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Rheumatoid arthritis

Efficacy of synthetic and biological DMARDs: a systematic literature review informing the 2025 update of the EULAR recommendations for the management of rheumatoid arthritis

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ABSTRACT

Objectives: This systematic literature review (SLR) updated evidence on the efficacy of disease-modifying antirheumatic drugs (DMARDs) and glucocorticoids (GCs) to inform the 2025 update of the European Alliance of Associations for Rheumatology (EULAR) management recommendations for rheumatoid arthritis (RA).

Methods: Medline (PubMed), Embase (OVID), Cochrane Central Register of Controlled Trials, and Web of Science were searched for randomised controlled trials (RCTs) of conventional-synthetic, biological, and targeted-synthetic DMARDs (csDMARDs, bDMARDs, tsDMARDs), as well as GCs and biosimilars, published from 14 January 2022 to 22 January 2025. Additional searches on DMARDs, GCs, and antifibrotics for RA-associated interstitial lung disease (RA ILD), and on DMARDs and GCs for preventing RA in at-risk individuals, were conducted from database inception to 22 January 2025.

Results: A total of 12,567 references were identified; 390 full-texts were reviewed, and 72 studies were included. Phase 3-4 RCTs evaluated csDMARDs (hydroxychloroquine, iguratimod, leflunomide, and methotrexate), bDMARDs (abatacept, otilimab, and ozoralizumab), and tsDMARDs (ivarmacitinib, peficitinib, and tofacitinib). Twelve novel compounds were assessed in phase 2 RCTs, and 3 articles investigated GCs. Strategic trials compared conventional therapies with bDMARD- or tsDMARD-based strategies and explored precision-medicine approaches such as synovial biopsy-guided treatment and therapeutic drug monitoring. Additional evidence addressed DMARD tapering. Two RCTs assessed antifibrotics (nintedanib and pirfenidone) for RA ILD, and 7 studies evaluated DMARDs for RA prevention in at-risk populations.

Conclusions: This SLR, together with the safety review, informed the 2025 update of the EULAR RA management recommendations. Although few phase 3 trials on novel agents were available, strategic and head-to-head studies provided important insights that enabled further refinement of the established treatment algorithm.

INTRODUCTION

Rheumatoid arthritis (RA) affects approximately 18 million people worldwide and can substantially impair health-related quality of life by causing persistent joint inflammation, progressive joint damage, reduced physical function, and systemic complications involving organs such as the lungs or the heart [1–3]. Effective treatment can prevent chronic pain and long-term disability, and substantially reduce the individual and societal burden of the disease [4].

The first European Alliance of Associations for Rheumatology (EULAR) recommendations for the management of RA with disease-modifying antirheumatic drugs (DMARDs) were published in 2010 [5]. The recommendations have been updated every 3 years since 6–8, with their ongoing evolution constantly shaped by the introduction of novel therapeutic agents with broadening mechanisms of action, as well as pivotal research on the optimal use of these therapies, like the well-established treat-to-target (T2T) principle [9].

Although fewer novel DMARDs have entered the market in recent years, head-to-head comparisons of available DMARDs and therapeutic strategy trials have become increasingly relevant. The focus of current research has therefore partly shifted from increasing the overall availability of DMARDs to optimising the use of existing DMARDs, and selecting the right option at each disease stage, while balancing benefits and risks of each therapy [10].

A distinct disease phenotype, RA-associated interstitial lung disease (RA ILD), has also gained increasing attention in recent years, and antifibrotic agents are currently under investigation [11]. In addition, the use of DMARDs to prevent disease onset in individuals at risk of developing RA, DMARD tapering and withdrawal, head-to-head comparisons, or precision-medicine approaches using synovial tissue histology and transcriptome analysis to predict treatment response have become frequently discussed topics in RA research [12–14].

Previous research questions were updated in response to these developments, and systematic literature reviews (SLRs) were conducted to collect all relevant published data. We report in this paper on the current update of the 2022 SLR on the efficacy of DMARDs and glucocorticoids (GCs) in RA [15,16], as well as additional searches on RA ILD and the prevention of RA in individuals at risk of developing the disease. The SLR on safety and disease monitoring, as well as the recommendations paper, were published separately [17,18].

METHODS

The EULAR standard operating procedure for the development of recommendations and points to consider, as well as the Cochrane Handbook for SLRs and Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines, were adhered to in this project [19–22].

The scope of the review was defined during an initial steering committee meeting held on 16 November 2024. Thirty-four research questions were defined in Population, Intervention, Comparator, Outcome (PICO) format, and a study protocol was distributed among all committee members, including a Patient Research Partner (SdS). Based on these, a literature search strategy was developed by an experienced librarian (JWS), and Medline (PubMed), Embase (OVID), The Cochrane Central Register of Controlled Trials (CENTRAL), and Web of Science, as well as conference abstracts from the 2023 and 2024 EULAR and American College of Rheumatology (ACR) annual meetings were screened without language restrictions. Hand-searched studies, as well as additional literature found through reference checking, were further included.

PICO questions and the detailed search strategies are provided in the Supplementary Appendix (Section S1). For the update of the 2022 efficacy SLR [15], randomised placebo (PLC)- or active-controlled trials (RCTs) studying DMARDs or GCs in adult patients with RA and published since 14 January

2022 (data cut of the previous SLR) were eligible for inclusion. The majority of research questions focused on the efficacy of DMARDs, both compared with PLC and in head-to-head studies with an active comparator, with or without background therapies, as well as on DMARD switching, tapering, and withdrawal. Studies on biosimilars and generics of synthetic DMARDs were also included. Unlike for the previous update, no separate SLR on GCs was conducted, as only a limited number of new studies had emerged since 2022. These studies were considered in the efficacy and safety searches.

In addition to the SLR updates, the steering committee agreed to expand the scope of the review to topics not specifically considered previously. Thus, 2 separate searches for RCTs investigating DMARDs, GCs, and antifibrotics in RA ILD, as well as for DMARDs and GCs in individuals at risk of developing RA, were conducted, including articles from database inception to present. Details on these additional searches are provided in the Supplementary Appendix (Section S1). Four research questions were formulated for RA ILD (Supplementary Appendix; Section S1.7.2) and 7 for the RA at-risk stage (Supplementary Appendix; Section S1.7.3). For all searches, studies with a duration of at least 6 months and a sample size of at least 50 participants were considered, but smaller trials were also included if the former were not available for a specific DMARD or topic. Only published manuscripts or conference abstracts were considered. The data cut was set as 22 January 2025.

Two researchers (VK and FL) screened 10% of all abstracts. As an agreement rate of >90% was achieved, the remaining articles were screened by 1 researcher (VK), and uncertainties were discussed with the methodologists (AK and RBML). Selected articles were then fully assessed for eligibility, and study and baseline characteristics as well as efficacy outcomes from finally included articles extracted into previously prepared spreadsheets (VK). Risk of bias (RoB) was assessed using the Cochrane Collaboration's tool for assessing RoB in RCTs (RoB 2) [23,24]. Random-effects meta-analyses were conducted for all PICOs with at least 2 eligible studies. For tapering and withdrawal studies, meta-analyses were not performed due to substantial heterogeneity in interventions, populations, and endpoints, as well as incompatible study designs, outcome definitions, and follow-up times across studies.

RESULTS

For the efficacy update, a total of 6999 abstracts were obtained in the database search, of which 4836 were screened after deduplication, 304 were selected for full-text reading, and 62 articles were finally included. For RA ILD, 1494 abstracts were screened after deduplication, of which 43 were selected for full-text reading, and 3 articles were finally included. For the RA at-risk SLR, 2610 articles were screened after deduplication, of which 43 were selected for full-text reading, and 7 were included. A summary of the 3 literature searches is provided in Figure 1.

A summary of all therapeutic compounds investigated is shown in Table 1 [25–94]. Detailed tabular overviews of all studies included, as well as the RoB analyses, baseline characteristics, and efficacy outcomes, are provided in the Supplementary Appendix (Sections S2-S7). We further provide meta-analyses by PICO in the Supplementary Appendix (Sections S4 and S7.4; Supplementary Figs S1-S6), where data permit. All studies that were not eligible for meta-analysis (due to substantial heterogeneity in outcomes, populations, or trial designs) were summarised descriptively. A tabular overview of all PICOs, eligible studies, and the rationale for conducting (or not conducting) meta-analyses is provided in Supplementary Sections S1.7.1 to S1.7.3.

