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Review

Monotherapy or combination therapy in PsA: current aspects

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***Abstract*:** Psoriatic arthritis (PsA) is an immune-mediated inflammatory disease with heterogeneity regarding its clinical features, mainly affecting the skin and the musculoskeletal system; additionally, extra-musculoskeletal manifestations and comorbidities are common, adding complexity to its treatment. In the last decades, a plethora of therapeutic options have been available, including conventional synthetic disease-modifying anti-rheumatic drugs (DMARDs), biological DMARDs (bDMARDs), and targeted synthetic DMARDs (tsDMARDs), and many recommendations have been published regarding the proper use of them in patients with PsA. In rheumatoid arthritis, the combination of conventional with bDMARDs or tsDMARDs is a common and recommended practice, whereas in PsA there is scarce data about the benefit of this combination. This review summarizes all the available data from randomized clinical trials, observational studies, and registries about the value of this therapeutic strategy.

Keywords: bDMARDs, combination therapy, csDMARDs, psoriatic arthritis, tsDMARDs

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Plain language summary

Use of b/tsDMARDs in PsA: with or without csDMARDs

Over the last years, many different b/ts DMARDs have been porven to be efficacious in psoriatic arthritis (PsA). Although in rheumatoid arthritis, it is established that most of these drugs work better in combination with conventional synthetic DMARDs (e.g methotrexate), this seems to be slightly different in PsA. Herein, we review the current literature about the combination therapy versus monotherapy of b/ts DMARDs in PsA. We present the results of this narrative review in a structured (per drug category) way, so that it is easier for the reader to find relevant information. There is no doubt that the currently available treatment options in PsA have changed the course of the disease and improved the functional status of the patients. However, as there is still a substantial proportion of patients who do not achieve remission or low disease activity, the need to find effective therapeutic regimens or follow different strategies is growing. In this direction, the combination of a conventional synthetic with biological or targeted synthetic DMARD does not seem to be more effective than the monotherapy of the latter. This seems to be more pronounced in the newer drug categories (anti-IL-17, anti-IL23 and JAKi) compared to the TNFi, where the co-administration of a csDMARD improves their survival.

Introduction

Psoriatic arthritis (PsA) is a chronic inflammatory disease, which falls under the umbrella of spondyloarthritis. PsA is a heterogeneous disease, exhibiting a wide variety of musculoskeletal manifestations, such as peripheral arthritis, axial involvement, enthesitis, and dactylitis.[1,2] Skin involvement is also common, with PsA displaying a prevalence of 6%–41% among patients with psoriasis (PsO).[3] Consequently, a "treat-to-target" approach, which would result in minimal disease activity (MDA), constitutes a challenging goal for the scientific community. Historically, many treatments have been submerged targeting different pathways in PsA.[4] Initiating the pharmacologic interventions with mere non-steroidal anti-inflammatory drugs (NSAIDs) or glucocorticoid administration and progressively escalating to conventional synthetic disease-modifying antirheumatic drugs (csDMARDs), up to targeted synthetic (tsDMARDs) and biologic (bDMARDs), numerous efforts have been undertaken to retain the effectiveness of its treatment to the longest.[5,6] While NSAIDs have been proven to alleviate the symptoms without having a significant effect on the progression of the disease, csDMARDs and especially methotrexate (MTX), as commonly used, have shown promising results in the cutaneous aspects of the disease, as well as in peripheral arthritis. On the contrary, treatment of individuals with axial involvement, dactylitis, or enthesitis usually necessitates tsDMARD or bDMARD addition.[7] Extra-musculoskeletal manifestations, such as uveitis and inflammatory bowel disease (IBD), along with a wide spectrum of comorbidities from which they usually suffer, including metabolic syndrome, cardiovascular diseases, fibromyalgia, and depression, further enhance the complexity of treatment decision.[8] With all these challenges under consideration, clinicians increasingly adopt combination strategies in their daily practice routine.[9]

Combination therapy versus monotherapy is thought to ameliorate the efficacy of the chosen bDMARD treatment and its consistency over time. As clinical experience and randomized clinical trials (RCTs), in both rheumatoid arthritis (RA) and PsO, have shown adding a csDMARD on top of a bDMARD therapy may act additively and synergistically, enhancing its treatment's positive results.[7,10] Furthermore, obstacles like secondary failure over time and anti-drug antibodies (abs) development, following the bDMARD administration, may be conquered to one point, prolongating the retention of the prior therapy. Finally, it is noteworthy that this strategy enables the decrease in csDMARD dosage in case of adverse events (AEs) occurrence.[10] However, as far as PsA is concerned, there is no satisfactory evidence of efficacy and safety based on RCTs, supporting the superiority of combination treatment. This is also reflected in the recommendations by European Alliance of Associations for Rheumatology (EULAR) and Group for Research and Assessment of Psoriasis and Psoriatic Arthritis (GRAPPA), which support that the combination therapy is not necessary to achieve a short-term response, even though a positive impact on immunogenicity has been noted.[2,5] In the same direction, American College of Rheumatology (ACR) outlines, at its latest recommendations update, the extra profit in maintaining MTX use, apart from the addition of bDMARDs in cases of severe cutaneous manifestations, or when uveitis co-exist. Nevertheless, these recommendations are based on low or even, very low levels of evidence.[1,3] Equally low is the evidence background for retaining the MTX administration during a tumor necrosis factor inhibitor (TNFi) transition, as it is considered to sustain TNFi efficacy.[3]

In this review, we present data related to the efficacy and safety profile of combination treatment versus monotherapy, extracted from RCTs and their open label extensions (OLE), post hoc analyses of subgroups, registries, and observational studies to demonstrate if that strategy is helpful in PsA treatment.

Tumor necrosis factor inhibitors

TNFi have been the pioneers in PsA biologic therapy since 2005, when the beneficial effect of the first TNFi was discovered.[11] Up to now, this drug class includes four monoclonal abs targeting the soluble TNFa, adalimumab (ADA), infliximab (IFX), certolizumab (CER), and golimumab (GOL), as well as etanercept (ETN), a soluble TNF decoy receptor. TNFi address the full spectrum of spondyloarthritis manifestations (except ETN in uveitis and IBD) and are recommended as first-line agents for multiple PsA domains (peripheral arthritis, nail disease, axial disease, enthesitis, dactylitis, PsO).[12]

The superiority of TNFi monotherapy or combination therapy with csDMARDs in PsA is a highly controversial issue that has been investigated in a blinded design, mainly as part of the original

TNFi RCTs, when subgroup analyses stratified by csDMARD use were utilized. Further observational insights are drawn by their complimentary long-term extension (LTE) studies, and these can be expanded by real-life data from international TNFi registries.

Original RCTs were conducted in individuals with active PsA, naïve or experienced in csDMARDs, but unresponsive to NSAIDs.

