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ABSTRACT. Objective. Several advanced therapies have been licensed across the related conditions of psoriatic arthritis (PsA), Crohn disease (CD), ulcerative colitis (UC), and noninfectious uveitis. We sought to summarize results from randomized controlled trials (RCTs) investigating the efficacy and safety of advanced therapies for these related conditions in patients with PsA.

Methods. We updated the previous systematic search conducted in 2013 with literature reviews of MEDLINE, Embase, and the Cochrane Library (from February 2013 to August 2020) on this subject; only those new studies are presented here. The quality of evidence was assessed using the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) framework.

Results. The number of RCTs meeting eligibility criteria were 12 for CD, 15 for UC, and 5 for uveitis. The tumor necrosis factor inhibitor (TNFi) class appears to be efficacious and safe across CD, UC, and uveitis, with the exception of etanercept. Interleukin 12/23 inhibitors (IL-12/23i) are efficacious for CD and UC. Phase II and III RCTs of Janus kinase inhibitors (JAKi) and IL-23i in CD and UC are promising in terms of efficacy and safety. IL-17i must be used with great caution in patients with PsA at high risk of inflammatory bowel disease (IBD). RCTs in uveitis have mainly studied adalimumab.

Conclusion. We have identified 32 recent RCTs in IBD and uveitis and updated recommendations for managing patients with PsA and these related conditions. A multispecialty approach is essential to effectively, safely, and holistically manage such patients. Advanced therapies are not equally efficacious across these related conditions, with dosing regimens and safety varying.

Key Indexing Terms: GRAPPA, psoriasis, psoriatic arthritis

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Psoriatic arthritis (PsA) is known to have a shared pathogenesis with inflammatory bowel diseases (IBD), such as Crohn disease (CD), ulcerative colitis (UC), and IBD-unclassified (IBD-U), and different forms of inflammatory eye disease. The evidence for this is derived from epidemiological and genetic studies showing shared heritability and familial clustering.¹⁻⁴

Cohort studies and metaanalyses estimate a lifetime risk of incident IBD in patients with spondyloarthritis (SpA) to be 4% to 14%, and perhaps higher in axial compared with peripheral SpA.^{1,3,4} Macroscopic intestinal inflammation is estimated to affect 30-44%^{2,5} and microscopic inflammation 46-66%^{2,6} of patients with SpA in general, but especially those with axial predominant SpA (axSpA).

Uveitis is characterized by inflammation of the uvea and is anatomically classified into anterior, intermediate, posterior, and panuveitic eye inflammation types. Approximately 30% to 40% of patients with uveitis have an associated immune-mediated inflammatory disease (IMID),^{7,8} while other infectious etiologies (viral, fungal, or bacterial) or injuries exist. A large number of uveitis cases do not fit into any well-defined diagnostic category and are labeled idiopathic. One of the differences between PsA

and axSpA is that in PsA, the acute anterior form of uveitis is less common.⁹ IMID has therefore been proposed as a more precise term for these and other overlapping conditions.¹⁰

Our objectives were to summarize results from recent RCTs in patients with IBD and/or uveitis and investigate the efficacy and safety of advanced therapies, which have also been tested in patients with PsA, to inform treatment choices in patients with PsA.

METHODS

Literature search. A systematic search was conducted in 2013 to inform the 2014 GRAPPA treatment recommendations for PsA.¹¹ We conducted an update of the 2013 systematic review to inform the 2021 update of the GRAPPA treatment recommendations regarding related conditions.¹² These related conditions included CD, UC, and uveitis (including noninfectious etiologies of acute and chronic anterior uveitis, posterior uveitis, and panuveitis). In the present paper, we present only the results of studies published since February 2013 until August 2020.

Inclusion/exclusion criteria. We sought to identify RCTs in patients with IBD or uveitis who were treated with pharmaceutical drugs recognized as treatments for PsA and that had a placebo comparator arm. Eligibility criteria are detailed in Table 1. Comprehensive searches were conducted of

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Table 1. Eligibility criteria for searches of RCTs in patients with IBD or uveitis treated with pharmaceutical drugs recognized as treatments for PsA.

Factor	Inclusion Criteria	Exclusion Criteria
Study design	RCTs of any design (individual or cluster randomization, step-wedge design). Secondary, post hoc, and subgroup analyses of individual RCTs. Extension studies of RCTs.	Secondary evidence (ie, systematic reviews, guidelines/recommendations, evidence-based synopses). Quantitative primary studies that are not RCTs (eg, nonrandomized controlled studies, before-and-after studies, cohort studies, case studies, case series). Qualitative studies. Conference abstracts. Editorials, commentaries, trial protocols, letters, etc.
Participants and conditions of interest	Adult populations (age \geq 18 yrs; if mixed ages, include if results for adults are reported separately or if most participants are adults). Diagnosis of IBD (UC, CD, subclinical colitis) or uveitis.	Pediatric only focus (< 18 yrs).
Interventions or exposures	Any DMARD, targeted synthetic or biologic drug or combination used in the treatment of PsA (oral, injection, IV).	Nonpharmacological interventions. NSAIDs only. Steroids only.
Comparisons or control groups	Any comparator (active, sham, PBO).	NA.
Outcomes of interest	Symptoms and signs including outcomes relating to disease activity and impact. Disease progression. Safety outcomes (AEs, side effects). Any length of follow-up will be considered.	
Setting	Any.	

AE: adverse event; CD: Crohn disease; DMARD: disease-modifying antirheumatic drug; IBD: inflammatory bowel disease; IV: intravenous; NA: not applicable; NSAID: nonsteroidal antiinflammatory drug; PBO: placebo; PsA: psoriatic arthritis; RCT: randomized controlled trial; UC: ulcerative colitis.

3 bibliographic databases (MEDLINE, Embase, and the Cochrane Library; see Supplementary Table 1 for MEDLINE search, available with the online version of this article) from February 19, 2013, to August 28, 2020. Open-label extension (OLE) and long-term extension (LTE) studies meeting eligibility criteria, but found to no longer have a control treatment arm, were excluded from further analysis.