In total, 4 studies assessed the efficacy of conventional-synthetic DMARDs (csDMARDs), 12 studies assessed the efficacy of biological DMARDs (bDMARDs) against PLC and/or csDMARDs, and 10 studies assessed the efficacy of targeted-synthetic DMARDs (tsDMARDs) against PLC and/or csDMARDs. Eight head-to-head studies and therapeutic strategy trials, and 3 studies on GCs were also included. Regarding DMARD tapering or withdrawal, 2 studies assessed csDMARD tapering, 4 studies assessed bDMARD tapering, 3 studies assessed tsDMARD tapering, and 2 studies assessed tapering of GCs. Eleven studies on biosimilars were available, whereas no RCTs on generics of tsDMARDs were found. In the additional searches, 2 studies were included on RA ILD, and 7 on the efficacy of DMARDs in the RA at-risk populations. Forty-four studies were designed as superiority trials, and 24 as noninferiority trials, with most of these trials having a predominantly strategic design (n = 4), or investigating tapering (n = 10) or biosimilars (n = 10).

In summary, 25 studies were judged as having low RoB, 7 as moderate RoB, 21 as high RoB (mostly due to their open-label design), and 3 as unclear. Twelve conference abstracts were not assessable for RoB.

Efficacy of csDMARDs

Four studies were included on csDMARDs, of which 1 was assessed as having a low RoB, 1 as moderate RoB, 1 as high RoB, and 1 study was only available as a conference abstract.

Iguratimod 25 mg twice daily monotherapy and in combination with methotrexate (MTX) 10 to 15 mg weekly was compared with MTX monotherapy in a 52-week double-blind RCT on 895 MTX-naïve patients from China (moderate RoB). Both iguratimod monotherapy and in combination with MTX were superior to MTX monotherapy with regard to clinical outcomes (ACR 20% improvement criteria [ACR20] response at week 52: 77.4%, 77.1%, and 65.9%, respectively), and noninferior with regard to radiographic progression (Δmodified total Sharp Score, mTSS, at week 52: 1.30, 0.99, and 1.67, respectively) [28].

Noninferiority of subcutaneous vs oral MTX (7.5 mg weekly and 8 mg weekly, respectively) was demonstrated in a multicentre, double-blind, randomised head-to-head study (low RoB) on 102 MTX-naïve patients from Japan (ACR20 response at week 12: 59.6% vs 51.0%; P = not significant [n.s.]) [25].

In a 12-week, single-centre, single-blind trial from China (high RoB), 60 DMARD-naïve patients were randomised to receive either MTX 10 to 15 mg weekly + hydroxychloroquine (HCQ) 400 mg once daily or MTX monotherapy. MTX + HCQ showed numeric benefits in composite scores and disease core sets when compared with MTX monotherapy (disease activity score of 28 joints using C-reactive protein, DAS28-CRP, at week 12: 2.29 vs 2.97; exploratory endpoint) [27].

MTX dose splitting into a morning and evening application failed to add clinically meaningful benefits to a conventional single-dose weekly MTX application in an open-label, 24-week study (n = 253; ΔDAS28-CRP at week 24: 2.40 vs 2.10; conference abstract) [26].

Efficacy of bDMARDs vs PLC and/or csDMARDs

Twelve studies compared bDMARDs with PLC or csDMARDs, of which 6 were assessed as low RoB, 3 as high

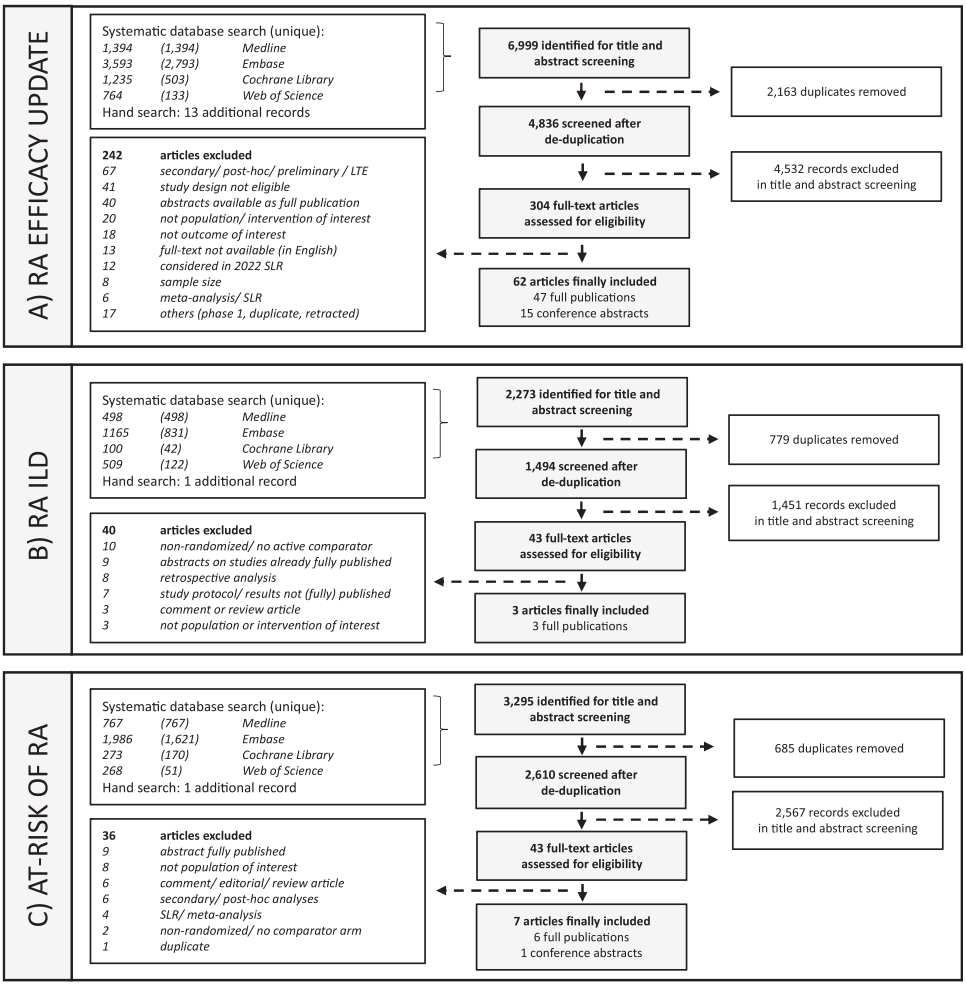

Figure 1. PRISMA flow chart illustrating the systematic literature review and study selection process. ILD, interstitial lung disease; LTE, long-term extension; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses; RA, rheumatoid arthritis; SLR, systematic literature review.

RoB, 2 as unclear, and 1 study was only available as a conference abstract.

Six double-blind phase 2 trials tested novel biological DMARDs against PLC: SM03, a B-cell-inhibiting anti-CD22 monoclonal antibody (mAb), showed superiority over PLC when combined with background MTX in a 24-week study on MTX insufficient responder (IR) patients from China (n = 155; ACR20 at week 24: 65.3% for SM03 6 × 600 mg intravenous application [i.v.], 56.9% for SM03 4 × 600 mg i.v., and 34.0% for PLC, $P = .002$ and $P = .024$ vs PLC, respectively; high RoB) [29]. Numeric benefits were observed with low-dose interleukin-2 (IL2), again when combined with MTX in MTX IR patients, in a 24-week, single-centre study from Beijing (n = 40; ACR20 at week 24: 76.5% for IL2 vs 56.5% for PLC; $P = .08$; high RoB) [35]. Peresolimab, a PD1 agonist, was superior to PLC when combined with background csDMARDs in csDMARD IR patients as well as in b/tsDMARD IR patients (42%) in a multinational, 12-week RCT (n = 98; ΔDAS28-CRP, at week 12: −2.1 [SE 0.18] for peresolimab 700 mg once every 4 weeks vs −1.0 [SE 0.26] for PLC; $P<.001$; low RoB) [30]. Of note, a recent phase 2b study presented after the data cut of this SLR could not confirm these positive results and was discontinued due to an unfavourable risk/benefit profile of the drug [95]. Dazodalibep, a soluble antagonist of CD40 ligand, showed significantly higher reductions in DAS28-CRP at week 16 in csDMARD IR and tumour necrosis factor alpha inhibitor (TNFi) IR patients (n = 78; ΔDAS28-CRP at week 16: −1.9 [SE 0.3], 2.0 [SE 0.3], −1.9 [SE 0.3], −1.8 [SE 0.3], vs −1.1 [SE 0.3], for various dosing regimens vs PLC; $P = .027$, $P = .036$, $P = .37$, $P = .48$; low RoB) [31]. Abiprubart, a CD-40-inhibiting mAb, showed benefits at week 12 in bDMARD/Janus kinase inhibitor (JAKi) IR (n = 78; ΔDAS28-CRP at week 12: −2.2 [−2.6 to −1.8] and −2.0 [−2.4 to −1.6] for Abiprubart 5 mg/kg weekly and once every 2 weeks vs −1.6 [−2.1 to −1.2] for PLC; $P = .047$ and $P = .21$ vs PLC, respectively; conference abstracts) [32,33]. No relevant benefits were observed with nipocalimab, a neonatal Fc receptor inhibiting mAb, in TNFi IR (n = 53; ΔDAS28-CRP at week 12: −1.0 [−1.7 to −0.4] vs −0.6 [−1.2 vs 0.1] for nipocalimab 15 mg/kg i.v. once every 2 weeks vs PLC; $P = .224$; unclear RoB) [34].