Starting with ADA, in its original double-blind RCT (ADEPT) approximately half of the 313 participants randomized either to ADA or to placebo, received concomitant MTX.[13] Subgroup analysis in the ADA group during the blinded 24-week period showed similar efficacy (ACR20/50/70 response scores) among MTX-treated and patients not treated with MTX, which continued for the 285 participants enrolled in the 48-week LTE study (Table 1). Radiographic changes were interchangeable between groups at 24 and 48 weeks (LTE). Combination therapy performed better at Psoriasis Area and Severity Index (PASI) 50 at 48 weeks (83% vs 55%), but this wasn't consistent at PASI 75/90/100 assessments. Safety signals were remarkable for 5 patients in the combination versus 3 patients in the monotherapy group, experiencing elevated liver enzymes in a total of 285 participants.[14] Along the same lines, another RCT reports similar ACR20/50/70 at week 12 for patients receiving ADA irrespective of baseline MTX or other csDMARD treatment (approximate ACR20, 40%; ACR50, 25%; ACR70, 15%).[15]

The first exploratory RCTs (IMPACT 1,2) for IFX in PsA were conducted in the early 2000s. IMPACT 1 (Table 1), a double-blind placebo-controlled 16-week trial, did not show the superiority of IFX monotherapy over combination therapy with either MTX or another csDMARD when ACR20 was considered and in PsA individuals in the active arm unresponsive to csDMARDs.[11] ACR20 results were verified in IMPACT 2 RCT, a trial with a similar design (Table 1).[16] A higher portion of patients in the IFX monotherapy group reported an ACR50 and ACR70 at the first blinded 14 weeks, but this difference was not sustained in the LTE. Elevated liver enzymes (>150 IU/L) were numerically more in the IFX monotherapy (4 vs 1) opposing to the combination therapy, and these were sustained during LTE.[16,17] PsO, as assessed by PASI75, improved equally across both groups. In patient-reported outcomes (Health Assessment Questionnaire, HAQ), IMPACT 2 displays a disproportionate mean improvement across groups, of 34.1% in combination therapy versus 61.6% in IFX monotherapy at 14 weeks, which aligned with the improvement for Short Form 36 (combination; Physical Component Score (PCS) 7.9 improvement, mental component score (MCS) 2.0 improvement versus monotherapy; PCS 10.1 improvement, MCS 5.3 improvement).[18]

ETN effectiveness over arthritis symptoms in csDMARD naïve PsA was investigated in 2 RCTs by Mease et al.[19,20] (Table 1). Investigators reported comparable clinical responses in patients receiving MTX and in patients not receiving MTX at all time points of assessment. In SEAM-PsA, when evaluated with Sharp/van der Heijde score (SHS), 94.7% of patients' radiographic examinations did not deteriorate regardless of MTX status. Skin improvement was reported to a similar degree in both groups, even when patients were stratified according to their baseline body surface area (BSA) status (⩾3% or ⩾10%). Nausea was more common in ETN combination therapy with MTX versus ETN monotherapy; however, the overall rate of AEs did not differ significantly across groups.

GO-REVEAL trial (Table 1), originally designed to explore the currently well-known therapeutic potential of GOL in patients with PsA, provides useful insights into this debate. Patients with active disease, experienced in csDMARDs, were recruited in a double-blind RCT and a 2-year LTE. This was the first TNFi RCT to show greater radiographic benefit of combined GOL and MTX therapy, as assessed by SHS, with sustained superiority over 2 years. Combined therapy exhibited slightly greater improvement in Nail Psoriasis Severity Index (NAPSI), dactylitis, and enthesitis scores, while ACR arthritis evaluation was similar between groups. Rates of AEs and skin improvements were interchangeable.[21–23]

CER was the latest TNFi monoclonal ab included in PsA's treatment armamentarium, showing favorable results in the RAPID-PsA trial and its complementary LTE (Table 1). Monotherapy with CER failed to show short- and long-term advantages over combination therapy when arthritis, skin, and safety signals were considered, while both regimes were equally beneficial.[24,25]

Beyond RCTs and LTEs, observational studies and (inter)national PsA registries provide insights

Table 1. Characteristics and results of TNFi randomized controlled trials.

	Investigators type name	PsA characteristics	Drug	PsA duration, mean (SD)	Duration of trial	ACR20 (%)			ACR50 (%)
ADA	Mease et al. RCT ADEPT (+LTE)	Moderate-to-severe activity Minimum NTJ/NSJ: 3/3 NSAIDs-IR TNF-naïve	Monotherapy	9.8 (8.3)	24 w (LTE 48 w)	61 (12 w)		50 (48 w)	36 (12 w)
			+ MTX			55 (12 w)		63 (48 w)	36 (12 w)
IFX	Antoni et al. RCT IMPACT	Severe activity csDMARD failure	Monotherapy	11.7 (9.8)	16 w	74 (16 w)			–
			+MTX			62.5 (16 w)			
			+other csDMARDs			68 (16 w)			
	Antoni et al. RCT IMPACT 2 (+LTE)	Active disease csDMARD and NSAID failure	Monotherapy	8.4 (7.2)	24 w (LTE 54 w)	57 (14 w)	51 (24 w)	61 (54 w)	**43 (14 w)**
			+MTX			60 (14 w)	57 (24 w)	57 (54 w)	**28 (14 w)**
ETN	Mease et al. RCT	Active disease, NSAIDs-IR minimum NTJ/NSJ: 3/3	Monotherapy	9	24 w	No significant differences in clinical response were observed between MTX strata			
			+MTX						
	Mease et al. RCT SEAM-PsA	Active disease MTX and bDMARDs naïve Minimum NTJ/NSJ: 3/3	Monotherapy	3.1 (6.0)	48 w	60.9 (24 w)		83.1 (48 w)	44.4 (24 w)
			+MTX	3.0 (6.0)		65.0 (24 w)		80.4 (48 w)	45.7 (24 w)
GOL	Kanavaugh et al. RCT GO-REVEAL (+LTE)	Active disease Minimum NTJ/NSJ: 3/3 despite NSAIDs and DMARDs use	Monotherapy	7.2 (6.8)	24 w	Benefit seen irrespective of MTX use (14 w)			
			+MTX						
	Kanavaugh et al. RCT GO-REVEAL LTE	Active disease Minimum NTJ/NSJ: 3/3 despite NSAIDs and DMARDs use	Monotherapy	7.2 (6.8)	LTE 52 w	Comparable clinical response rates, **slightly greater Improvement in NAPSI, dactylitis, and enthesitis scores (LTE) in +MTX group**			
			+MTX						
	Kanavaugh et al. RCT GO-REVEAL LTE	Active disease Minimum NTJ/NSJ: 3/3 despite NSAIDs and DMARDs use	Monotherapy	7.2 (6.8)	LTE 104 w	58.6–72 (104 w)			43.1–52 (104 w)
			+MTX			67.3–70.4 (104 w)			49.1–50.7 (104 w)
CER	Mease et al. RCT RAPID-PsA +LTE	Active disease Minimum NTJ/NSJ: 3/3 ⩾1 DMARD failure ESR ⩾28 mm/h or CRP >7.9 mg/L	Monotherapy	–	24 w (LTE 216 w)	50% (12 w)		83.3% (216 w)	57.7 (96 w)
			+csDMARDs			56.8% (12 w)		79.7% (216 w)	65.5 (96 w)

(Continued)

	ACR70 (%)		**Radiology, mTSS (mean (SD)) or SHS (%)**	**AEs**	**Skin, PASI 50/75/90/100 or BSA improvement (mean (SEM) %)**
38 (48 w)	23 (12 w)	29 (48 w)	mTSS (24 w): −0.2 (1.59)	Elevation of ALT in 3 patients	**55**/48/38/28 (48 w)
49 (48 w)	17 (12 w)	31 (48 w)	mTSS (24 w): −0.2 (1.17)	Elevation of ALT in 5 patients	**83**/72/59/41 (48 w)
	–		–	–	**–**
40 (24 w)	**21 (14 w)**	32 (24 w)	–	**4 patients had >150 IU/L ALT, AST** **LTE:** Overall similar rate of AE, **less infusion reactions, less elevated ALT, AST, and antibody (+) in MTX group**	–/48/–/– (54 w)
43 (24 w)	**9 (14 w)**	21 (24 w)		**1 patient had >150IU/L ALT, AST**	–/53/–/– (54 w)
63.0 (48 w)	29.2 (24 w)	39.7 (48 w)	SHS: 94.7% did not progress (48 w)	Any AE (67.7%) Serious AE (6.7%) **Nausea (6.4%)**	69.8 (2.7) (⩾3% BS BSA) 74.2 (3.3) (⩾10% BS BSA) 24 w
60.2 (48 w)	27.7 (24 w)	39.7 (48 w)	SHS: 94.7% did not progress (48 w)	Any AE (76.1%) Serious AE (6%) **Nausea (14.4%)**	75.5 (3.7) (⩾3% BS BSA) 81.6 (2.6) (⩾10% BS BSA) 24 w
			SHS: 92% did not progress (24 w)	Treatment with MTX did not appear to affect transaminase levels (14 w)	Benefit of GOL at week 14 was observed irrespective of MTX use
			SHS: 98.5% did not progress (24 w)		
			SHS change from BS to 52 w: 0.07 (1.49)	Similar rate of AE	–
			SHS change from BS to 52 w: −0.45 (1.65)		
	24–37.4 (104 w)		**MTX group showed numerically less progression (week 104)**	–	71–83/46–73/27–51/–
	29.1–33.8 (104 w)				74–89/62–71/38–54/–
59.5 (216 w)	45.1 (96 w)	40.5 (216 w)	–	Similar rate of AE	–/78.1/–/– (216 w)
65 (216 w)	45.5 (96 w)	54.5 (216 w)			–/79.2/–/– (216 w)