Data extraction. Unique article titles and abstracts were screened by a single coauthor against predefined eligibility criteria (Table 1). Full-text articles of those remaining were independently assessed by pairs of coauthors (formed based upon volunteering for this duty) for eligibility, with a third reviewer (DRJ or MEH) consulted in the case of disagreements. No significant disagreements were encountered. Included studies underwent data extraction and assessment for risk of bias using the Cochrane risk of bias tool by 1 coauthor and were independently checked by a second coauthor (NC), with a third reviewer (DRJ or MEH) consulted in the case of disagreements.¹³ No significant disagreements were encountered.

GRADE rating. Each eligible trial was assessed using the GRADE-level assessment of quality of evidence.¹⁴ Several coauthor group meetings were undertaken to reach a consensus on recommendation for (strong/weak), recommendation against (strong/weak), or no recommendation (no, insufficient, or conflicting evidence) for each agent. The GRADE recommendations were made based on prior reviews and the updated RCTs.¹²

Ethics. This paper does not require ethical or institutional review board approval.

RESULTS

We screened 311 full-text articles and reviewed 72 potential RCTs (Figure); 40 were excluded because of lack of controls or missing outcome data. We included 32 eligible RCTs for review: 12 RCTs for CD (Table 2), 15 RCTs for UC (Table 3), and 5 RCTs for uveitis (Table 4).

RCTs of CD.

Twelve RCTs met eligibility criteria for final reporting, as shown in Table 2.¹⁵⁻²⁶ Since 2013, no new primary studies comparing adalimumab (ADA) or golimumab (GOL) with placebo have been published. Several treatments had OLE or LTE studies without a placebo arm and were excluded. No study reported if the subjects had concomitant PsA, SpA, inflammatory arthritis, psoriasis, or uveitis.

TNFi. The PREVENT RCT¹⁵ studied 297 biologic-experienced cases with ileocolonic resection and anastomosis (Table 2). Participants randomized to infliximab (IFX) vs placebo were no more likely to attain the study's primary endpoint of no clinical recurrence at week 76, nor was efficacy found for most secondary endpoints. IFX was only statistically significantly better than placebo as measured by the probability of endoscopic recurrence.

IL-12/23i: Ustekinumab. The phase III UNITI portfolio of RCTs testing ustekinumab (UST) induction and maintenance therapy in patients with CD who are TNFi-naïve ($n = 761$) and TNFi-inadequate responders (IR; $n = 397$) showed consistent and statistically significant efficacy of UST (p40-specific subunit inhibitors of IL-23) over placebo for the primary and most secondary endpoints, without new safety signals, both at week 6 and week 44 (Table 2).^{16,17}

IL-23i: Risankizumab. A phase II RCT of risankizumab (RZB; p19-specific subunit inhibitors of IL-23) enrolled 121 CD cases and stratified by steroid-IR, conventional synthetic-IR, and TNFi-IR.¹⁸ RZB at 600 mg (but not 200 mg) was significantly