Ozoralizumab (OZO), a TNF-inhibiting nanobody, demonstrated superiority over PLC when combined with background MTX in 381 MTX IR patients from Japan in the phase 2/3 OHZORA trial (unclear RoB). ACR20 response rates at week 16 were 79.6% for OZO 30 mg once every 4 weeks, 75.3% for OZO 80 mg once every 4 weeks, and 37.3% for PLC ($P < .001$ for both); radiographic progression was low overall and comparable between groups (ΔmTSS at week 24: 0.6 for OZO 30 mg once every 4 weeks, 0.4 for OZO 80 mg once every 4 weeks, 0.8 for PLC; P = n.s. for both comparisons) [39].

Otilimab (OTI), a granulocyte-monocyte colony-stimulating factor (GM-CSF) inhibiting mAb, was tested against PLC as well as against active comparators (tofacitinib [TOFA] and sarilumab [SAR]) in the phase 3, multinational ContRAst programme (all low RoB). OTI 90 mg weekly and 150 mg weekly were superior to PLC in ContRAst 1 and ContRAst 2, but not in ContRAst 3,

Table 1
Overview of all compounds considered in the current literature review

SLR	Intervention	No of studies	Compounds investigated	Target	REF
2025 efficacy update	Efficacy of csDMARDs	4	Methotrexate	Dihydrofolate reductase/ AICAR transformylase	[25,26]
			Hydroxychloroquine	Uncertain	[27]
			Iguratimod	COX-2, otherwise uncertain	[28]
	Efficacy of bDMARDs vs PLC and/or csDMARDs	6	SM03	CD22	[29]
			Peresolimab	PD1	[30]
			Dazodalibep	CD40 ligand	[31]
	Phase 2		Abiprubart	CD40	[32,33]
			Nipocalimab	FcRN	[34]
			Low-dose IL2	Treg upregulation	[35]
	Phase 3	6	Otilimab	GM-CSF	[36,37]
			Abatacept	CD80/86	[38]
			Ozoralizumab	TNF	[39]
			Denosumab	RANKL	[40]
	Efficacy of tsDMARDs vs PLC and/or csDMARDs	6	Obefazimod	miR-124	[41]
			Elsbrutinib	BTK	[42]
			TAS-5313	BTK	[43]
	Phase 2		BMS-986142	BTK	[44]
			AP1189 (Resomelagon)	MC1/MC3 R	[45,46]
	Phase 3	4	Peficitinib	JAK1-3	[47]
			Ivarmacitinib	JAK1	[48]
			Tofacitinib	JAK1-3	[49,50]
	csDMARDs strategies	1	csDMARD combination	Various	[51]
	bDMARDs vs bDMARDs and/or csDMARD	4	Methotrexate + GCs + leflunomide vs methotrexate + GCs + etanercept	Dihydrofolate reductase/ AICAR + GR + DHODH vs dihydrofolate reductase/ AICAR + GR + TNF	[52]
			Certolizumab pegol vs abatacept vs tocilizumab vs active conventional therapy	TNF vs CD80/86 vs IL6R	[53]
			Etanercept vs tocilizumab vs rituximab	TNF vs IL6R vs CD20	[13]
			Abatacept vs adalimumab	CD80/86 vs TNF	[54,55]
	tsDMARDs vs tsDMARDs	1	TLL-018 vs tofacitinib	JAK1 vs JAK1-3	[56,57]
	Therapeutic drug monitoring	2	Adalimumab dose titration to 5 mg/L vs 2 mg/L serum concentration	TNF	[58,59]
			TDM-based treatment switching vs random switching	TNF/others	[60]
	Efficacy of GCs	3	Prednisone (or equivalent)	GR	[61]
			ABBV3373	TNF, GR	[62]
			AZD9567	GR	[63]
	Tapering of csDMARDs	2	Methotrexate	Dihydrofolate reductase/ AICAR transformylase	[64]
			Any csDMARD		[14]
	Tapering of bDMARDs	4	Any TNFi	TNF	[65,66]
			Tocilizumab	IL6R	[67]
			Abatacept	CD80/86	[38,67]
	Tapering of tsDMARDs	3	Tofacitinib	JAK1-3	[68,69]
			Baricitinib	JAK1-2	[70]
	Tapering of GCs	2	Prednisone (or equivalent)	GR	[71]
			Hydrocortisone	GR	[72]
	Biosimilars	11	Etanercept BS	TNF	[73]
			Infliximab BS	TNF	[74–76]
			Adalimumab BS	TNF	[77,78]
			Golimumab BS	TNF	[79]
			Rituximab BS	CD20	[80]
			Tocilizumab BS	IL6R	[81–84]
RA ILD	Efficacy of antifibrotics in RA ILD	2	Nintedanib	FGFR, PDGFR, VEGFR	[85,86]
			Pirfenidone	TGF-β, TNF-α, IL1	[87]
Individuals at risk of developing RA	Efficacy of DMARDs in the at-risk period	7	Hydroxychloroquine	Uncertain	[88]
			Dexamethasone	GR	[89]
			Atorvastatin	HMG-CoA reductase	[90]
			Methotrexate	Dihydrofolate reductase/ AICAR transformylase	[91]
			Rituximab	CD20	[92]
			Abatacept	CD80/86	[93,94]

AICAR, 5-aminoimidazole-4-carboxamide ribonucleotide; bDMARD, biological disease-modifying antirheumatic drug; BTK, Bruton's tyrosine kinase; CD, cluster of differentiation; csDMARD, conventional-synthetic disease-modifying antirheumatic drug; DHFR, dihydrofolate reductase; DHODH, dihyroorotate dehydrogenase; FcRN, neonatal Rc receptor; FGF, fibroblast growth factor; GC, glucocorticoid; GM-CSF, granulocyte-monocyte colony-stimulating factor; GR, glucocorticoid receptor; HMG-CoA, 3-hydroxy-3-methylglutaryl-coenzyme A; IL, interleukin; ILD, interstitial lung disease; JAK, janus kinase; MC, melanocortin; miR-124, microRNA-124; PD-1, programmed cell death protein 1; PDGF, platelet-derived growth factor; R, receptor; REF, reference; RA, rheumatoid arthritis; RANK, receptor activator of nuclear factor kB; SLR, systematic literature review; TDM, therapeutic drug monitoring; TGF-β, transforming growth factor-beta; TNF, tumour necrosis factor; Tregs, regulatory T cells; tsDMARD, targeted-synthetic disease-modifying antirheumatic drug; VEGF, vascular endothelial growth factor.

and were inferior to TOFA or SAR in all 3 trials. In ContRAst 1 (MTX IR population on concomitant MTX), the ACR20 response rates at week 12 were 54.7% for OTI 90 mg weekly, 50.9% for OTI 150 mg weekly, 63.6% for TOFA 5 mg twice daily, and 42.7% for PLC ($P = .0023$, $P = .0362$, $P < .001$ vs PLC, respectively) [36]. In ContRAst 2 (csDMARD and bDMARD IR population on concomitant csDMARD), the ACR20 response rates at week 12 were 54.9% for OTI 90 mg weekly, 54.5% for OTI 150 mg weekly, 71.1% for TOFA 5 mg twice daily, and 32.5% for PLC ($P < .001$ for all arms vs PLC) [36], and in ContRAst 3 (csDMARD, bDmard, and JAKi IR on concomitant csDMARD), the ACR20 response rates at week 12 were 44.8% for OTI 90 mg weekly, 50.7% for OTI 150 mg weekly, 57.5% for SAR 200 mg once every 2 weeks, and 37.7% for PLC ($P < .001$ for all arms vs PLC) [37].

The multinational, phase 3b AVERT-2 trial compared abatacept (ABA) 125 mg weekly + MTX with PLC + MTX for induction and maintenance of remission (REM) in anticitrullinated peptide antibody (ACPA)-positive, DMARD-naïve patients with early RA (low RoB). The study consisted of a 56-week induction period and a 48-week de-escalation period. The primary endpoint, simplified disease activity index (SDAI) REM, was not met: ABA 125 mg weekly was not superior to MTX for induction of SDAI REM at week 24 (SDAI ≤3.3: 21.3% for ABA + MTX vs 16.0% for PLC + MTX; $P = .2359$), whereas the endpoint was met at week 52 (SDAI ≤3.3: 29.8% for ABA + MTX vs 15.3% for PLC + MTX; $P = .0021$), and radiographic progression was significantly lower in the ABA group (ΔmTSS at week 52: 0.5 [SD 2.3] for ABA + MTX vs 2.5 [SD 6.2] for PLC + MTX; $P < .001$) [38]. However, the study period after the 6-month primary endpoint did not adhere to the T2T principle, and it is well established that bDMARDs reduce progression of joint damage even in clinical nonresponders [96–99].