Significant differences between groups are depicted in bold.
ACR, American College of Rheumatology; ADA, adalimumab; AE, adverse effects, ALT, alanine aminotransferase, AST, aspartate transaminase; bDMARDs, biologic disease-modifying antirheumatic drugs; BS, baseline, BSA, body surface area; CRP, C-reactive protein; csDMARDs, conventional synthetic disease-modifying antirheumatic drugs; ESR, erythrocyte sedimentation rate; ETN, etanercept; GOL, golimumab; IFX, infliximab; IR, inadequate response; LTE, long-term extension; mTSS, modified Total Sharp Score; MTX, methotrexate; NAPSI, Nail Psoriasis Severity Index; NSAIDs, non-steroidal anti-inflammatory drugs; NSJ, number of swollen joints; NTJ, number of tender joints; PASI, Psoriasis Area and Severity Index; PsA, psoriatic arthritis; RCT, randomized clinical trial; SD, standard deviation; SEM, standard error; SHS, Sharp/van der Heijde score; TNFi, tumor necrosis factor a inhibitor; w, week(s).

extrapolated from longitudinal TNFi and/or csDMARD administration (Table 2).

The BSRBR registry in the United Kingdom, evaluating 596 biologics naïve PsA individuals, exhibited that combined therapy (TNFi and MTX or another csDMARD) had no greater effect on EULAR responses than TNFi monotherapy over 6 months of follow-up.[26] This comes in agreement with findings presented by the Norwegian registry, showing similar efficacy-related findings not only for EULAR responses but also for ACR20/50/70 and modified Disease Activity Index for Psoriatic Arthritis (mDAPSA) results.[27] The opposite was the case for 15,332 TNFi naïve PsA individuals evaluated by a large EuroSpA, reporting better response rates for combination over monotherapy at 12 months.[28]

NOR-DMARD (Norway) registry, recruiting TNFi naïve PsA individuals since 2000, concluded in favor of combination therapy for better TNFi survival (especially for ADA and IFX). However, the mHAQ score at baseline and after combination or monotherapy treatment did not differ among groups.[27] Longer drug retention period was also highlighted for IFX–MTX coadministration group versus IFX monotherapy in DANBIO (Denmark) and ICEBIO (Iceland) registries in biologic naïve individuals relying on 12-month data.[29] Swedish registry displayed the superiority of concomitant TNFi and MTX therapy in drug survival independent of arthritis pattern, which was further attributed to MTX protection over AEs.[30]

So far, data from registries are not concluding. The CORRONA registry provides conflicting results and challenges combination superiority at drug survival. TNFi persistence was interchangeable across groups in this large (519 participants) US-based registry, when all TNFi (ADA, ETN, IFX, other) were considered [30.8 (13.7–67.1) vs 32.4 (12.0–NA)], months ((median (IQR)). Strikingly, drug survival was longer for ETN monotherapy ($p = 0.01$) and IFX combination therapy ($p = 0.02$).[31] Additionally, as it arises from the ATTRA registry (unites the Czech Republic, Switzerland, Greece, Italy, and the UK registry), when each country is examined separately, in all but the Italian database, individuals on combination therapy had longer survival on their first TNFi than those on monotherapy.[32]

Another important parameter in the debate concerns time and rates of remission. CORRONA registry shows a similar median time to remission in the combination versus monotherapy group (20.7 vs 25.1 months; $p = 0.56$) with complimentary results from the Euro-PsA registry reporting improved remission rates for combination therapy with IFX or ADA but not with ETN.[28,31]

Overall, focusing on elemental and core PsA evaluations, namely ACR improvement scores and cutaneous assessment scores through either PASI or BSA, TNFi solely contribute to ameliorating PsA manifestations. It seems that TNFi and csDMARDs combined administration in everyday clinical practice achieves better TNFi retention rates and consequently less switching of drugs due to inefficacy or AEs.

Interleukin-17 inhibitors

The armamentarium of PsA treatment expanded significantly after the approval of interleukin (IL)-17, IL-12/23, and IL-23 inhibitors. As the loss of efficacy over time and the "difficult-to-treat" phenotypes were always a common problem among all class therapies, subgroup analyses with csDMARD combination therapy were additionally conducted to evaluate their efficacy.[10]

Regarding IL-17 inhibitors, secukinumab (SEC), ixekizumab (IXE), and bimekizumab are approved for PsA therapy. The FUTURE 2 trial was a phase III, double-blind RCT, assessing the efficacy, safety, and tolerability of SEC for 2 years, with an LTE of 5 years. In total, 397 individuals were randomized 1:1:1:1 to receive subcutaneous administrations of 300 mg, 150 mg, 75 mg, and placebo and were assessed at baseline, weeks 1, 2, 3, and 4, and every 4 weeks thereafter, from which 248 patients completed the OLE. With 47% of the population receiving concomitant MTX, ACR20 response rates were comparable among combination and monotherapy groups. Similarly, this was also applied for ACR50 and ACR70, at weeks 104, as well as for weeks 208 and 260 assessments (Table 3). No data for cutaneous manifestations and safety were extracted regarding this comparison.[33,34] Likewise, FUTURE 3, an RCT for SEC autoinjector with analogous design, reported interchangeable ACR20 and ACR50 response rates at week 24 (Table 3).[35] These assessments were consistent through 52 weeks of treatment. Lastly, MAXIMISE, a phase III RCT of 52 weeks duration, assessed the

Table 2. Characteristics and results of TNFi registries.