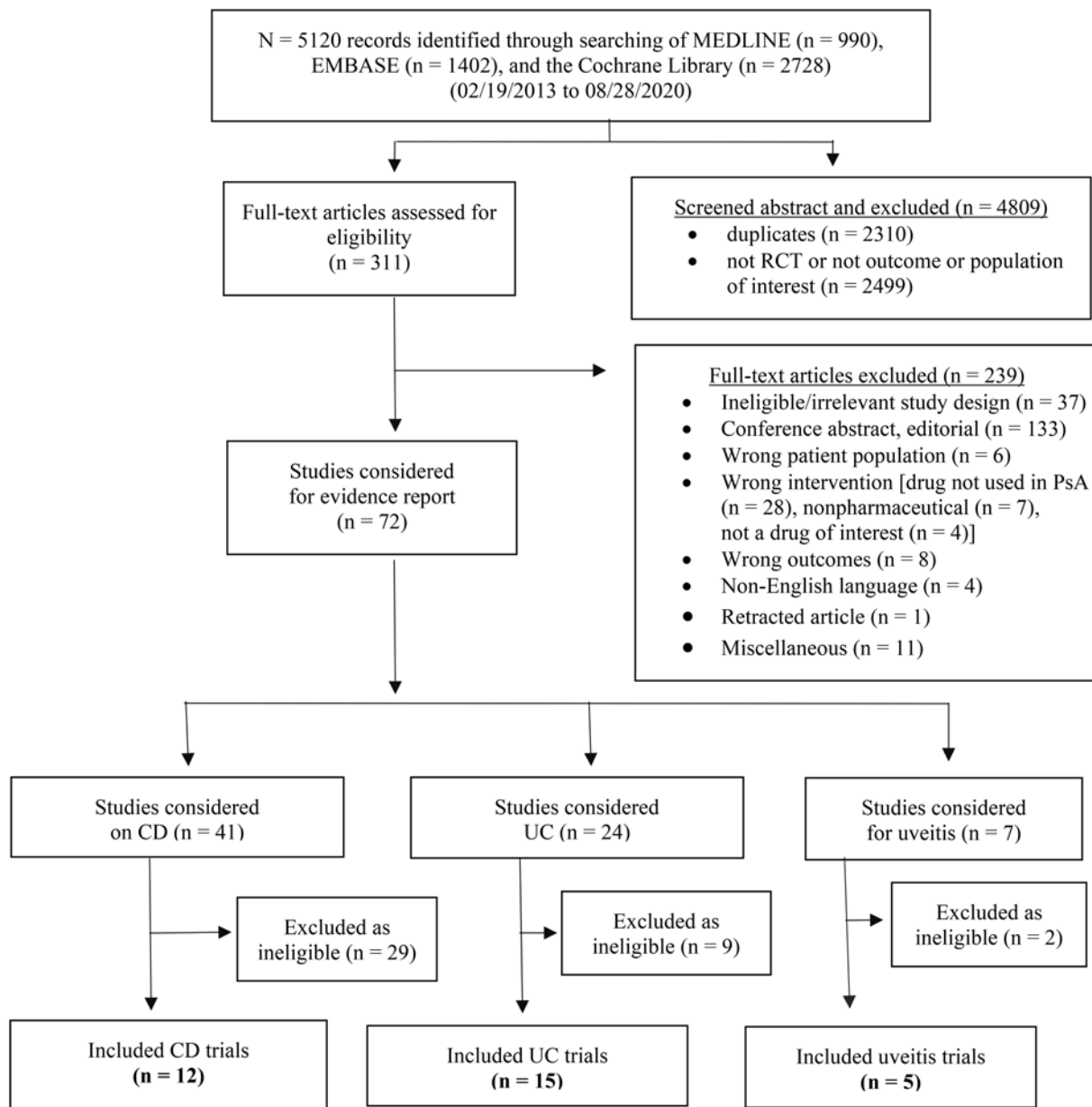


Figure. Flowchart of the study selection process for RCTs of CD, UC, and uveitis with treatments used in PsA. CD: Crohn disease; PsA: psoriatic arthritis; RCT: randomized controlled trial; UC: ulcerative colitis.

more efficacious than placebo across all primary and secondary endpoints, with no new safety signals.¹⁸ A phase III study for this agent is in progress.

IL-23i: MEDI2070. A phase IIa RCT of MEDI2070 (IL-23i, subsequently called brazikumab) enrolled 121 TNFi-IR cases and stratified by lines of TNFi previously used.¹⁹ MEDI2070 was significantly more likely than placebo to attain the primary endpoint (100-point improvement in the Crohn's Disease Activity Index [CDAI] at week 8) and efficacy was also found for several secondary endpoints. Phase III studies for this agent are in progress.

IL-17i: Brodalumab. Targan et al demonstrated a detrimental effect of brodalumab (BRO; IL-17A receptor antagonist) on

CD in a study of 130 steroid-IR, conventional synthetic-IR, and biologic-naïve CD cases (Table 2).²⁰ Despite eligibility criteria only permitting the recruitment of patients with mild severity CD, patients treated with placebo were far more likely to achieve the primary endpoint (150 point improvement in CDAI at week 6) than all BRO dose groups. Placebo and BRO groups were not statistically different for secondary endpoints.

IL-6i: PF-04236921. PF-04236921 (IL-6i) was tested in a dose-ranging phase II RCT of 247 TNFi-IR cases with CD.²¹ The 50 mg dose was more likely than placebo to attain the primary endpoint (70-point improvement in CDAI at week 12), but few secondary endpoints showed efficacy (Table 2).

JAKi: Tofacitinib. The JAKi tofacitinib (TOF), has been tested

Table 2. Advanced therapy PBO-controlled RCTs in Crohn disease. Efficacy and safety results for new studies from February 2013 to August 2020.

Medication Class vs PBO	Author, Year	N	(1) Primary and (2) Key Secondary Endpoints	Endpoints Met	Study Limitations
IFX	Regueiro 2016 ¹⁵	297	(1) Clinical recurrence at wk 76 (2) Endoscopic recurrence at wk 76 (2) Clinical recurrence at wk 104 (2) CDAI change at wk 104	IFX = PBO IFX > PBO IFX = PBO IFX = PBO	Entry restricted to CD cases who had had ileocolonic resection with ileocolonic anastomosis. Moderate-high risk of bias as domains poorly reported in the study.
UST	Feagan 2016 ¹⁶	761	(1) CDAI-100p or CDAI < 150 at wk 6 (2) CDAI remission at wk 8 (2) CDAI-70p at wk 8 (2) CRP decrease at wk 8 (2) Calprotectin decrease at wk 6	Both UST > PBO (UST 130 mg = UST 6 mg/kg) Both UST > PBO Both UST > PBO Both UST > PBO Both UST > PBO	-
	Sands 2018 ¹⁷	761	(2) IBDQ-MCID at wk 8 (2) SF-36 PCS at wk 8 (2) SF-36 MCS at wk 8	Both UST > PBO No difference UST 6 mg/kg > PBO	A paper focused on PROMs.
	Feagan 2016 ¹⁵	397	(1) CDAI < 150 at wk 44 (2) CDAI-70p at wk 44 (especially if remission after induction) (2) IBDQ decrease at wk 44	Both UST > PBO (UST Q8W = UST Q12W) Both UST > PBO UST Q8W = UST Q12W Both UST > PBO (UST Q8W = UST Q12W)	TNFi-IR mandated; otherwise, low risk of bias in the study.
	Sands 2018 ¹⁶	397	(2) IBDQ-MCID at wk 44 (2) SF-36 PCS-MCID at wk 44 (2) SF-36 MCS-MCID at wk 44	UST Q8W > PBO UST Q8W > PBO Both UST > PBO	A paper focused on PROMs.
RZB	Feagan 2017 ¹⁸	121	(1) CDAI ≤ 150 at wk 12 (2) CDAI-100p at wk 12 (2) CDEIS ≤ 4 at wk 12 (2) IBDQ at wk 12 (2) HRQOL at wk 12	600 mg > PBO (not 200 mg) 600 mg > PBO (not 200 mg) 600 mg > PBO (not 200 mg) 600 mg > PBO (not 200 mg) 600 mg > PBO (not 200 mg)	Low risk of bias in the study.
MEDI2070	Sands 2017 ¹⁹	121	(1) CDAI-100p at wk 8 (1) CDAI ≤ 150 at wk 8 (2) CRP decrease (2) Calprotectin decrease	700 > PBO No difference 700 > PBO 700 > PBO	TNFi-IR mandated; otherwise, low risk of bias in the study.
BRO	Targan 2016 ²⁰	130	(1) CDAI ≤ 150 at wk 6 (2) CDAI-100p at wk 6 (2) CDAI-Δ at wk 6 (2) CRP (2) Calprotectin	PBO > all BRO groups No difference No difference No difference No difference	Several exclusions compared with other studies. Therefore, likely milder severity CD cohort than in clinical practice, consequently contributing to the risk of bias in the study.
PF-04236921	Danese 2019 ²¹	247	(1) CDAI-70p at wk 12 (2) CDAI remission (2) CRP decrease (2) Calprotectin decrease (2) IBDQ score (2) Change in EQ-5D	50 mg > PBO 50 mg > PBO All doses > PBO No difference No difference No difference	TNFi-IR mandated; otherwise, low risk of bias in the study.
TOF	Sandborn 2014 ²²	139	(1) CDAI-70p at wk 4 (2) CDAI-100p at wk 4 (2) CRP decrease at wk 4 (2) Calprotectin decrease at wk 4 (2) IBDQ-10 at wk 4	No difference No difference 15 mg > PBO 15 mg > PBO No difference	Moderate risk of bias: high screening fail rate (41%); very high PBO response rate leading to inadvertent selection bias.
	Panes 2017 ²³	180	(1) CDAI-100p or CDAI < 150 at wk 24 (2) CRP decrease at wk 24	No difference (either dose) TOF 10 > PBO	-
FILGO	Vermeire 2017 ²⁴	174	(1) CDAI at wk 10 (2) Histopathology (2) SES-CD (2) IBDQ-QoL (2) PRO2	FILGO 200 > PBO FILGO 200 > PBO No difference FILGO 200 > PBO FILGO 200 > PBO	Low risk of bias.