Denosumab, a receptor activator of nuclear factor kappa-B ligand (RANKL) inhibitor, failed to show significant benefits over PLC for inhibition of bone erosion progression, measured by high-resolution peripheral qualitative computed tomography scans, within 24 weeks in 43 patients with active RA and progressive bony erosions on stable csDMARDs from Japan (Δbone erosion depth: −0.57 mm [−1.5 to 0.4] for denosumab 60 mg once every 6 months vs −0.22 mm [−1.0 to 0.5] for PLC; $P = .27$; high RoB) [40]. These data confirm findings obtained using conventional radiography; however, in that study, denosumab had shown no clinical efficacy, and no inhibition of the progression of cartilage damage was observed [100].

Efficacy of tsDMARDs vs PLC and/or csDMARDs

Ten studies on tsDMARDs were considered, of which 2 were graded as low RoB, 2 as moderate RoB, 2 as high RoB, and 1 as unclear. Three conference abstracts were not assessed for RoB.

Obefazimod, a microRNA-124 upregulator, was well tolerated and showed numeric benefits when combined with MTX in a 12-week, dose-finding, safety-endpoint, phase 2a study (moderate RoB), in 60 MTX and/or TNFi IR (ΔDAS28-CRP at week 12: −0,72 [SD 1.1] for obefazimod 100 mg once daily, −1.41 [SD 1.5] for obefazimod 50 mg once daily, and −0.60 [SD 1.0] for PLC; $P = .727$ and $P = .043$ vs PLC) [41]. Fixed combination of elsubrutinib, an irreversible Bruton's tyrosine kinase inhibitor (BTKi), with upadacitinib (UPA), a JAK1/2 selective inhibitor, was superior to PLC and background csDMARD at week 12 in a multinational phase 2 study in 242 bDMARD IR (high RoB), but with efficacy driven predominantly by the JAKi, while elsubrutinib monotherapy failed to show superiority over PLC (ΔDAS28-CRP −2.56 [−2.9 to −2.3] for the BTK/JAK combination, −1.52 [−1.9 to −1.2] for elsubrutinib 60 mg once daily, −2.87 [−3.2 to −2.5] for UPA 15 mg once daily, and −1.12 [−1.6 to −0.6] for PLC; $P < .001$ for BTK/JAK combination and UPA monotherapy vs PLC; P = n.s. for BTK monotherapy vs PLC) [42]. TAS-5315, another irreversible BTKi, demonstrated numeric but not statistical superiority over PLC in a Japanese, 12-week phase 2 study in 91 MTX IR (ACR20 at week 12: 78.9% vs 60.06%, $P = .053$; unclear RoB) [43]. BMS-986152, a reversible BTKi, was not superior to PLC and background MTX in a 12-week, multinational phase 2 study on 248 patients with IR to MTX and up to 2 TNFi (ACR20 at week 12: 36% for BMS 100 mg, 42% for BMS 200 mg, and 31% for PLC; all P = n.s.; low RoB) [44]. Resomelagon, a melanocortin 1 and 3 receptor agonist, was investigated in the phase 2b EXPAND study after promising results from the prior phase 2a BEGIN study, but it failed to meet its primary and key secondary endpoints (n = 113; ACR20 at week 12: 55% vs 56%; P = n.s.; both conference abstracts) [45,46].

The pan-JAK inhibitor peficitinib (PEFI) demonstrated superiority over PLC in a phase 3 study (moderate RoB) in 385 MTX IR from China, Korea, and Taiwan (ACR20 at week 24: 56.6% for PEFI 100 mg once daily, 56.3% for PEFI 150 mg once daily, and 24.2% for PLC; $P < .001$ for both) [47].

Ivarmacitinib (IVAR), a JAK1 selective inhibitor, was superior to PLC in 566 MTX IR from China (low RoB), and met its primary endpoint as well (ACR20 at week 24: 70.4% for IVAR 4 mg once daily, 75.1% for IVAR 8 mg once daily, and 40.4% for PLC; $P < .001$ for both) [48].

TOFA 5 mg twice daily was compared with MTX for treatment induction in DMARD-naïve patients in 2 open-label RCTs. TOFA was not superior to MTX 25 mg weekly in a single-centre study from Bangladesh (n = 100; DAS28-CRP low disease activity [LDA] at week 12: 34.7% for TOFA vs 35.3% for MTX; $P = .95$; high RoB) [49], but superior to MTX 10 to 15 mg weekly + a 1-shot betamethasone 1 mL muscle injection in a single-centre study from Beijing (n = 100; ΔSDAI >50% at week 12: 29.3% for TOFA vs 7.5% for MTX; $P = .025$; conference abstract) [50].

An overview of all phase 3 studies comparing bDMARDs and tsDMARDs with PLC and/or csDMARD in csDMARD, bDMARD, or JAKi IR patients is provided in Table 2 [101–103]. Detailed efficacy outcomes are listed in the Supplementary Appendix (Sections S3.1.2 and S3.1.3).

Head-to-head studies on bDMARDs and tsDMARDs (with or without background csDMARDs)

Four head-to-head studies of bDMARDs vs tsDMARDs were included, of which 2 were graded as high RoB, and 2 were only available as conference abstracts.

The 48-week, multicentre, assessor-blinded, phase 4 NORD-STAR trial (high RoB) compared csDMARD combination therapies (20 mg oral prednisolone quickly tapered and discontinued at week 36 + MTX or sulfasalazine [SSZ] + HCQ + MTX + intraarticular GC injections) with 3 bDMARD strategies (certolizumab pegol [CZP] 200 mg subcutaneous application [s.c.] once every 2 weeks + MTX, ABA 125 mg s.c. weekly + MTX and tocilizumab [TCZ] 8 mg/kg i.v. once every 4 weeks or 162 mg s.c. weekly), in 812 DMARD-naïve patients with early RA. MTX was up-titrated to 25 mg weekly within 4 weeks if tolerated. No clinically meaningful differences between the treatments had been observed at week 24 (primary endpoint). At week 48, clinical disease activity index (CDAI) REM rates were 52.3% for CZP,

Table 2
Phase 3 studies comparing bDMARDs or tsDMARDs with placebo and/or csDMARDs, in csDMARD insufficient responders, bDMARD IR, or JAKi IR

Study	RoB	Treatment	No. pts	Week	ACR20 (%)	ACR50 (%)	ACR70 (%)
csDMARD IR							
Takeuchi et al, 2022 (OHZORA) [39]	Unclear	PLC + MTX	75	16	37.3	12.0	2.7
		Ozoralizumab 30 mg i.v. once every 4 wk + MTX	152		79.6[c]	55.9[c]	34.2[c]
		Ozoralizumab 80 mg i.v. once every 4 wk + MTX	154		75.3[c]	50.6[c]	27.9[c]
Fleischmann et al, 2023 (ContRAst 1) [36]	Low	PLC + MTX	256	12	42.7	12.2	3.5
		Otilimab 90 mg s.c. once weekly + MTX	513		54.7[b]	23.3[d]	8.5[d]
		Otilimab 150 mg s.c. once weekly + MTX	510		50.9[a]	20.0[d]	6.1
		Tofacitinib 5 mg p.o. twice daily + MTX	258		63.6[c]	34.1[d]	13.9[d]
Yang et al, 2023 [47]	Moderate	PLC + csDMARD	128	24	24.2	3.1	3.1
		Peficitinib 100 mg p.o. once daily + csDMARD	129		56.6[c]	27.9[c]	12.4[b]
		Peficitinib 150 mg p.o. once daily + csDMARD	128		56.3[c]	27.3[c]	11.7[a]
Liu et al, 2024 [48]	Low	PLC ± csDMARD	188	24	40.4	15.4	6.9
		Ivarmacitinib 4 mg p.o. once daily ± csDMARD	189		70.4[c]	46.0[c]	22.2[c]
		Ivarmacitinib 8 mg p.o. once daily ± csDMARD	189		75.1[c]	57.1[c]	31.7[c]
csDMARD IR/ bDMARD IR							
Fleischmann et al, 2023 (ContRAst 2) [36]	Low	PLC + csDMARD	270	12	32.5	9.5	4.2
		Otilimab 90 mg s.c. once weekly + csDMARD	545		54.9[c]	21.6[d]	6.9
		Otilimab 150 mg s.c. once weekly + csDMARD	539		54.5[c]	25.1[d]	9.6[d]
		Tofacitinib 5 mg p.o. twice daily + csDMARD	271		71.1[c]	39.4[d]	18.9[d]
csDMARD IR/ bDMARD IR/ JAKi IR							
Taylor et al, 2023 (ContRAst 3) [37]	Low	PLC + csDMARD	79	12	37.7	11.5	6.1
		Otilimab 90 mg s.c. once weekly + csDMARD	156		44.8	18.2	5.9
		Otilimab 150 mg s.c. once weekly + csDMARD	158		50.7	22.5[a]	10.8
		Sarilumab 200 mg s.c. once every 2 wk + csDMARD	156		57.5[b]	25.9[a]	13.3