Investigators name country	PsA characteristics	Drug	PsA duration	Follow-up	Efficacy				Drug survival		Remission
					ACR20/50/70 (%)	EULAR response %	mDAPSA (Δ), mean (SD)	DAS28-CRP (Δ)			
Kristensen et al. SSATG registry (Sweden)	Active PsA TNFi-naïve	Monotherapy (ADA, ETN, IFX)	9.4 (4.2–17.8) median (IQR)	1 year	–	67 (12 m)	–	–	**TNFi monotherapy showed significantly lower drug survival due to adverse events**		–
		+MTX	7.9 (3.7–15.0) median (IQR)			69 (12 m)					
Saad et al. BSRBR registry UK	Biologic naïve	Monotherapy (ADA, ETN, IFX)	12.4 (8.7) mean (SD)	18 m	–	79.5 (6 m)	–	–	–		–
		+MTX				78.1 (6 m)					
		+other csDMARD				73.3 (6 m)					
Fagerli et al. NOR-DMARD (Norway)	TNFi-naïve	Monotherapy (ADA, ETN, or IFX)	5.1 (1.1–11.7) median (IQR)	3 years	56.1/40.9/24.2 (6 m)	60.8 (6 m)	–33.9 (40.5) (6 m)	–	**Better TNFi survival (1st and 2nd year) with concomitant MTX especially for ADA, IFX. MTX decreased hazard of TNFi termination**		–
		+ MTX	5.5 (1.6–12.7) median (IQR)		59.6/36.2/26.2 (6 m)	48.5 (6 m)	–29.6 (50.5) (6 m)	–			
Glintborg et al. DANBIO (Denmark) and ICEBIO (Iceland) registries	TNFi-naïve	Monotherapy (IFX)	7 (3–13) median (IQR)	1 year	–	–	–	–	**Drug survival was shorter in patients not receiving concomitant MTX**		–
		+MTX									
Mease et al. CORRONA registry (USA)	Biologic naïve	Monotherapy (ADA, ETN, IFX, other)	6.2 (7.2) mean (SD)	2.1 ±2.2 years	–	–	–	–	30.8 (13.7–67.1) ((median (IQR))	Similar drug survival for monotherapy or combination **Drug survival was longer for ETN monotherapy ($p = 0.01$) and IFX combination therapy ($p = 0.02$)**	Similar median time to achieve remission in combination vs monotherapy group (20.7 vs 25.1 m; $p = 0.56$)
		+csDMARDs	6.4 (7.5) mean (SD)						32.4 (12.0–NA) ((median (IQR))		

(Continued)

Table 2. (Continued)

Investigators name country	PsA characteristics	Drug	PsA duration	Follow-up	Efficacy				Drug survival	Remission
					ACR20/50/70 (%)	EULAR response %	mDAPSA (Δ), mean (SD)	DAS28-CRP (Δ)		
Lindström et al. EuroSpA collaboration (Czech Republic, Denmark, Finland, Iceland, Italy, Norway, Portugal, Romania, Slovenia, Spain, Sweden, Switzerland, and Turkey)	Biologic naïve	Monotherapy (ADA, ETN, IFX, GOL, CER) +csDMARD	6.2 (7.3) mean (SD) 6.3 (7.1) mean (SD)	1 year	–	–	–	**Better outcomes in the co-medication groups**	Considerable variation across countries	**Clinical remission at 12 m in overall comedication group versus monotherapy group was 1.25 (1.12–1.41) favoring comedication. OR for MTX comedication compared with monotherapy for IFX (1.55 (1.21–1.98)) and ADA (1.45 (1.23–1.72)), and ETN (1.12 (0.95–1.31))**
Thomas et al. ATTRA registry (Czech Republic, Switzerland, Greece, Italy, UK)	Biologic naïve	Monotherapy (ADA, ETN, IFX) +csDMARD	–	–	–	–	–	Rate of DAS28 change did not differ between groups	**In all but the Italian database, patients on combination therapy had longer survival on their first TNFi than those on monotherapy**	–

Significant differences between groups are depicted in bold.
ACR, American College of Rheumatology; ADA, adalimumab; CER, certolizumab; CRP, C-reactive protein; csDMARDs, conventional synthetic disease-modifying antirheumatic drugs; DAS, disease activity score; EULAR, European Alliance of Associations for Rheumatology; ETN, etanercept; GOL, golimumab; IFX, infliximab; IQR, interquartile range; m, months; mDAPSA, modified Disease Activity Index for Psoriatic Arthritis; MTX, methotrexate; OR, odds ratio; PsA, psoriatic arthritis; SD, standard deviation; TNFi, tumor necrosis factor a inhibitor.

efficacy of SEC on individuals with active axial disease, naïve to bDMARDs, with or without a stable dose of MTX co-administration. The primary endpoint was the Assessment of SpondyloArthritis international Society (ASAS) 20 response at week 12, which was achieved with both SEC dose regimens (300 and 150 mg s.c.) without superiority for the MTX–SEC subgroup. Of 498 individuals randomized, 425 completed week 52. ASAS20 responses maintained their equiveillance between the two groups (Table 3).[36] It should be mentioned that neither study assessed the impact of combination therapy on other manifestations of PsA.

Regarding IXE, a post hoc analysis of its approval trials accumulates most of the evidence toward the potential superiority of combination treatment. Combe et al., extracting data from SPIRIT P1 and SPIRIT P2, two double-blind, phase III RCTs, assessed the efficacy and safety of IXE for 52 weeks, in active PsA individuals, regardless of prior TNFi experience, comparing subgroups with and without concomitant MTX. At SPIRIT trials, patients were randomized to receive IXE 80 mg every 2 weeks, every 4 weeks, ADA 40 mg (up to week 24 only in SPIRIT-P1) every 2 weeks, or placebo. Even though this analysis focuses on patients receiving stable doses of MTX (183 patients, 40.2%), the ones who changed the dosage, due to inadequate response (IR) at week 16 or after rheumatologists' counseling between weeks 24 and 52, were also included. During the double-blind period (24 weeks), ACR20/50/70 were similar or higher for the IXE monotherapy group (Table 3). Similarly, at week 52, superiority in ACR response rates was also noted for the IXE monotherapy group toward the group of concomitant MTX in stable doses. Nonetheless, this was not the case, when all the individuals taking MTX were involved, regardless of dose stability. No differences between the two subgroups were noticed. Regarding disease control, indicated by the disease activity index for psoriatic arthritis (DAPSA), low disease activity (LDA), or MDA measurements at week 52, the two groups had no difference. However, it should be noted that the group receiving IXE administration every 2 weeks achieved higher rates of monotherapy success compared to the IXE-MTX co-administration group. In the former group, more Treatment-Emergent Adverse Events (TEAEs) were also noticed (Table 3). In general, no discrepancies have been reported over the safety profile.[37] Expanding the assessment period to 3 years, Coates et al. analyzed the efficacy, safety, and contribution of IXE on decelerating the radiographic disease progression. Individuals receiving IXE Q4W were randomized into 3 groups: 89 patients received monotherapy, 88 received concomitant MTX, and 113 received IXE combined with any csDMARD (MTX, MTX sodium, sulfasalazine, leflunomide, cyclosporine, hydroxychloroquine, or hydroxychloroquine sulfate). Adjustment to concomitant csDMARDs was allowed during the extension periods. All IXE active treatment groups (irrespective of MTX concomitant use) displayed remarkable improvement in all aspects of the disease activity and health-related quality of life (QoL), compared to placebo. However, in terms of safety, AEs were more frequent in patients receiving IXE as monotherapy. Higher IRs for infections, though not serious, and injection site reactions were observed, although biased possibly, since patients with a high risk of infection could have interrupted csDMARDs concomitant use.[38] Another post hoc analysis from SPIRIT P1, a head-to-head comparison with ADA, estimated the efficacy and safety of IXE, with or without concomitant MTX administration in bDMARDs naïve individuals presenting with both active PsO and PsA, for 52 weeks (no adjustment in MTX dose till week 24). Combined ACR50 and PASI100 response (primary endpoint) and secondary endpoints, such as MDA response, resolution of enthesitis (as assessed by SPARCC (SpondyloArthritis Research Consortium of Canada) enthesitis = 0), and NAPSI score improvement, were achieved with IXE regardless of MTX concomitant use. Numerical difference was noted only in very low disease activity response (Table 3). Moreover, function outcomes and QoL reports were lower in the MTX group compared with those of the monotherapy group. Safety data were consistent between the two groups with only numerical differences in hepatotoxicity and cytopenia in favor of the monotherapy group and infections in favor of the MTX group.[39]

An additional arrow in the quiver of IL-17A inhibitors is bimekizumab, a monoclonal IgG1 ab that selectively inhibits IL-17A and IL-17F. European Medicines Agency in 2023 approved bimekizumab for PsA treatment through two RCTs: BE-COMPLETE, BE-OPTIMAL, and their OLEs. All these trials included patients with concomitant csDMARDs, but none of them have provided special data for these subpopulations so far.[40–43]

Table 3. Characteristics and results of IL-17i trials.