Table 2. Continued.

Medication Class vs PBO	Author, Year	N	(1) Primary and (2) Key Secondary Endpoints	Endpoints Met	Study Limitations
UPA	Mohamed 2020 ²⁵	220	(1) Dose-response at wk 16 (1) Safety	Dose-related response, especially 24 mg QID > PBO No dose-safety association observed	High attrition of 27% in PBO compared with UPA groups, contributing to risk of bias in the study.
	Sandborn 2020 ²⁶	220	(1) Clinical remission at wk 16 (1) Endoscopic remission at wk 12/16	All UPA doses = PBO Higher UPA doses > PBO	

BRO: brodalumab; CD: Crohn disease; CDAI: Crohn's Disease Activity Index; CDEIS: Crohn's Disease Endoscopic Index of Severity; CRP: C-reactive protein; EQ-5D: EuroQol 5-dimension questionnaire; FILGO: filgotinib; HRQOL: health-related quality of life; IBDQ-10: 10-item Inflammatory Bowel Disease Questionnaire; IBDQ-MCID: Inflammatory Bowel Disease Questionnaire minimal clinically important difference; IBDQ-QoL: Inflammatory Bowel Disease Questionnaire quality of life; IFX: infliximab; MCS: mental component summary; NR: not reported; p: point; PBO: placebo; PCS: physical component summary; PRO2: patient-reported composite score; PROM: patient-reported outcome measure; Q12W: every 12 weeks; Q8W: every 8 weeks; QID: 4 times daily; RZB: risankizumab; SES-CD: Simplified Endoscopy Score for Crohn's Disease; SF-36: 36-item Short Form Health Survey; TNFi-IR: inadequate response to tumor necrosis factor inhibitor; TOF: tofacitinib; UPA: upadacitinib; UST: ustekinumab.

Table 3. Advanced therapy PBO-controlled RCTs in UC. Efficacy and safety for new studies from February 2013 to August 2020.

Medication Class vs PBO	Author, Year	N	(1) Primary and (2) Key Secondary Endpoints	Endpoints Met	Study Limitations and Population
ADA	Suzuki 2014 ²⁷	273	(1) Clinical response, mucosal healing, and remission at wks 8 and 52	Induction with ADA 160/80 mg led to early response and mucosal healing.	Efficacy and safety of ADA in Japanese patients with moderately to severely active UC. ADA 80/40 (80 mg at wk 0 then 40 mg every other wk) vs ADA 160/80 (160/80 mg at wk 0/2 then 40 mg every other wk) vs PBO. 52-week efficacy of ADA in patients with moderately to severely active UC who failed CS and/or immunosuppressants. Results of 52 wk open-label follow-up of patients with moderate to severe UC who participated in ULTRA 1. ITT-A3 is ITT amended protocol. Originally 2 arms, now 3 arms: ADA 160/80 mg (160 mg at wk 0, 80 mg at wk 2) and 40 mg at wks 4 and 6, vs ADA 80/40 (80 mg at wk 0, 40 mg at wk 2, 4, and 6), vs PBO. ITT-E is any version of protocol. Patients who received ≥ 1 injection of study drug enrolled at any time. 1-yr maintenance outcomes among patients with moderately to severely active UC who responded to induction therapy with ADA: subgroup analyses from ULTRA 2.
	Reinisch 2013 ²⁸	576	(1) Clinical remission, clinical response, and mucosal healing at wk 52 for ITT-A3 and ITT-E groups	Rates of remission, response, and healing similar for both groups. ADA effective for maintaining clinical remission.	
	Sandborn 2013 ²⁹	ULTRA 2: 248	(1) Clinical response, remission, and mucosal healing at wk 52 (2) Steroid-free remission and steroid discontinuation rates	49.6% achieved clinical response, 30.9% clinical remission, and 43.1% mucosal healing at wk 52. 21.1% achieved steroid-free remission and 37.8% were steroid-free.	
	Colombel 2014 ³⁰	ULTRA 1: 600 ULTRA 2: 1094	(1) Remission, mucosal healing, and improved QOL assessed in ULTRA 1 and 2 up to wk 208 (2) Maintenance of remission and mucosal healing in ULTRA 3	ADA more effective than PBO in maintaining remission rates, mucosal healing, and improved QOL up to 4 yrs.	