ACPA, anticitrullinated peptide antibody; ACR20, American College of Rheumatology 20% improvement criteria [101]; bDMARD, biological disease-modifying antirheumatic drug; csDMARD, conventional-synthetic disease-modifying antirheumatic drug; IR, insufficient response; i.v., intravenous application; mTSS, van der Heijde modified total Sharp Score [102]; MTX, methotrexate; p.o., per os; PLC, placebo; pts, patients; RA, rheumatoid arthritis; REF, reference; RoB, risk of bias; s.c., subcutaneous application; SDAI, simplified disease activity index [103]; tsDMARD, targeted-synthetic disease-modifying antirheumatic drug.
Primary endpoint analyses:
[a] ≤0.05,
[b] ≤0.01,
[c] ≤0.001;
[d] *P* value not calculated, but ≤.05.

59.3% for ABA, and 51.9% for TCZ, vs 39.2% for csDMARDs, and this secondary endpoint was reached for CZP and ABA, but not for TCZ (P = .021, <.001, and .030, respectively; multiplicity-adjusted significance level α of 2.5%). These results should be interpreted in light of the trial's open-label design, the follow-up beyond typical T2T timepoints, and the fact that bDMARDs were not tapered while oral GC bridging therapy was discontinued at week 36. Numeric benefits were also observed with biological therapies for secondary endpoints, whereas radiographic progression was generally low in the study, and no between-group differences were detected (ΔmTSS at week 48: 0.47 [0.3-0.6] for CZP, 0.62 [0.5-0.8] for ABA, 0.50 [0.4-0.6] for TCZ, and 0.45 [0.3-0.6] for csDMARDs; all P = n.s.) [53].

In the 48-week, open-label STRAP and STRAP-EU trials (high RoB), 226 patients with IR to csDMARDs and no prior bDMARD exposure were stratified using synovial biopsy results at baseline (combined histological and molecular classification into B-cell-poor and B-cell-rich groups) and prior MTX exposure, and were randomly assigned to etanercept (ETA) 50 mg s.c. weekly, TCZ 162 mg s.c. weekly or rituximab (RTX) 1000 mg i.v. at weeks 0 and 2. No differences were observed in ACR20 response rates and key secondary outcomes for the combined ETA and TCZ arm vs RTX, neither in the B-cell-poor population (primary endpoint analysis) nor in the B-cell-rich subgroup (ACR20 at week 16 in B-cell-poor population 60% vs 59%, P = .97, and in B-cell-rich population 74% vs 68%, P = .37, for combined ETA and TCZ vs RTX, respectively) [13]. As for now, the presence or absence of B-cells by histology or transcriptomics is therefore not predictive of the response to B-cell targeting by anti-CD20 compared with ETA or TCZ [13,104].

In the 24-week, single-blind AMPLIFIED study (conference abstract), 338 patients with early RA with IR to MTX, ACPA titres >3× upper limit of normal and positive rheumatoid factor titres (dual seropositivity), as well as presence of the shared epitope human leukocyte antigen risk allele, were randomised to receive ABA 125 mg s.c. weekly or adalimumab (ADA) 40 mg s.c. once every 2 weeks. Efficacy outcomes were comparable between both compounds (ACR 50% improvement criteria [ACR50] at week 24: 59% for ABA vs 60% for ADA; P = n.s.) [54,55].

TLL-018, a JAK1 selective inhibitor, was superior to TOFA 5 mg twice daily in a Chinese phase 2 study (conference abstract) involving 101 patients with IR to MTX, bDMARDs (50%), and JAKi (30%). ACR50 response rates at week 12 were 48.0% for TLL-018 10 mg twice daily, 65.4% for TLL-018 20 mg twice daily, 72.0% for TLL-018 30 mg twice daily, vs 41.7% for TOFA 5 mg twice daily, but full study results are yet to be published, and further confirmation is needed from the ongoing phase 3 trial (NCT06020144) [56,57].

Strategic trials

Four therapeutic strategy trials were additionally included, of which 2 were assessed as high RoB, and 2 conference abstracts were not graded.

Therapeutic drug monitoring (TDM)-guided dose titration in ADA responders (stable doses for ≥28 weeks) was assessed in a 24-week, single-blind, noninferiority ADDORA-LOW trial (conference abstract). Sixty-two patients were randomly assigned to ADA dose titration to either 5 mg/L or 2 mg/L serum concentration. Mean-time weighted (MTW) DAS28-CRP rates at week 24 were comparable between both groups, while injections were expectedly less frequent in the 2 mg/L group [58,59]. ADDORA-SWITCH then assessed triple-blinded, TDM-guided switching to ETA or a non-TNFi b/tsDMARD after insufficient response to ADA 40 mg once every 2 weeks (conference abstract). ADA concentrations were measured before switching therapy. In the TDM-guided arm, patients with ADA concentrations <1.0 mg/L were switched to ETA (another TNFi), whereas all others were switched to a non-TNFi b/tsDMARD. In the random switching arm, patients could switch DMARD at their own and their physician's discretion. MTW DAS28-CRP levels were comparable in both groups after 24 weeks, indicating no added benefit of TDM-guided switching over random switching in this study [60].

Benefits of treatment intensification for initial nonresponders ('second hit') were tested in DMARD-naïve patients with early RA or undifferentiated arthritis in the 26-week, open-label, Amsterdam COBRA-T2T trial (high RoB). A total of 190 patients were stratified into a high-risk and low-risk group at baseline (disease activity score of 44 joints [DAS44] >3.7 and/or poor prognostic factors). The high-risk group (n = 150) received COBRA-light (MTX 10 mg weekly increased to 25 mg weekly and prednisolone 30 mg once daily, tapered to 7.5 mg once daily) for 13 weeks, and when treatment nonresponders (no EULAR good response; n = 31) were randomised into a COBRA-light continuation group or a COBRA-plus escalation group (MTX 25 mg weekly + prednisolone 60 mg once daily tapered to 7.5 mg once daily + SSZ 2 g once daily + HCQ 400 mg once daily), which were continued for another 13 weeks. The low-risk group (n = 40) started MTX monotherapy (10 mg once daily increased to 25 mg once daily), and nonresponders (n = 15) were randomised to MTX continuation or escalation to COBRA-light (MTX 10 mg once daily increased to 25 mg once daily and prednisolone 30 mg once daily, tapered to 7.5 mg once daily). A high number of patients responded well to the initial treatment strategies (EULAR good response or DAS44 <1.6 at week 13: 73% in the high-risk group, and 43% in the low-risk group). Treatment escalation to COBRA-plus (MTX 25 mg weekly + prednisolone 60 mg once daily tapered to 7.5 mg once daily + SSZ 2 g once daily + HCQ 400 mg once daily) for nonresponders in the high-risk group was superior to treatment continuation (EULAR good response or DAS44 <1.6 at week 26, for week 13 nonresponders: 12/15 with intensification, and 4/16 with continuation), albeit increasing also the number of (mostly mild) adverse events. No relevant differences were observed between the escalation and maintenance groups in the low-risk group (EULAR good response or DAS44 <1.6 at week 26, for week 13 nonresponders: 4/8 with intensification, and 3/7 with continuation) [51].

T2T strategies after failure of induction therapy with MTX 15 mg once daily and prednisone 30 mg tapered to 5 mg once daily (COBRA slim protocol) were assessed in 276 patients in the 104-week, open-label, CareRA2020 trial (high RoB). One hundred forty-two patients (51%) achieved DAS28-CRP <2.6 within 32 weeks with the initial MTX + GC (COBRA slim strategy). One hundred twenty-two patients with DAS28-CRP >3.2 through weeks 8 to 32, or DAS28-CRP ≥2.6 at week 32, were randomly assigned to a bio-induction strategy (MTX 15 mg weekly + prednisone 5 mg once daily + ETA 50 mg s.c. weekly for 24 weeks; n = 55) or a csDMARD combination strategy (MTX 15 mg weekly + prednisone 5 mg once daily + leflunomide 10 mg once daily; n = 55). After that, treatment was given at the physician's discretion. The primary endpoint was the area under the DAS28-CRP curve at week 104, which was comparable between groups. At week 28 after randomisation, however, DAS28-CRP <2.6 rates were higher in the bio-induction group (59% for bio-induction vs 44% for csDMARD combination), and overall b/tsDMARD use through week 104 was lower in patients who received the biologic earlier (35% for bio-induction vs 53% for COBRA avant-garde) [52].