	Investigators type name	PsA characteristics	Drug	Duration of trial	ACR20 (%)			ACR50 (%)			ACR70 (%)		
SEC	McInnes et al. RCT FUTURE 2	Active disease Minimum NTJ/NSJ: 3/3 NSAIDs, csDMARDs-IR and TNFi-IR or naïve	SEC 75/150/300 mg + MTX	5 years (data up to 104 w)	15/64/54 (24 w)	46/57/67 (52 w)	46/60/69 (104 w)	10/35/33 (24 w)	27/37/46 (52 w)	26/37/49 (104 w)	2/25/14 (12 w)	15/20/22 (52 w)	14/26/34 (104 w)
					45/48/55 (24 w)	55/72/60 (52 w)	54/70/71 (104 w)	28/35/38 (24 w)	34/41/42 (52 w)	31/35/53 (104 w)	11/16/27 (12 w)	17/20/27 (52 w)	16/20/33 (104 w)
	McInnes et al. RCT FUTURE 2	Active disease Minimum NTJ/NSJ: 3/3 NSAIDs, csDMARDs-IR and TNFi-IR or naïve	SEC 150/300 mg + MTX	5 years (data from 104 to 260 w)	62/77 (156 w)	72/74 (208 w)	75/85 (260 w)	35/50 (156 w)	53/49 (208 w)	38/58 (260 w)	–		
					78/73 (156 w)	78/68 (208 w)	74/63 (260 w)	42/59 (156 w)	50/44 (208 w)	47/38 (260 w)			
	Nash et al. RCT FUTURE 3	Active disease Minimum NTJ/NSJ: 3/3 NSAIDs, csDMARDs-IR and TNFi-IR or naïve	SEC 150/300 mg +MTX	3 years	35/54 (24 w)			13/39 (24 w)			–		
					51/43 (24 w)			27/30 (24 w)					
					ASAS20 (%)								
	Baraliakos et al. RCT MAXIMISE	Active spondylitis BASDAI ⩾4, spinal pain score ⩾40 ⩾2 NSAIDs-IR Biologic naïve	SEC 150/300 mg +MTX	52 weeks	67/61 (12 w)			77–79/66–80 (52 w)					
					67/67 (12 w)			82–83/84–85 (52 w)					

(Continued)

Table 3. (Continued)

	Investigators type name	PsA characteristics	Drug		Duration of trial	ACR20 (%)	ACR50 (%)	ACR70 (%)	DAPSA LDA	TEAEs
IXE	Comble et al. Post hoc Analysis of SPIRIT-P1 and SPIRIT-P2 (2 RCTs)	Active disease Minimum NTJ/NSJ: 3/3 bDMARD naïve (P1) 1 or 2 bDMARD-IR and ⩾1 csDNARD-IR (P2)	IXE Q4W	+ MTX STABLE	52 w	**38.8% (52 w)**	**35.8% (52 w)**	**37.1% (52 w)**	52.9% (52 w)	Similar with monotherapy group
				Monotherapy		66.3% (52 w)	55.3% (52 w)	48.4% (52 w)	52.6% (52 w)	Similar with monotherapy group
				+/– MTX adjusted		56.1% (52 w)	40.2% (52 w)	38.6% (52 w)	–	–
			IXE Q2W	+ MTX STABLE		Similar with Q4W case	Similar with Q4W case	Similar with Q4W case	40.8% (52 w)	**Proportion > with + MTX**
				Monotherapy		Similar with Q4W case	Similar with Q4W case	Similar with Q4W case	**54.9% (52 w)**	**Proportion > with + MTX**
				+/– MTX adjusted		56.1% (52 w)	26.2% (52 w)	26.7% (52 w)	–	–

	Investigators type name	PsA characteristics	Drug		Duration of trial	ACR20 + PASI 50	ACR20	ACR50	ACR70	PASI 100	MDA	VLDA	NAPSI = 0	SPARCC index = 0	HAQ-DI ⩾0.5	TEAEs
	Smolen et al. Open label SPITIT H2H	Active disease Minimum NTJ/NSJ: 3/3 and BSA ⩾3% ⩾1 csDNARD and bDMARD/tsDMARD naïve	IXE Q4W *n*: 117	–	52 w	39.7 % (w52)	83/116 (71.6)	52.6% (52 w)	47/116 (40.5)	76/116 (65.5)	56/116 (48.3)	32/116 (27.6)	57/83 (68.7)	41/78 (52.6)	63/116 (54.3)	92 (79.3)
			+ MTX *n*: 167			38.9 % (w52)	114/167 (68.3)	47.9% (w52)	53/167 (31.7)	106/167 (63.5)	78/167 (46.7)	34/167 (20.4)	72/108 (66.7)	66/111 (59.5)	77/167 (46.1)	117 (70.1)

ACR, American College of Rheumatology; ASAS, Assessment of SpondyloArthritis International Society; BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; BSA, body surface area; bDMARD, biologic disease-modifying antirheumatic drug; CRP, C-reactive protein; csDMARD, conventional, synthetic disease modifying antirheumatic drug; DAPSA, Disease Activity index for Psoriatic Arthritis; HAQ-DI, Health Assessment Questionnaire Disability Index; IL, interleukin; IR, inadequate response; IXE, ixekizumab; LDA, low disease activity; MDA, minimal disease activity; MTX, methotrexate; NAPSI, Nail Psoriasis Severity Index; NSAIDs, non-steroidal anti-inflammatory drugs; NSJ, number of swollen joints; NTJ, number of tender joints; PASI, Psoriasis Area and Severity Index; PsA, psoriatic arthritis; PsO, psoriasis; Q2W, every 2 weeks; Q4W, every 4 weeks; RCT, randomized clinical trial; SEC, secukinumab; SPARCC, SpondyloArthritis Research Consortium of Canada; TEAEs, Treatment Emergent Adverse Events; TNFi, tumor necrosis factor a inhibitor; VLDA, very-low disease activity; w, weeks.

In conclusion, there is no evidence proving the superiority of combination treatment versus anti-IL-17 monotherapy.

IL-12/IL-23 inhibitors and IL-23 inhibitors

As more light was shed in the pivotal role of IL-23 in PsA pathogenesis,[44] two monoclonal abs (guselkumab (GUS) and risankizumab (RKZ)), binding with high affinity and specificity to the p19 subunit, have been added to the treatment armamentarium.[44] DISCOVER 1 was the first double-blind, phase III RCT to assess the efficacy and safety of GUS in the treatment of active PsA in individuals with previous failure to one or two bDMARDs. The primary endpoint of ACR20 response at week 24 was achieved, irrespective of concomitant MTX use (Table 4).[45] This was also supported by DISCOVER 2, an RCT of a similar design, evaluating the efficacy, safety, and structural damage in patients with active PsA, naïve to bDMARDs, stratified by the usage of concomitant csDMARDs (Table 4). COSMOS, a phase IIIb, RCT, randomizing PsA individuals with TNFi-IR, to receive GUS 100 mg every 8 weeks or placebo, revealed consistent results in subgroup analysis based on the concomitant use of MTX (Table 4).[46] No differences in safety profile occurred except for higher rates of liver toxicity in patients receiving MTX, concurrently, also supported by OLE of DISCOVER 2 trials.[47]