Table 3. Continued.

Medication Class vs PBO	Author, Year	N	(1) Primary and (2) Key Secondary Endpoints	Endpoints Met	Study Limitations and Population
GOL	Gibson 2016 ³¹	1240	(1) Assess safety and maintenance of efficacy from end of main study through the first year	Patients on SC GOL every 4 wks through 2 yrs maintained clinical benefits and reduced CS use. No new safety signals observed.	Maintenance of efficacy and continuing safety of GOL for active UC: PURSUIT-SC maintenance study extension through 1 yr. Efficacy and safety of GOL 52-week maintenance therapy in Japanese patients with moderate to severely active UC: a phase III, double-blind, randomized, PBO-controlled study (PURSUIT-J study). Induction phase was 200 mg at wk 0 and 100 mg at wk 2 through 6 wks. Then entered maintenance phase at 100 mg vs PBO every 4 wks for 52 wks.
	Hibi 2017 ³²	144	(1) Clinical response through maintenance at wk 54	Patients on SC GOL maintained clinical response at wk 54 (56.3%) vs PBO (19.4%).	
	Sandborn 2014 ³³	1064	(2) Clinical remission and mucosal healing at maintenance wk 30 and 54	At wk 30 and 54, 50% achieved clinical remission vs PBO (6.5%), and 59.4% experienced mucosal healing vs PBO (16.1%).	
			(1) Phase III endpoint clinical response at wk 6	Rates of clinical response at wk 6 were 51.0% and 54.9% for patients given 200 mg/100 mg and 400 mg/200 mg GOL vs 30.3% PBO.	
	Sandborn 2014 ³⁴	464	(2) Clinical remission, mucosal healing, and change in IBDQ scores	Rates of remission, healing, and change in IBDQ greater for both GOL groups vs PBO ($P < 0.05$).	
			(1) Clinical response/remission at wk 54	Clinical remission and had mucosal healing (27.8% and 42.4%) than patients given PBO (15.6% and 26.6%; $P = 0.004$ and $P = 0.002$, respectively) or 50 mg GOL (23.2% and 41.7%, respectively).	
Rutgeerts 2015 ³⁵	291	(1) Dose-response relationship	No dose-response was observed in Phase II. Efficacy with single-dose GOL IV induction was lower than expected.	RCT: a PBO-controlled study of IV GOL induction therapy for UC. PURSUIT-IV study: Phase II: 1:1:1:1 at 1, 2, or 4 mg/kg Phase III: 1:1:1 at 2 or 4 mg/kg	
		(2) Clinical remission and mucosal healing	No difference between receiving GOL vs PBO.		
MTX	Carbonnel 2015 ³⁶	111	(1) Steroid-free remission at wk 16	MTX not superior to PBO.	MTX is not superior to PBO in inducing steroid-free remission but induces steroid-free clinical remission in a larger proportion of patients with UC.
			(2) Clinical remission and endoscopic healing without steroids at wk 16 and/or wk 24	No difference.	
	Herfarth 2018 ³⁷	179	(1) Patients who remained relapse free and in remission at wk 48 without use of steroids/other medication	MTX not superior to PBO in preventing relapses, maintaining of steroid-free response, or remission in UC.	

Table 3. Continued.

Medication Class vs PBO	Author, Year	N	(1) Primary and (2) Key Secondary Endpoints	Endpoints Met	Study Limitations and Population
APR	Danese 2020 ³⁸	170	(1) Clinical remission at wk 12 (defined by total Mayo score < 2)	Not met. 30 mg = 31.6% 40 mg = 21.8% PBO = 12.1%	APR: 30 mg (n = 57) APR: 40 mg (n = 55) PBO: (n = 58)
TOF	Panes 2015 ³⁹	194	(1) Effect of TOF on PROs (IBDQ) and (IBD PRITI) at wk 8	IBDQ score: improvement significantly greater for TOF 15 mg BID vs PBO. On IBD PRITI, most patients reported satisfaction for 15 mg BID.	0.5 mg or 3 mg or 10 mg or 15 mg or PBO BID.
	Sandborn 2017 ⁴⁰	1 and 2: 598 and 541 Sustain: 593	(1) OCTAVE Induction 1 and 2: Remission at wk 8 (2) OCTAVE Sustain: Remission at wk 52	OCTAVE 1: remission in 18.5% patients vs 8.2% PBO OCTAVE 2: remission in 16.6% patients vs 3.6% PBO Remission 34.3% for 5 mg patients and 40.6% for 10 mg vs 11.1% PBO	TOF as induction and maintenance therapy for UC. 3 phase III trials: OCTAVE Induction 1 and 2, OCTAVE Sustain. OCTAVE Induction 1 and 2: 10 mg BID vs PBO for 8 wks. OCTAVE Sustain: 5 or 10 mg vs PBO for 52 wks.
UST	Sands 2019 ⁴¹	Induction: 961 Maintenance: 523	(1) Clinical remission at wk 8 (Induction) (2) Clinical remission at wk 44 (Maintenance)	Remission at wk 8 higher for patients who received 130 mg (15.6%) or 6 mg/kg (15.5%) than PBO (5.3%). Remission at wk 44 higher for patients given 90 mg every 12 wks (38.4%) or every 8 wks (43.8%) than PBO (24%).	UST as induction and maintenance therapy for UC. 8-wk induction trial: 130 mg IV vs weight-range-based dose (6 mg/kg) vs PBO. 44-wk maintenance trial: 90 mg every 12 wks or 8 wks vs PBO.