All head-to-head trials and strategic trials are summarised in the Supplementary Appendix (Sections S2.1.4, S2.3.4, and S3.1.4).

Biosimilars

Eleven studies assessed the efficacy of biosimilars, of which 9 were available as full publications, and 2 as conference abstracts. Six studies were graded as low RoB, 1 as moderate, and 2 as high RoB. Again, conference abstracts were not assessed for RoB. Summaries are provided in the Supplementary Appendix (Sections S5.1 and S5.2). All trials met their primary endpoint. Seven studies assessed TNFi biosimilars [73–79], 3 studies assessed novel TCZ biosimilars [81–83], and 1 study assessed an RTX biosimilar [80]. No studies on generic versions of JAK inhibitors were identified.

Efficacy of GCs

ABBV-3373, an antibody-conjugate of a TNFi and a GC receptor modulator (GCRM), was tested against reference ADA 80 mg once every 2 weeks in a 24-week, double-blind, phase 2 trial in 48 MTX IR patients, as well as against 242 patients from historical ADA cohorts of prior studies (high RoB). The compound was superior to historical ADA, but not to in-trial ADA (ΔDAS28-CRP −2.65 for ABBV-3373, −2.13 for historical ADA, and −2.51 for in-trial ADA) [62]. The GCRM AZD9567 was noninferior to prednisone 20 mg once daily in a 2-week, multicentre, phase 2 study of 21 csDMARD IR patients from the Netherlands and Sweden (moderate RoB) [63], suggesting that a nonsteroidal drug that modulates the GC receptor may have similar efficacy as GCs.

The 52-week, double-blind CORRA study (moderate RoB) assessed the impact of 2 GC bridging strategies on radiographic progression in 395 MTX-naïve patients with early RA (disease duration <3 years). Patients pretreated with MTX 15 mg weekly therapy or other csDMARDs in the 4 weeks leading up to baseline were treated with prednisolone 60 mg once daily, prednisolone 10 mg once daily or PLC. GCs were tapered and withdrawn within 12 weeks, and subsequent treatment was chosen at the physicians' discretion. The primary endpoint was the ΔmTSS at week 52. Composite scores and disease core sets significantly improved in both GC arms through week 12 (end of GC bridging phase; CDAI <2.8: 23.4% for prednisolone 60 mg once daily, 26.3% for prednisone 10 mg once daily, and 11.3% for PLC; $P <$ .001 for both), but no significant benefits were observed after 1 year with regard to radiographic progression as well as clinical endpoints when compared with MTX + PLC (ΔmTSS at week 52: 1.0 [SD 2.0] for prednisone 60 mg once daily, 1.1 [SD 2.2] for prednisone 10 mg once daily, and 1.1 [SD 1.5] for PLC; CDAI <2.8 at week 52: 23.4% for prednisolone 60 mg once daily,

25.0% for prednisone 10 mg once daily, and 16.4% for PLC; P = n.s. for both comparisons). Of note, no difference was observed between the high-dose (60 mg once daily) and low-dose (10 mg once daily) arms in the induction period and at the 1-year timepoint, suggesting a sufficient control of early disease activity also with the lower initial steroid dosing in most patients [61].

Studies of DMARD tapering and/or withdrawal

Eleven studies were considered on DMARD tapering, of which 2 were graded as low RoB, 1 as moderate RoB, and 8 as high RoB, mostly due to their open-label trial designs.

Tapering and/or withdrawal of GCs

Blinded withdrawal of low-dose prednisone (5 mg once daily to 0) or PLC was assessed in a 12-week extension of the 2-year double-blind GLORIA trial (n = 158; high RoB) [105]. Changes in DAS28-ESR were marginal in both groups, and disease activity was comparable at week 12 (DAS28-ESR: 2.9 in the prednisone withdrawal group, Δ0.2 [SD 1.0] from baseline, vs 3.1 in the PLC withdrawal group, Δ0.0 [SD 0.8] from baseline) [71].

The 52-week, double-blind STAR trial (moderate RoB) investigated a hydrocortisone replacement strategy, comparing it to standard prednisone tapering. One hundred 2 patients in LDA (DAS28-ESR ≤3.2 for at least 3 months) with stable low-dose GC (5 mg once daily) were randomly assigned to hydrocortisone taper (20 mg once daily for 3 months, reduced to 10 mg once daily for 3 months, followed by withdrawal) or standard prednisone taper (dose reduction by 1 mg/d every month until discontinuation). Fifty-five per cent and 47% of the patients could successfully withdraw GCs within 12 months in the hydrocortisone and prednisone tapering groups, respectively, with no relevant between-group difference (P = .4) [72].

Tapering and/or withdrawal of csDMARDs

Dose titration of background MTX combined with ADA was tested in the 48-week, open-label, multicentre, MIRACLE study (high RoB). A total of 291 MTX-naïve patients from Japan, South Korea, and Taiwan were treated with MTX monotherapy for 24 weeks, which was uptitrated to the maximum tolerated dose within 12 weeks (effectively 10-15 mg weekly). Patients not in SDAI REM by week 24 (n = 134) were then randomly assigned to ADA 40 mg once every 2 weeks with continuation of MTX at maximum tolerated dose (mean 13.2 mg weekly), or to ADA + MTX reduction to half dose (mean 7.6 mg weekly) at week 36. SDAI REM rates at week 48 were 38% and 44% for maximum and reduced dose MTX, respectively, indicating that MTX dose reduction was noninferior to full-dose continuation after adding ADA in MTX IR patients (Δ6.4%, 95% CI: −7.0% to 19.8%) [64].

ARCTIC REWIND was a 3-year, open-label, multicentre, tapering or withdrawal study from Norway (high RoB). Patients with stable controlled disease activity (defined as DAS44 <1.6 and no swollen joints) for at least 1 year on stable csDMARD mono- or combination therapy were randomised to csDMARD continuation for 36 months (n = 80), csDMARD reduction to half dose for 36 months (n = 42) or csDMARD reduction to half dose for 12 months followed by complete csDMARD withdrawal (n = 38). Flare-free survival was reached by 80%, 57%, and 38% of patients in the stable dose, half dose, and half dose to withdrawal groups, respectively (adjusted hazard ratio, for flare: half dose vs stable dose: 2.9, 95% CI: 1.5-5.9; half dose to withdrawal vs stable dose: 4.2; 95% CI: 2.2-8.2), indicating a significantly higher risk of flares after csDMARD dose reduction and/or withdrawal, but also the possibility to sustain REM despite complete treatment withdrawal in about one-third of all patients at least for the duration of the study [14].

Tapering and/or withdrawal of bDMARDs

The 72-week, assessor-blinded, phase 4 ESCoRT trial (high RoB) compared 2 DMARD tapering strategies in a 72-week trial in csDMARD IR patients from China. One hundred seventeen patients were included to receive maintenance therapy after response to a 12-week induction therapy with a TNFi (ETA biosimilar 50 mg weekly) and MTX (10-20 mg weekly). Sixty-seven (57%) reached LDA or REM (DAS28-CRP ≤3.2) within 12 weeks and were randomised to the following 3 treatment arms: (1) continuation of ETA 50 mg s.c. weekly + MTX for 60 weeks (n = 21), (2) csDMARD triple therapy (add-on of SSZ 2 g once daily + HCQ 400 mg once daily) for 12 weeks, followed by ETA withdrawal and maintenance of csDMARD triple therapy for 48 weeks (n = 24), and (3) withdrawal of ETA at week 12 and maintenance of MTX monotherapy for 48 weeks (n = 22). Relapse rates at week 60 were 85% in the ETA withdrawal (MTX monotherapy) group, 35% in the TNFi + MTX maintenance group, and 46% in the csDMARD triple therapy group (P = .004 for MTX vs TNFi + MTX, and P = .019 for MTX vs csDMARD TRIPLE). CsDMARD triple therapy was more cost-effective than ETA + MTX maintenance, while comparably effective for relapse prevention in this study [65].

In the open-label ARCTIC REWIND TNFi study (high RoB), patients with stable controlled disease activity on TNFi (DAS44 <1.6 and no swollen joints) for at least 1 year were randomised to stable TNFi continuation (n = 47) or TNFi dose reduction to half for 4 months, followed by complete TNFi withdrawal (n = 52). Flare rates (defined as DAS >1.6, DAS increase of ≥0.6 and SJC ≥2) at month 12 were significantly higher in the TNFi withdrawal group than in the continuation group (63% vs 5%, respectively; Δ58%, 95% CI: 42%-74%; P < .001), although DAS44 <1.6 could be regained in a majority of flare patients after restarting DMARD therapy (DAS44 REM rates at month 12: 88% for continuation vs 85% for tapering) [66].