RKZ is another humanized IgG1 monoclonal ab that binds to the p19 subunit and downregulates the IL-23/IL-17 pathway, controlling the inflammatory cascade. Two double-blind phase III, multicenter RCTs, studies assessed its efficacy in limiting PsA activity. KEEPsHAKE 1 included 964 individuals with csDMARDs-IR disease, randomized to receive RKZ 150 mg or placebo over 24 weeks. Approximately, the same percentage of each group (76.0% vs 76.7%) received concomitant csDMARDs. Superiority in ACR20 response was noted for RKZ-treated patients versus placebo, regardless of the co-existence of csDMARDs (Table 4).[48,49] In KEEPsHAKE 2, 444 individuals being intolerant or resistant to $\leqslant$2 biological therapies and/or $\geqslant$1 csDMARDs were randomized to RKZ or placebo therapy for 24 weeks. Open-label treatment with RKZ followed till week 208. Even though patients in the placebo group marked higher ACR20 response rates with concomitant csDMARDs use (27% other csDMARD, 36% MTX, 16 mere placebo), adding MTX or other csDMARDs in RKZ-treated patients appeared profitless (Table 4). Notably, there is a lack of evidence in favor of combination therapy, regarding cutaneous or periarticular manifestations, structural damage, physical function, mental health, and QoL.[50] Nevertheless, anti-IL-23 is highly combined with MTX in everyday clinical practice, for patients with long-standing, treatment-resistant, active PsA, as it is revealed by CorEvitas PsA/SpA Registry (22 from 104 patients).[51]

Ustekinumab (UST), a monoclonal ab binding to the p40 subunit of both IL-23 and IL-12, had been the first bDMARD approved, after TNFi, for PsA treatment. PSUMMIT 1 and PSUMMIT 2, two double-blind, placebo-control crossover trials, assessed the efficacy and safety of UST in patients with active PsA for over 6 months, despite the prior use of NSAIDS and csDMARDs. In PSUMMIT 2, participants could also have been unsuccessfully treated with biologic therapy. A total of 615 individuals were randomized, in PSUMIMIT 1, to receive subcutaneous UST 90 mg, 45 mg, or placebo, from which 49.5%, 48.3%, 46.6%, respectively, received concomitant MTX in a mean dose of 15 mg, stable from baseline till week 52. Although ACR20 and PASI75 at week 24, the two primary endpoints, were achieved for both groups of active therapies, the differences with the placebo ones were numerically higher for patients receiving monotherapy than for those receiving concomitant MTX. However, the significance of it was not tested since it was not the prespecified purpose of the study (Table 5).[52] The same conclusion was withdrawn from PSUMMIT 2, in which 300 patients were randomized with the same method and stratified by concomitant MTX use and body weight 47.1% from the placebo group, 52.4% with UST 45 mg and 49.5% with UST 90 mg was under combination treatment with MTX. An improvement according to ACR20 was achieved in higher rates for the UST active treatment group. The difference between placebo and UST was greater in the monotherapy group. The same applied to PASI75 score (Table 5).[53]

The efficacy and safety of UST in active PsA irrespective of MTX co-administration were also supported in the post hoc analysis of PSUMMIT, which pooled data for biologic naïve patients from both studies.[54] At the real-world level, the BIOPURE registry revealed that concomitant MTX use had no effect on treatment retention. From 160 patients with PsA starting UST after csDMARDs and bDMARDs failure or

Table 4. Characteristics and results of IL-23i trials.[1]

	Investigators type name	PsA characteristics	Drug	Duration of trial	ACR20		Investigators type name	PsA characteristics	Drug	Duration of trial	ACR20
GUS	Deodhar et al. RCT DISCOVER 1	Active disease Minimum NTJ/NSJ: 3/3 CRP ⩾ 0.3 mg/dL APM-IR or csDMARD-IR or NSAIDS-IR and 30% 2 ⩾ bDMARDs-IR	GUS 4 w +MTX	52 w	76(59%) 24 w 45(62%) 24 w	RZK	Kristensen et al. RCT DISCOVER 1 (+OLE)	Active PsA Or CRP ⩾ 0.3 mg/dL and active plaque PsO And ⩾1 csDMARD	RZK + MTX	24 w + 204 w OLE	55.5% (24 w) 57.9% (24 w)
			GUS 8 w +MTX		66(52%) 24 w 35(52%) 24 w						
	Mease et al. RCT DISCOVER 2	Active disease Minimum NTS/NJS: 5/5 CRP ⩾ 0.6 mg/dL APM-IR or csDMARD-IR or NSAIDS-IR And b/tsDMARD naïve	GUS 4 w +MTX	104 w	156 (64%) 24 w 92 (63%) 24 w		Östör et al. RCT DISCOVER 2	Active PsA and active plaque PsO And Bio-IR and/or csDMARD-IR	RZK + MTX	24 w	53.4% (24 w) 50.4% (24 w)
			GUS 8 w +MTX		159 (64%) 24 w 85 (60%) 24 w						
	Coates et al. RCT COSMOS	Active disease-active or documented plaque PsO or current nail disease And bDMARD-IR	GUS 8 w +MTX	1 year	84 (44.4%) 24 w 52 (49.5%) 24 w		–				

ACR, American College of Rheumatology; APM, apremilast; bDMARD, biologic disease-modifying antirheumatic drug; CRP, C-reactive protein; csDMARD, conventional, synthetic disease modifying antirheumatic drug; DMARD-IR, disease-modifying antirheumatic drug-inadequate response; GUS, guselkumab; IL, interleukin; IR, inadequate response; MTX, methotrexate; NSAIDs, non-steroidal anti-inflammatory drugs; NSJ, number of swollen joints; NTJ, number of tender joints; OLE, open label extension; PsA, psoriatic arthritis; PsO, psoriasis; RCT, randomized clinical trial; RZK, rizankizumab; w, weeks.

Table 5. Characteristics and results of IL-12/23i trials.[2]

	Investigators type name	PsA characteristics	Duration of trial	Drug	ACR20 (24 w)	PASI 75 (75 w)		
UST	McInnes et al. RCT PSUMMIT-1	Active disease Minimum NTJ/NSJ: 5/5 CRP ⩾ 0.3 mg/dL and plaque psoriasis current/ documented and csDMARD-IR and/or NSAIDs-IR	52 w + 108 w (OLE)	UST 45 mg	44/106 (41.5%)	51/79 (64.6%)		
				UST 45 mg +MTX	43/99 (43.4%)	32/66 (48.5%)		
				UST 90 mg	55/103 (53.4%)	55/80 (68.8%)		
				UST 90 mg +MTX	46/101 (45.5%)	38/69 (55.1%)		
				Placebo	22/110 (20.0%)	6/80 (7.5%)		
				Placebo +MTX	25/96 (26.0%)	10/66 (15.2%)		
	Ritchlin et al. RCT PSUMMIT-2	Active disease Minimum NTJ/NSJ: 5/5 CRP ⩾ 0.3 mg/dL and plaque psoriasis current/ documented and csDMARD-IR and/or NSAIDs-IR And bDMARD-IR	52 w	UST 45 mg	18/49 (36.7%)	22/41 (53.7%)	**SAE 60 w (*n*: 15)**	
				UST 45 mg +MTX	27/54 (50.0%)	19/39 (48.7%)	UST	3.4%
				UST 90 mg	25/53 (47.2%)	23/42 (54.8%)		
				UST 90 mg +MTX	21/52 (40.4%)	22/39 (56.4%)	UST + MTX	7.1%
				Placebo	7/55 (12.7%)	1/51 (2.0%)		
				Placebo +MTX	14/49 (28.6%)	3/29 (10.3%)		

ACR, American College of Rheumatology; bDMARD, biologic disease-modifying antirheumatic drug; CRP, C-reactive protein; csDMARD, conventional, synthetic disease-modifying antirheumatic drug; IL, interleukin; IR, inadequate response; MTX, methotrexate; NSAIDs, non-steroidal anti-inflammatory drugs; NSJ, number of swollen joints; NTJ, number of tender joints; OLE, open label extensions; PASI, Psoriasis Area and Severity Index; PsA, psoriatic arthritis; RCT, randomized clinical trial; SAE, serious adverse event; UST, ustekinumab; w, weeks.

intolerance, the retention rate through week 12 was 76% when combined with MTX and 73% as monotherapy.[55] Searching for evidence on maintenance or even addition of MTX on UST treatment, MUST, a phase IIIb RCT of non-inferiority, was conducted between January 2017 and April 2021. Of 173 patients, 88 were randomized to take MTX and 85 placebo. Disease activity score 28 at week 24 and at week 52, along with safety, were assessed without proving the superiority of combination therapy. However, in a post hoc, sex-disaggregated analysis of MUST, it was shown that women had more AEs associated with MTX than men (38% vs 18%). Furthermore, though exploratory and in a "hypothesis-generated" way, male patient group seemed to have their enthesitis respond faster with MTX addition than UST monotherapy, at week 24. This was not applied to the female patient group, and at week 52, the difference in males had also disappeared.[56]

Table 6. Characteristics and results of APM trials.