ADA: adalimumab; APR: apremilast; BID: 2 times daily; CS: corticosteroid; CUCQ: Crohn's and Ulcerative Colitis Questionnaire; GOL: golimumab; IBD PRITI: Inflammatory Bowel Disease Patient-Reported Treatment Impact survey; IBDQ: Inflammatory Bowel Disease Questionnaire; ITT: intent-to-treat analysis; IV: intravenous; MTX: methotrexate; OCTAVE: Oral Clinical Trials for Tofacitinib in Ulcerative Colitis; PBO: placebo; PRO: patient-reported outcome; QOL: quality of life; SC: subcutaneous; TOF: tofacitinib; UC: ulcerative colitis; ULTRA: Ulcerative Colitis Long-Term Remission and Maintenance with Adalimumab; UST: ustekinumab.

in 1 phase II RCT^{22,23} reported at week 4 and at week 24, as shown in Table 2. The 139 steroid-IR, conventional synthetic-IR, and/or biologic-IR cases were stratified by baseline CDAI, then randomized to TOF 1 mg/day, 5 mg/day, 15 mg/day, or placebo. The primary endpoint (70-point improvement in CDAI at week 4) was statistically no different in the TOF arms vs the placebo arm. The secondary endpoints (100-point improvement in CDAI and 10-item IBD Questionnaire) did not show efficacy.²² TOF has not attained regulatory approvals for CD, and no phase III studies are in progress.

JAKi: Filgotinib. A phase II RCT of another JAKi, filgotinib (FILGO), recruited 174 conventional synthetic-IR cases with CD and randomized participants to either FILGO (100 mg 4 times daily [QID] or 200 mg QID) or placebo.²⁴ FILGO (200 mg) was found to be significantly more likely than placebo to attain the primary endpoint of CDAI improvement at week 10 and most secondary endpoints. The safety profile was clinically acceptable and risk of bias was low.²⁴ Phase III RCTs are in progress.

JAKi: Upadacitinib. A phase II dose-ranging RCT tested 5 doses of upadacitinib (UPA; JAKi) in 220 steroid-IR, conventional synthetic-IR, and/or biologic-IR cases (Table 2).²⁵ During the 16-week induction, the higher doses of UPA were most efficacious, without altering safety profiles. However, by week 52 there

was no significant difference in the primary endpoint (clinical remission) between the UPA arms and placebo.²⁶ Endoscopic remission was statistically more likely with higher-dose UPA than placebo.²⁶ Phase III RCTs are in progress.

Summary of treatments for CD. Coauthor consensus meetings reviewed the several large high-quality RCTs of TNFi and 1 large RCT of UST and made a strong recommendation for both (Table 5). For IL-23i, good efficacy was seen for RZB and MEDI2070, but this was only supported by 1 RCT for each; thus, the group made a weak recommendation for IL-23i in CD, pending the publication of further results. JAKi treatments (UPA and FILGO) have weak recommendations for, whereas TOF, which did not show efficacy in CD, was given a weak recommendation against use. The group agreed on a strong recommendation against IL-17i in CD, given the lack of improvement in CD seen with BRO compared with placebo. As there was only 1 medium-sized RCT of IL-6i, there was insufficient evidence to make a recommendation. No recent studies were found for GOL or etanercept (ETN).

RCTs of UC

A total of 23 studies were screened and 15 were eligible for review, as shown in Table 3,²⁷⁻⁴¹ with 8 studies excluded because of long-term maintenance or a lack of control group.

Table 4. Advanced therapy PBO-controlled RCTs in noninfectious uveitis. Efficacy and safety in new studies from February 2013 to August 2020.

Medication Class vs PBO	Author, Year	n	(1) Primary and (2) Key Secondary Endpoints	Endpoints Met	Study Limitations and Population
ADA	Jaffe 2016 ⁴²	117	(1) Time to treatment failure occurring at or after wk 6 (2) Change in anterior chamber cell grade, vitreous haze grade, and BCVA (2) AEs and SAEs	Patients on ADA less likely to have treatment failure than PBO (24 wks vs 13 wks). Change better in ADA group than PBO. More AEs and SAEs for ADA vs PBO.	Patients with active noninfectious uveitis. Patients assigned to receive ADA (a loading dose of 80 mg followed by a dose of 40 mg every 2 wks) or matched PBO. All patients received a mandatory prednisone burst followed by tapering of prednisone over the course of 15 wks.
	Nguyen 2016 ⁴³	226	(1) Time to treatment failure	Treatment failure in 39% patients in the ADA group vs 55% patients in the PBO group Time to treatment failure: ADA > 18 months vs 8.3 months in PBO.	Patients with inactive noninfectious uveitis controlled by corticosteroids (VISUAL II). ADA: n = 115 Control: n = 111
	Mackensen 2018 ⁴⁴	25	(2) Risk of uveitis flare and loss of visual acuity (1) Improved BCVA (> 2 lines) at 3 months	ADA significantly lowered risk of uveitic flare or loss of visual acuity. ADA superior over PBO in severe ocular inflammation.	Patients with different forms of refractory uveitis. ADA: n = 10 Control: n = 15
SEC	Letko 2015 ⁴⁵	37	(1) % of patients with treatment response (2) % of patients with remission	30 mg/kg + 10 mg/kg produced higher response and remission rates than 300 mg + 30 mg/kg IV dose. Statistically and clinically superior to 300 mg SC dose.	Patients with noninfectious uveitis requiring steroid-sparing immunosuppressive therapy. SEC 300 mg SC vs 30 mg/kg IV vs 10 mg/kg IV vs saline IV/SC (PBO).
MTX vs MMF ^a	Niemeyer 2017 ⁴⁶	80	(1) Treatment success (BCVA) (2) QOL (IND-VFQ, SF-36)	No significant difference between 2 arms for change in BCVA. Significant overall improvement in visual acuity and function in patients for both arms. However, mental health score of SF-36 decreased.	Patients with intermediate, posterior, and panuveitis.

^aNo PBO arm. ADA: adalimumab; AE: adverse event; BCVA: best corrected visual acuity; IND-VFQ: Indian Vision Function Questionnaire; IV: intravenous; MMF: mycophenolate mofetil; MTX: methotrexate; PBO: placebo; QOL: quality of life; RCT: randomized controlled trials; SAE: serious adverse events; SC: subcutaneous; SEC: secukinumab; SF-36: 36-item Short Form Health Survey.