Progressive, disease-activity-driven spacing of ABA and TCZ injections was evaluated in ToLEDo, a 2-year, open-label, noninferiority trial from France and Monaco (high RoB). Patients in stable REM (DAS28-ESR ≤2.6 for at least 6 months), and with no structural progression for at least 1 year on ABA or TCZ, were randomised to treatment continuation (n = 115) or interval spacing (n = 114). In the spacing group, injection intervals were prolonged every 3 months when DAS28 <1.6 was maintained at the respective follow-up visit, until discontinuation of DMARDs, or spacing was reversed to the previous step in case of a flare (defined as DAS28-ESR >3.2). Seventy of 111 patients (63%) could taper or even withdraw their bDMARD throughout the trial, but flare rates and structural progression were ultimately higher in the spacing group than in the maintenance group (flare rates 67% for spacing and 24% for maintenance, Δ43%, 95% CI: 30%-55%; and ΔmTSS 5.0 for spacing vs 2.5 for maintenance, Δ2.5, 95% CI: −0.3 to 5.3), and noninferiority could not be demonstrated. The use of DAS28 for the definition of REM can be considered as suboptimal for this study due to the impact of IL6Ri on acute-phase reactants [67].

The 48-week de-escalation period of the AVERT-2 trial (low RoB) investigated blinded ABA or MTX tapering and withdrawal. Patients considered as responders in the induction period receiving ABA + MTX were re-randomised to treatment continuation (n = 50), ABA spacing and withdrawal while continuing MTX (n = 50), or MTX withdrawal while continuing

ABA monotherapy (n = 47). SDAI REM could be sustained in 74%, 48%, and 57% of patients, and radiographic progression was low in the majority of patients in all 3 arms (exploratory endpoints) [38].

Tapering and/or withdrawal of tsDMARDs

Tapering of TOFA was investigated in a 24-week, open-label study from Shanghai (high RoB), where 122 TOFA 5 mg twice daily responders (DAS28-ESR LDA or REM for at least 3 months) were randomised to TOFA continuation, TOFA tapering to 5 mg once daily, and complete TOFA withdrawal. Maintenance of DAS28 LDA or REM was higher in the continuation group (95.1%) than in the reduction or withdrawal groups (64.3% and 20.5%, respectively) [68]. Another 104-week, open-label study from Japan (high RoB) investigated 48 patients in more stringent REM on TOFA + MTX (CDAI ≤2.8 for at least 12 months), who were randomised to rapid TOFA withdrawal (MTX monotherapy) or MTX withdrawal (TOFA monotherapy). CDAI REM was sustained in 29% in the TOFA withdrawal group and 50% in the MTX withdrawal group [69]. Blinded BARI dose reduction to 2 mg once daily was tested in the RA-BEYOND long-term extension (LTE) study (low RoB). BARI responders (CDAI LDA/REM, CDAI ≤10, for at least 3 months) were randomised to treatment continuation or dose reduction to half (n = 498 in each group). CDAI LDA rates at week 96 were 60% for tapering, and 70% for continuation, and rescue to full-dose BARI could recapture disease control (CDAI ≤10) in most patients with a flare (CDAI >10). Of note, adverse events, especially serious infections, were lower in the tapering group [70].

Tables 3 and 4 [106] summarises all studies on DMARD tapering and/or withdrawal. Further details are again provided in the Supplementary Appendix (Sections S2.1.6, S2.2.6, S2.3.6, and S3.1.6).

RA-associated interstitial lung disease

Two RCTs assessed the efficacy of antifibrotic therapies in patients with RA ILD (both low RoB). The 52-week, double-blind, phase 3 INBUILD trial investigated nintedanib, a tyrosine kinase inhibitor involved in fibrosis and angiogenesis, in 663 patients with progressive fibrosing ILD (fibrosis on high-resolution computed tomography [hrCT] of >10%; forced vital capacity [FVC] ≥45%; diffusion capacity of the lung for carbon monoxide [DLCO] 30%-80%) [107]. Among them, 13.4% (n = 89) had RA ILD. In this subgroup, nintedanib 150 mg twice daily added to standard of care (SOC) therapy significantly slowed decline in FVC through week 52 compared with PLC added to SOC (−83 mL/y vs −199 mL/y; Δ117 mL/y; 95% CI: 7-226; P = .037), although discontinuation due to adverse events (primarily diarrhoea) was more frequently reported in the intervention group [85,86].

Pirfenidone, another antifibrotic and anti-inflammatory agent, was assessed in the 52-week, double-blind, phase 2 TRIAL1 study in 123 patients with RA ILD (>10% parenchyma involvement on hrCT or positive lung biopsy, FVC ≥40%, DLCO ≥30%, <10% relative change in prebronchodilator FVC). Although the primary endpoint (ΔFVC ≥10% or death at week 52) was not met in this study, pirfenidone 2403 mg once daily significantly reduced the decline in FVC compared with PLC (−66 mL/y vs −146 mL/y; nominal P = .0082) [87].

Study characteristics and study results are listed in the Supplementary Appendix (Section S6). No RCTs evaluating the efficacy of other currently available DMARDs for the treatment of RA ILD were identified.

Trials on DMARDs in individuals at risk of developing RA

A total of 7 trials were included, of which 6 were available as full publications [89−94], and 1 as an abstract [88]. One study assessed DMARDs in autoantibody-positive individuals without clinical symptoms [88], 3 in autoantibody-positive individuals with arthralgia [89,90,94], 3 in an autoantibody-positive population with arthralgia and subclinical arthritis on imaging [91−93], and 1 study also included autoantibody-negative individuals with arthralgia and subclinical arthritis on imaging [91]. Six studies were graded as having low RoB [89−94], while 1 study reported as a conference abstract was not assessed for RoB [88].

Table 3
Studies on tapering and/or withdrawal of glucocorticoids and csDMARDs

Study	RoB	Primary endpoint	Week	Treatment arm	No. pts	EP	Between-group comparison
Tapering and/or withdrawal of glucocorticoids							
Almayali et al, 2023 (GLORIA) [71]	High	ΔDAS28-ESR	12	Glucocorticoid 5 mg once daily -> tapering and withdrawal	79	0.2 (0.1)	P = .12 (NI met)
				PLC -> tapering and withdrawal	79	0.0 (1.2)	RR for flare: 1.37, 95% CI: 0.95-1.98
Ruyssen-Witrand et al, 2025 (STAR) [72]	Moderate	Successful glucocorticoid discontinuation	52	Hydrocortisone 20 mg once daily for 3 mo to 10 mg once daily for 3 mo to withdrawal	53	55%	P = .4 (NI met)
				Prednisone taper of 1 mg/d every mo until discontinuation	49	47%	
Tapering and/or withdrawal of csDMARDs							
Tamai et al, 2023 (MIRACLE) [64]	High	SDAI remission (SDAI ≤3.3) at week 48	48	ADA 40 mg once every 2 wk + MTX maximum tolerated dose (13.2 mg once weekly)	68	38%	Δ6.4%, 95% CI: −7.0%-19.8% (NI met)
				ADA 40 mg once every 2 wk + MTX half dose (7.6 mg once weekly)	66	44%	
Kjørholt et al, 2024 (ARCTIC REWIND) [14]	High	Flare-free survival through month 36 (flare: DAS44 >1.6 and ΔDAS44 ≥0.6 and SJC44 ≥2)	156	Stable-dose csDMARD for 36 mo	80	80%	Risk of flare:
				Half-dose csDMARD for 36 mo	42	57%	aHR 2.9, 95% CI: 1.5-5.9, for half dose vs stable-dose csDMARD
				Half-dose csDMARD for 12 mo, followed by csDMARD withdrawal for 24 mo	38	38%	aHR 4.2, 95% CI: 2.2-8.2, for half dose to withdrawal vs stable dose (NI not met)

ADA, adalimumab; aHR, adjusted hazard ratio; CI, confidence interval; csDMARD, conventional-synthetic disease-modifying antirheumatic drug; DAS28-ESR, disease activity score using 28 joints and erythrocyte sedimentation rate; DAS44, disease activity score using 44 joints; EP, endpoint; MTX, methotrexate; NI noninferiority; PLC, placebo; RA rheumatoid arthritis; RCT randomised controlled trial; RoB risk of bias; SDAI, simplified disease activity index [103]; SJC44, swollen joint count out of 44 joints.