Investigators type name	PsA characteristics	Drug		Duration of trial	ACR20 (%)	AEs	
Cutolo et al. RCT phase III PALACE 2	Active PsA Minimum NTJ/ NSJ: 3/3 bDMARD and/ or csDMARD-IR (excluded when >3 DMARDs or >1 TNFi)	APM monotherapy	20 mg	52 weeks	28.6 (16 w)	–	
			30 mg		22.4 (16 w)		
		+csDMARDs	20 mg		41.2 (16 w)		
			30 mg		36.6 (16 w)		
Edwards et al. RCT phase III PALACE 3	Active PsA Minimum NTJ/ NSJ: 3/3 bDMARD and/or csDMARD-IR (excluded when >3 DMARDs or > 1 TNFi) ⩾one plaque psoriasis ⩾2 cm in size	APM monotherapy	20 mg	52 weeks	23 (16 w)	Common AEs were generally similar regardless of csDMARD use	Diarrhea 17% (24 w) 13% (52 w)
			30 mg		39 (16 w)		
		+csDMARDs	20 mg		32 (16 w)		Diarrhea 15% (24 w) 14% (52 w)
			30 mg		42 (16 w)		

ACR, American College of Rheumatology; AEs, adverse effects; APM, apremilast; bDMARDs, biologic disease-modifying antirheumatic drugs; csDMARDs, conventional synthetic disease-modifying antirheumatic drugs; IR, inadequate response; NSJ, number of swollen joints; NTJ, number of tender joints; PsA, psoriatic arthritis; RCT, randomized clinical trial; TNFi, tumor necrosis factor inhibitor; w, week(s).

In general, despite the extended investigation neither in the case of IL-12/23 inhibitor, nor of anti-IL-23, the addition of MTX proved to contribute to the disease control. This is also reflected in PsA Greek Registry, where anti-IL-17 and anti-IL-23 were more commonly used as monotherapy compared to TnFi treatments.[57]

Apremilast and abatacept

Besides acting directly toward inflammatory cytokines, other pharmaceutical options assist in reducing PsA activity. Apremilast (APM) is a phosphodiesterase 4 inhibitor, which downregulates the production of proinflammatory cytokines by impeding the conversion of cAMP to AMP. PALACE clinical studies evaluated the effectiveness of APM in ameliorating most aspects of the PsA. In PALACE 2, 484 active PsA individuals, regardless of prior treatment with bDMARDs or csDMARDs, were randomized to receive APM 30 mg, 20 mg, or placebo for 52 weeks, stratified by concurrent use of csDMARDs. Maintenance of them was acceptable, with the mean dosage of MTX (csDMARD most commonly used) being similar among the groups. The primary endpoint ACR20 at week 16 was achieved in both groups of active APM, with or without concomitant MTX, although numerically higher in the MTX group. Besides, the monotherapy population was very limited in providing available evidence on treatment differences (Table 5).[58]

In PALACE 3, an RCT of similar design, individuals with both active PsA and skin lesions were enrolled. In total, 505 patients were stratified according to concurrent csDMARD use and BSA. The percentage of combination treatment in each group along with the mean dosage of MTX was equal. Higher ACR20 response rates at week 16 were achieved in APM groups versus placebo, irrespective of MTX co-administration, with only numerical differences without statistical significance (Table 6). AEs were generally the same with and without csDMARDs.

Regarding real-world evidence, an Italian multicenter observational retrospective study showed that concomitant use of csDMARD along with APM 30 mg assisted the dactylitis resolution in month 12 (multivariate analysis: 3.84 (1.30–11.31) $p=0.01$). They assessed 96 individuals with enthesitis and 118 with dactylitis, 28.1% and 25.4% of whom, respectively, received concomitant use of csDMARD.[59] A cohort study, from

Table 7. Characteristics and results of JAKi randomized controlled trials.

Investigators type name	PsA characteristics	Drug		Duration of trial	ACR20 (%)		ACR50 (%)		ACR70 (%)		Enthesitis (24 w) (LEI = 0, %)	Dactylitis (24 w) (LDI = 0, %)	AEs	Skin PASI 75/90/100 (16 weeks, %)
Nash et al. RCT SELECT-PsA 1 and 2	Active PsA Minimum NTJ/ NSJ: 3/3 IR or intolerance to ⩾bDMARD or ⩾csDMARD	UPA monotherapy (30%)	UPA 15 mg	24 w	58.7 (12 w)	57.7 (24 w)	29.6 (12 w)	42.3 (24 w)	11.6 (12 w)	22.8 (24 w)	42.1	58.5	Similar frequency of AEs and serious AEs **ALT, AST, and CPK elevation were more common in the combination groups**	50/28.3/14.2
			UPA 30 mg		70.6 (12 w)	70.1 (24 w)	42.6 (12 w)	46.7 (24 w)	19.8 (12 w)	29.9 (24 w)	49.3	66		**65.7**/50.9/36.1
		+ ⩾nbDMARDs (70%)	UPA 15 mg		69.2 (12 w)	73.4 (24 w)	38.1 (12 w)	50.1 (24 w)	14 (12 w)	26.8 (24 w)	53.3	76.1		62.6/40.8/29
			UPA 30 mg		74.8 (12 w)	73.9 (24 w)	48.9 (12 w)	54.7 (24 w)	23.4 (12 w)	33.1 (24 w)	54.7	80.3		**57.5**/46.4/31.8

All results are shown as raw data. Placebo-subtracted significant differences between groups are depicted in bold.
ACR, American College of Rheumatology; AEs, adverse effects; ALT, alanine aminotransferase; AST, aspartate transaminase; bDMARDs, biologic disease-modifying antirheumatic drugs; CPK, creatine phosphokinase; csDMARDs, conventional synthetic disease-modifying antirheumatic drugs; IR, inadequate response; JAKi, Janus kinase inhibitors; LDI, leeds dactylitis index; LEI, leeds enthesitis index; nbDMARDs, nonbiologic disease-modifying antirheumatic drugs; NSJ, number of swollen joints; NTJ, number of tender joints; PASI, Psoriasis Area and Severity Index; PsA, psoriatic arthritis; RCT, randomized clinical trial; UPA, upadacitinib; w, week(s).

Greece, assessing the APM effectiveness and safety, in 167 patients with early PsA, naïve to biologic therapies and csDMARD-IR, exhibited no statistical superiority of combination therapy in clinical disease activity index for PsA response rate at week 52. Finally, Haddad et al. examined the factors that contribute to APM discontinuation. From January 2016 to June 2021, data were extracted for 568 PsA individuals treated with APM, from a large health database in Israel.[60] In the mean persistence period of 6.1, 95% confidence interval (5.2–6.9) months, co-use of MTX showed no effect in APM discontinuation (log-rank $p = 0.957$).

