary Endpoint (weeks)
Ritchlin Ann Rheum Dis 2014 (PSUMMIT II)[9] Double-blinded	Ustekinumab (2 doses) vs Placebo (N=312)	5.1	11.3	21.7	8.4	10.5 mg/L	57.7%	49.7%;	ACR20, EULAR response PASI75	24 *
Kavanaugh A Ann Rheum Dis 2014 (PALACE I)[10] Double-blinded	Apremilast (2 doses) vs Placebo (N=504)	7.5	12.7	22.9	8.6	0.95 mg/dL	9.3%	65% baseline DMARD use (mostly mtx);	ACR20, EULAR response	16
McInnes IB Lancet 2015 (SUTURE II)[12] Double-blinded	Secukinumab (3 doses) vs Placebo (N=397)	NR	11.5	22.5	12.9≠	NR	35%	47%;	ACR20	24 *
Mease PJ NEJM 2015 (SUTURE I)[11] Double-blinded	Secukinumab (2 doses) vs Placebo (N=606)	NR	13.4	24.1	13.8	NR	29.4%	60.7%;	ACR20	24 *
Coates LC Lancet 2015 (TiCOPA)[20] Open-label	Tight Control vs Standard Care (N=206)	0.8	5.0	9.0	1.9	6.9 mg/dL	0%	N/A	ACR20	48 **
Mease PJ Ann Rheum Dis 2016 (SPIRIT-P1)[13] Double-blinded	Ixekizumab (2 doses) vs Placebo vs Adalimumab (reference arm) (N=417)	6.7	11.0	20.1	6.1	14.1 mg/L	0%	54.2% (any cs-DMARD 64%)	ACR20	24 *
Mease PJ ACR 2016 (ASTRAEA)[16] Double-blinded	Abatacept vs Placebo (N=424)	8.5	11.6	20.2	7.3≠	14.1	61%	60%	ACR20	24
Mease PJ ACR 2016 (OPAL Broaden)[15]	Tofacitinib (2 doses) vs Placebo vs Adalimumab (reference	6.1	11.5	19.6	9.2	4.8 mg/L	0%	84% (other csDMARD 16%)	ACR20	12

Study	Comparison	PsA duration (yrs)	Swollen joints	Tender Joints	Mean PASI	CRP	TNFi IR	MTX use	Primary Outcome	Primary Endpoint (weeks)
Double-blinded	arm) (N=422)									
Gladman DD ACR 2016 (OPAL Beyond)[14] Double-blinded	Tofacitinib (2 doses) vs Placebo (N=394)	9.4	11.8	21.9	7.8	5.0 mg/L	100%	72% (other csDAMRD 28%)	ACR20	12

* early escape at 16 weeks

** option to switch to TNFi at 24weeks

† estimate calculated from Table 1 in the paper which provides medians instead of mean

‡ calculated for patients with BSA>3% (48% of patients in FUTURE II)

Of note, while most studies used a 66/68 joint count, some did not specify and three used a 76/78 joint count (ADEPT, FUTURE I and II).