Table 5. Summary of GRADE recommendations for advanced treatments for CD, UC, and uveitis.

Indication	Strong Recommendation for	Weak Recommendation for	Weak Recommendation Against	Strong Recommendation Against	No Recommendation ^a
CD	TNFi (ADA, IFX, CZP) IL-12/23i (UST)	IL-23i (RZB, MEDI2070) JAKi (UPA, FILGO) csDMARD (MTX)	TNFi (ETN) JAKi (TOF)	IL-17i (SEC)	IL-6i (insufficient evidence) GOL (no study)
UC	TNFi (ADA, IFX, GOL) IL-12/23i (UST) JAKi (TOF)		PDE4i (APR)	csDMARD (MTX)	CZP (no study) ETN (no recent study) IL-17i (insufficient evidence)
Uveitis		TNFi (ADA) TNFi (non-RCT for IFX, CZP, GOL) csDMARD (MTX)	TNFi (ETN)		IL-17i (insufficient evidence)

Recommendations were based on available evidence from reviews and the current updated review. ^aNo recommendation: no RCTs or insufficient or conflicting evidence. ADA: adalimumab; APR: apremilast; CD: Crohn disease; csDMARD: conventional synthetic disease-modifying antirheumatic drug; CZP: certolizumab pegol; ETN: etanercept; FILGO: filgotinib; GOL: golimumab; GRADE: Grading of Recommendations Assessment, Development, and Evaluation; IFX: infliximab; IL-12/23i: interleukin 12/23 inhibitor; IL-17i: interleukin 17 inhibitor; IL-23i: interleukin 23 inhibitor; IL-6i: interleukin 6 inhibitor; JAKi: Janus kinase inhibitor; MTX: methotrexate; PDE4i: phosphodiesterase-4 inhibitor; RCT: randomized controlled trial; RZB: risankizumab; TNFi: tumor necrosis factor inhibitor; TOF: tofacitinib; UC: ulcerative colitis; UPA: upadacitinib; UST: ustekinumab.

ADA. The efficacy and safety of ADA compared to placebo has been reported in active UC in 4 RCTs.²⁷⁻³⁰ Two trials, Ulcerative Colitis Long-Term Remission and Maintenance with Adalimumab (ULTRA 1 (N = 576) and ULTRA 2 (N = 248), evaluated an 8-week induction therapy with ADA and demonstrated better remission, mucosal healing, and quality of life (QOL) compared to placebo.^{28,29} During the ULTRA 3 trial, an additional trial focusing on TNFi-experienced patients, lower response rates compared to TNFi-naïve patients were observed,²⁹ with similar efficacy and safety seen at year 4.³⁰ A RCT performed in Japan found 23.2% of patients treated with ADA achieved remission by week 52, and 32.5% of the patients were able to taper down corticosteroids.²⁷

GOL. GOL, another TNFi biologic, was studied in 5 RCTs.³¹⁻³⁵ The PURSUIT trials included 2 6-week inductions trials, a maintenance study and a study in a Japanese cohort.^{31,33-35} The PURSUIT-M trial demonstrated early clinical response to GOL treatment.³¹ The phase III trial, PURSUIT-J (N = 144) demonstrated that subcutaneous GOL maintained clinical efficacy to week 54 among induction responders.³² More patients randomized to GOL in PURSUIT-SC achieved a clinical response at 6 weeks and were more likely to achieve remission and mucosal healing.³³ In PURSUIT-IV (N = 291), a single-dose IV administration of GOL in patients with moderate-to-severe UC did not lead to significant improvements in clinical outcomes.³⁵

Methotrexate. Two RCTs determined that methotrexate (MTX) was not superior to placebo in induction of steroid-free remission among patients with UC who are steroid-dependent.^{36,37} Further, the prevention of UC relapse was not significantly different between groups during the 48-week maintenance part of this trial.³⁷

Apremilast. An oral inhibitor of phosphodiesterase 4, apremilast (APR), was evaluated in a phase II RCT in patients with active UC, but showed no efficacy compared to placebo.³⁸

TOF. The Oral Clinical Trials for Tofacitinib in Ulcerative Colitis (OCTAVE) portfolio of trials studied TOF in adults with active UC.^{39,40} In the phase II trial (N = 194), patients on TOF (15 mg) reported a significant improvement of symptoms from baseline compared with placebo.³⁹ In the induction trials, TOF (10 mg) twice daily achieved clinical remission in 18.5% of OCTAVE 1 patients and 16.6% of OCTAVE 2 patients.⁴⁰ The OCTAVE Sustain (N = 593) maintenance phase further confirmed the efficacy of TOF, with 40.6% of patients taking 10 mg twice daily and 34.3% of patients taking 5 mg twice daily achieving clinical remission, compared with only 11.1% of patients taking placebo.⁴⁰ In terms of safety, there was similar increased risk of herpes zoster as was seen in rheumatoid arthritis and psoriasis trials, with a higher rate of serious infection compared with placebo.⁴⁰

UST. A large RCT of UST (N = 961) with an 8-week induction and 44-week maintenance found UST was more effective than placebo for reducing UC remissions.⁴¹

Summary of treatments for UC. Based on our review and our coauthor consensus meetings (Table 5), a strong recommendation was made for TNFi (ADA and GOL), JAKi (TOF), and

IL-12/23i (UST), all with a low risk of bias. For the phosphodiesterase-4 inhibitor (APR), there is a single small study that did not show efficacy in UC and so the group made a weak recommendation against. For MTX, as both RCTs did not show efficacy in UC, a strong recommendation against was given. No recent RCTs for ETN or certolizumab pegol were found.