Another therapeutic option is Abatacept, a cytotoxic T-lymphocyte-associated protein 4-Ig human fusion protein that prevents the activation of naïve T-helper (Th)-1 and Th-17 cells by inhibiting critical CD28 co-stimulation, thereby downregulating cytokine release. Two double-blind RCTs, ASTRAEA and an investigator-initiated study, by Mease et al., where 70% and 60% of patients received concomitant MTX analyzed no data relative to combination treatment. Only a post hoc analysis of them conducted to reveal poor prognostic factors for abatacept effectiveness include MTX covariant to their assessment, without proving any significant correlation to abatacept response.[61–63] In conclusion, little evidence supports further efficacy of APM combined with csDMARDs, especially from the real-world setting, unlike Abatacept where no additional profit has been proven.

Janus kinase inhibitors

The newest drug class in the therapeutic field of inflammatory arthritis, since the discovery of the pathogenetic role of Janus kinase (JAK)/signal transducer and activator of transcription (STAT) pathway, are the JAK inhibitors (JAKi).[64] These are tsDMARDs with different JAK selectivity and include tofacitinib (TOFA), baricitinib, upadacitinib (UPA), and filgotinib. Hitherto, only TOFA and UPA are approved for PsA treatment.

JAKi are recommended as first-line agents for a wide array of PsA manifestations,[12] whereas concomitant csDMARDs therapy is not established as standard of care due to a lack of research data supporting this strategy. More specifically, there is a lack of evidence for TOFA plus csDMARD efficacy over TOFA monotherapy in patients with PsA. The effectiveness of TOFA, either 5 mg two times per day or 10 mg two times per day, has been demonstrated in two phase III RCTs enrolling active PsA individuals with IRs to csDMARDs or TNFi. However, no subgroup analysis for csDMARDs was conducted, as all participants were already on background csDMARD treatment during recruitment.[65,66] A post hoc analysis evaluating the impact of varying MTX doses on the efficacy and safety of TOFA was conducted.[67] When participants were grouped by background MTX dose, $\leqslant 15$ or >15 mg/week, and TOFA higher or lower doses, results are perplexing; TOFA's efficacy of 5 mg two times per day was numerically better in combination with higher treatment doses of MTX (>15 mg/week) versus lower doses ($\leqslant 15$ mg/week) for musculoskeletal and skin symptoms, while the opposing was true for TOFA 10 mg two times per day.[67] A unique RCT, a sub-study of OPAL Balance, addressed the issue of per os MTX discontinuation in 179 patients with PsA after achieving stable treatment in synergy with TOFA. Interestingly, both groups (TOFA plus MTX or TOFA plus placebo) did not differ in disease activity (Psoriatic Arthritis Disease activity Score - PASDAS) or functionality scores (Health Assessment Questionnaire Disability Index) at 6 months after MTX withdrawal, with a generally similar rate of AEs except for elevated liver enzymes in the MTX group.[68]

To make matters more challenging, SELECT-PsA 1 and 2 are the only RCTs providing valid insights to the debate for UPA's assessment, accumulating all the evidence for JAKi so far. Adding to it, no real-life data involving patients with more complex medical backgrounds and comorbidities are reported to date, despite long-standing JAKi use in clinical practice.[69]

The original studies for UPA (SELECT PsA 1,2) included 1916 patients with active PsA who had IR or intolerance to at least one bDMARD or csDMARD. Subgroup analysis of these UPA groups (15 and 30 mg) according to non-biologic disease-modifying antirheumatic drugs (nbDMARD) baseline treatment is shown in Table 7. Noteworthily, for efficacy assessment, no treatment strategy was superior to the other when arthritis, enthesitis, and dactylitis were considered. Differences in HAQ were also unremarkable between groups. Pooled together, there was a similar frequency of AEs and serious AEs;, however, in close sub-category inspection, mild transaminase and creatine phosphokinase

elevation were more common in the combination groups.[70] Safety warnings from a longitudinal UPA investigation of approximately 3 years also report similar AEs among treatment groups (for MTX), except for a numerically higher rate of elevated transaminase with MTX combination therapy.[69] In the original trials, placebo-subtracted significant differences between groups are depicted in PsO improvement (PASI75) for UPA 30 mg monotherapy compared to UPA 30 mg plus nbDMARD, which was not consistent with results from UPA 15 mg groups and for PASI90 and PASI100.

Overall, UPA was effective and safe with or without nbDMARDs in PsA, allowing treatment flexibility in peripheral arthritis. The possible additive benefit of JAKi combination therapy in PsA with predominant spondylitis remains elusive, as csDMARDs are not recommended for axial disease.[12]

Conclusion

There is no doubt that the currently available treatment options in PsA have changed the course of the disease and improved the functional status of the patients. However, as there is still a substantial proportion of patients who do not achieve remission or LDA, the need to find effective therapeutic regimens or follow different strategies is growing. In this direction, the combination of a conventional synthetic with bDMARDs or tsDMARD does not seem to be more effective than the monotherapy of the latter. This seems to be more pronounced in the newer drug categories (anti-IL-17, anti-IL-23, and JAKi) compared to the TNFi, where the co-administration of a csDMARD improves their survival.

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Author contributions

Elpida Skouvaklidou: Writing – original draft.

Paraskevi Avgerou: Writing – original draft.

Konstantinos D. Vassilakis: Writing – review & editing.

George E. Fragoulis: Conceptualization; Project administration; Writing – review & editing.

Nikolaos Kougkas: Writing – original draft.

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Competing interests

The authors declare that there is no conflict of interest.

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Appendix

Abbreviations

ab(s)	antibody(-ies)
ACR	American College of Rheumatology
ADA	adalimumab
AE	adverse effects
AMP	adenomonophosphate
APM	apremilast
ASAS	Assessment of SpondyloArthritis international Society
bDMARDs	biologic disease-modifying antirheumatic drugs
BSA	body surface area
cAMP	cyclic adenosine monophosphate
CER	certolizumab
CPK	creatine phosphokinase
csDMARDs	conventional synthetic disease-modifying antirheumatic drugs
DAPSA	disease activity index for psoriatic arthritis
DAS	disease activity score
ETN	etanercept
EU	European Union
EULAR	European Alliance of Associations for Rheumatology
GRAPPA	Group for Research and Assessment of Psoriasis and Psoriatic Arthritis
GOL	golimumab
GUS	guselkumab
HAQ	Health Assessment Questionnaire
IBD	inflammatory bowel disease
IFX	infliximab
IRs	inadequate response
IXE	ixekizumab
JAKi	Janus kinase inhibitors
JAK	Janus kinase
LDA	low disease activity
LTE	long term extension
MCS	Mental Component Score
MDA	minimal disease activity
mDAPSA	modified Disease Activity Index for Psoriatic Arthritis
MTX	methotrexate
NAPSI	Nail Psoriasis Severity Index
nbDMARDs	non biologic disease-modifying antirheumatic drugs
NSAIDs	non-steroidal anti-inflammatory drugs
PASI	Psoriasis Area and Severity Index
PCS	Physical Component Score
PsA	psoriatic arthritis
PsO	psoriasis
QoL	quality of life
RA	rheumatoid arthritis
RCT	randomized clinical trial
RKZ	risankizumab
SEC	secukinumab
SF-36 PCS	Short Form 36
SHS	Sharp/van der Heijde score
STAT	signal transducer and activator of transcription
T2T	treat-to-target
TEAEs	treatment emergent adverse events
Th	T-helper cells
TNFi	tumor necrosis factor a inhibitors
TOFA	tofacitinib
tsDMARDs	targeted synthetic disease-modifying antirheumatic drugs
UPA	upadacitinib
UST	ustekinumab
VLDA	very low disease activity
w	week