RCTs of uveitis

A total of 7 RCTs were screened and 5 RCTs (Table 4) were eligible.⁴²⁻⁴⁶ Corticosteroids have long been the standard treatment for patients with ocular inflammation; however, their long-term use confers risks to patients.^{47,48} We sought to summarize the RCTs of uveitis treatments, other than corticosteroids, that are also commonly used to treat patients with PsA.

ADA. Three RCTs assessed the efficacy of ADA in treating flares of uveitis and improvement in visual acuity scores.⁴²⁻⁴⁴ In 2 trials, patients received prednisone at baseline along with ADA treatment, which was then tapered and stopped during the trial.^{42,43} ADA demonstrated steroid-sparing effects and flares of uveitis were delayed compared with the placebo group.^{42,43} A small RCT in cases of refractory noninfectious uveitis showed significant reduction in ocular inflammation in the ADA group.⁴⁴

Secukinumab. Secukinumab (SEC; IL-17i) demonstrated efficacy in a small trial of acute-on-chronic noninfectious uveitis.⁴⁵ Patients with uveitis receiving intravenous (at significantly higher doses than are used in clinical practice) vs subcutaneous SEC responded faster and with greater likelihood of remission.⁴⁵ Perhaps subcutaneous SEC did not attain sufficient concentrations for uveitis treatment in this trial.

MTX. One RCT evaluated the QOL in patients with uveitis treated with either MTX or mycophenolate mofetil.⁴⁶ Although the visual symptoms improved, the overall physical health scores did not show improvement and mental health-related QOL scores declined.

Summary of treatments for uveitis. Uveitis presents a challenge to make definitive recommendations, as studies were done in a uveitis cohort and extrapolated to PsA. The 2 large RCTs and 1 smaller RCT of ADA in uveitis, with low risk of bias, allowed the group to make a weak recommendation for TNFi (Table 5), except for ETN, with a weak recommendation against. A small comparison trial led to a weak recommendation for MTX based on improved QOL indicators. There was only 1 small trial in SEC that met our criteria, and the consensus was that there was insufficient evidence to make a recommendation from this single study.

DISCUSSION

In keeping with our eligibility criteria, in this review we have only reported on RCTs in the Results section. In the forthcoming Discussion, we will highlight and signpost the reader to notable non-RCT studies for further reading.

Our review of the literature demonstrated that not all treatments used for PsA are also effective for IBD and/or uveitis, dosing regimens can vary, there can be safety considerations, and reimbursement depends upon the indication. We propose that

the outcomes of these trials may be extrapolated to patients with PsA with comorbid IBD or uveitis, and thus be used to personalize their treatment, keeping in mind that we are currently lacking RCTs conducted in people with PsA and these related conditions.

Given the varying clinical phenotypes and natural histories that our patients with IMIDs can manifest, a multispecialty approach is essential to effectively, safely, and holistically manage these patients. As a result, therapeutic algorithms are becoming more complex, with an increasing proportion of patients needing a more personalized approach, independent of algorithms.⁴⁹ This is an approach increasingly advocated by international recommendations, including GRAPPA 2021,¹² the American College of Rheumatology,⁵⁰ and the European Alliance of Associations for Rheumatology 2019 treatment recommendations for PsA.⁵¹ The aim is to more effectively diagnose different IMID manifestations, intervene early to prevent clinical sequelae — especially those that are irreversible, reduce disease activity in multiple domains to prevent morbidity and irreversible damage, prevent disease related complications, and improve prognosis and QOL.

Treatment choices for PsA may be affected by treatments for comorbid conditions. For example, IL-17i has been shown to exacerbate known CD. There is now strong evidence based upon 2 independent phase II RCTs that IL-17 antagonists exacerbate CD^{20,52} and would therefore be contraindicated in patients with PsA and active CD. The same may be applied to IL-17i use in UC.

There are numerous high-quality studies supporting TNFi use (except ETN) in UC, both as monotherapy and combined with conventional synthetic agents. The JAKi TOF has proven effective in UC, albeit not in CD. Further studies of other JAKi (UPA and FILGO) and IL-23i are in progress for UC and CD. Although MTX has been widely used in clinical practice for UC, only recently have there been well-designed RCTs evaluating MTX in UC. Surprisingly, both RCTs did not support MTX to induce steroid-free remission or prevent relapses, compared to placebo.³⁶

The RCTs of uveitis discussed in this review should serve to inform treatment choices in patients with PsA suffering with uveitis in the absence of specific studies in PsA. In severe or untreated cases of uveitis, for example, one must initiate prompt treatment in order to prevent vision loss, which still accounts for 10% to 15% causes of legal blindness in the United States and carries significant personal and societal impact.^{7,47} ADA is the first TNFi approved for intermediate, posterior, and panuveitis. However, there is still a major need for more RCTs to better inform treatment recommendations. In particular, there are few/no RCTs in the various subsets of uveitis and no studies of prognosis of uveitis in patients with PsA. ETN use is not recommended in patients with PsA with concomitant uveitis because of its poor efficacy for uveitis and the risk uveitis poses for irreversible eye damage, including blindness. Some studies (not eligible for our review) found anti-TNF agents in ankylosing spondylitis and juvenile idiopathic arthritis, and azathioprine in Behcet disease were effective for uveitis.^{53,54} Efforts to convene international expert consensus are underway to develop guidance on biologic therapy for noninfectious uveitis.⁴⁷

In conclusion, we have identified recent RCTs in IBD and uveitis that should be considered when managing patients with PsA and these related conditions. For some classes of treatment there is consistent efficacy, whereas for other classes there appears to be differential efficacy across IMID domains. One must be cognizant of differences in safety profiles between different biologics, and the emerging small-molecule therapies. Small-molecule therapies might be more prone to off-target effects that may make their efficacy and safety more difficult to handle as a class. As our therapeutic armamentarium for IMIDs is increasing, we are entering an exciting era of greater multi-specialty collaboration, which will also pose unique challenges.

ONLINE SUPPLEMENT

Supplementary material accompanies the online version of this article.

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