Table 4
Studies on tapering and/or withdrawal of bDMARDs and tsDMARDs

Tapering and/or withdrawal of bDMARDs							
Zhao et al, 2022 (ESCoRT) [65]	High	Relapse rate (DAS28-CRP > 3.2 with an increase of ≥0.6)	60	TNFi + MTX maintenance for 60 wk	20	35%	csDMARD triple therapy and TNFi + MTX comparable (P = .491; NI met), and superior to MTX monotherapy (P = .019 & P = .004)
				TNFi + MTX + HCQ + SSZ for 12 wk; followed by TNFi discontinuation and csDMARD triple for 48 wk	22	46%	
				TNFi + MTX for 12 wk; followed by TNFi discontinuation and MTX monotherapy for 48 wk	20	85%	
Lillegraven et al, 2023 (ARCTIC REWIND TNFi) [66]	High	Flare-free survival through month 12 (flare: DAS44 >1.6 & ΔDAS44 ≥0.6 & SJC44 ≥2)	52	Stable TNFi for 12 mo (± csDMARD)	47	63%	Δ58%, 95% CI: 42%-74%; P < .001 (NI not met)
				TNFi tapering to half for 4 mo, followed by complete TNFi withdrawal for 8 mo (± csDMARD)	52	5%	
Kedra et al, 2024 (ToLEDo) [67]	High	ΔDAS44 (slope difference) (flare rates; DAS28-ESR >3.2)	104	Abatacept/tocilizumab maintenance (± csDMARD)	115	24%	Slope difference 0.10, 95% CI: −0.10 to 0.31 (NI not met; margin 0.25) Risk of flare: Δ43%, 95% CI: 30%-55% Structural progression: Δ14%, 95% CI: −6.7% to 34%
				Disease activity guided abatacept/tocilizumab interval spacing to withdrawal (± csDMARD)	113	67%	
Emery et al, 2023 (AVERT-2) [38]	Low	Sustained SDAI remission (SDAI ≤3.3)	48	Abatacept once weekly + MTX continuation for 48 wk	50	74%	Exploratory endpoints (no significance testing)
				Abatacept spacing to once every 2 wk + MTX for 24 wk; followed by PLC + MTX for 24 wk	50	48%	
				Abatacept once weekly monotherapy for 48 wk	47	57%	
Tapering and/or withdrawal of tsDMARDs							
Wang et al, 2023 [68]	High	Sustained DAS28-ESR low disease activity/remission	24	Tofacitinib 5 mg twice daily continuation	41	95%	
				Tofacitinib 5 mg once daily tapering	42	64%	
				Tofacitinib withdrawal	39	21%	
Kubo et al, 2023 (XANADU) [69]	High	Sustained CDAI remission	52	Tofacitinib discontinuation (MTX continuation)	24	29%	
				MTX discontinuation (TOFA continuation)	24	50%	
Edwards et al, 2025 (RA-BEYOND LTE) [70]	Low	Maintenance of CDAI low disease activity/remission; time to relapse (CDAI > 10)	96	Baricitinib 4 mg once daily + csDMARD	498	70%	
				Baricitinib 2 mg once daily + csDMARD	498	60%	

bDMARD, biological disease-modifying antirheumatic drug; CDAI, Clinical Disease Activity Index [106]; csDMARD, conventional-synthetic disease-modifying antirheumatic drug; DAS28-CRP, disease activity score using 28 joints and C-reactive protein; DAS28-ESR, disease activity score using 28 joints and erythrocyte sedimentation rate; DAS44, disease activity score using 44 joints; HCQ, hydroxychloroquine; IR, incidence rate; LTE, long-term extension; MTX, methotrexate; NI, noninferiority; PLC, placebo; RA, rheumatoid arthritis; RCT, randomised controlled trial; RoB, risk of bias; SDAI, Simplified Disease Activity Index [103]; SJC44, swollen joint count out of 44 joints; SSZ, sulfasalazine; TNFi, tumour necrosis factor inhibitor; tsDMARD, targeted-synthetic disease-modifying antirheumatic drug.

Regarding progression towards clinical arthritis, 5 studies failed to demonstrate relevant benefits. No impact was observed with steroid injections [89], HCQ [88], and statins [90]. A single infusion of RTX delayed arthritis onset by approximately 12 months, with a subsequent catch-up effect [92], and a 12-month course of MTX in patients with subclinical arthritis on magnetic resonance imaging (MRI) did not prevent RA onset after 3 years, albeit improving subclinical inflammation and patient-reported outcomes during the active treatment period [91].

Significant delays in arthritis onset were observed with ABA in 2 studies on autoantibody-positive individuals with arthralgia (the APIPPRA study) [94], as well as subclinical arthritis on MRI (the ARIAA study) [93]. Also in these trials, though, a catch-up effect was noted after stopping ABA treatment, and extension studies of both trials presented at EULAR 2025 showed no difference between groups after 4 to 5 years.[108,109] Figure 2 provides an overview of RCTs conducted in the RA at-risk population. A detailed summary as well as baseline and outcome data are provided in the Supplementary Appendix (Section S7).

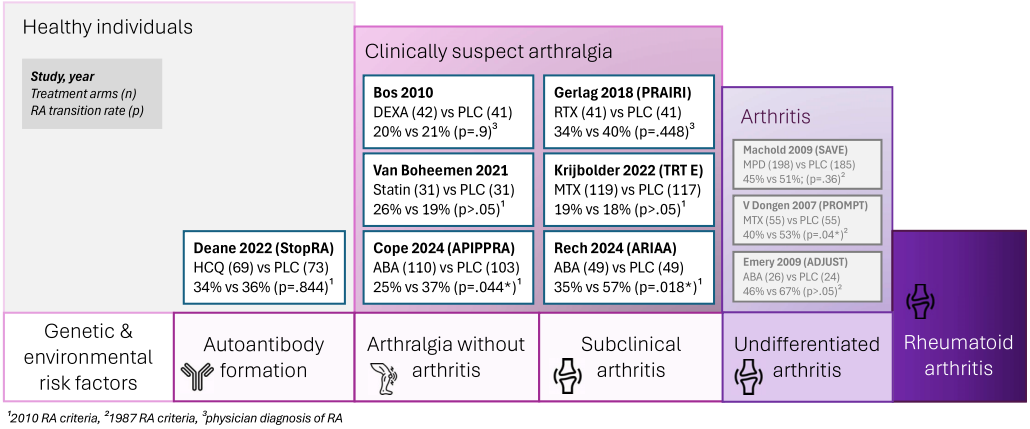

Figure 2. Randomised controlled trials investigating RA prevention in at-risk individuals. ABA, abatacept; DEXA, dexamethasone; HCQ, hydroxychloroquine; MPD, methylprednisolone; MTX, methotrexate; n, number of patients; p, P value; PLC, placebo; RA, rheumatoid arthritis; RTX, rituximab.

Random-effects meta-analyses of progression rates to RA are also shown in the Supplementary Appendix (Section S7.4, Supplementary Figs S5 and S6), which further display the catch-up effect after treatment withdrawal in the LTE trials of those studies that initially met their primary endpoint (the APIPRA and ARIAA trials) [108,109].

DISCUSSION

This SLR was conducted to inform an international expert task force formulating the 2025 update of the EULAR recommendations for the management of RA with DMARDs and GCs.

Compared with previous SLRs, fewer novel compounds were investigated, while strategic trials became increasingly relevant. Included studies were mostly heterogeneous with respect to trial designs, populations, or interventions, which allowed quantitative synthesis only for selected PICOs. In addition, a substantial proportion of studies were graded with moderate or high concerns on RoB and/or enrolled relatively small patient samples. These limitations were considered by the task force and substantially reduced the weight of such studies on the formulation of the updated recommendations.

MTX remains the anchor drug for treatment initiation in RA. The positive benefit-risk balance of the first-line strategy of MTX plus short-term GC bridging was confirmed in various studies, with a substantial proportion of patients responding well to this initial therapy. Whereas earlier EULAR algorithms had differentiated nonresponders based on the presence or absence of poor prognostic factors, recent data (such as from the CareRA trials) support that nonresponse to initial MTX or other csDMARDs is in itself an indicator of an unfavourable prognosis. These findings, along with the increasing availability of cost-effective biosimilars, support the timely step-up to a bDMARD or a tsDMARD (considering established risk factors) in such patients, with stepping up to a csDMARD combination therapy remaining a valid alternative in selected patients.

Regarding bDMARDs and tsDMARDs, several novel compounds were investigated in phase 2 trials but have to be further evaluated in larger phase 3 programmes before they can be used in the clinic. Positive phase 3 data were available for a TNFi nanobody and 2 JAKi, the pan-JAK inhibitor PEFI, as well as IVAR, a selective inhibitor of JAK1, while a GM-CSF inhibitor was effective but failed to demonstrate superiority over established therapies. ABA did not meet its primary endpoint in the phase 3 AVERT-2 study in early RA compared with MTX and showed no superiority over ADA in a head-to-head comparison in dual seropositive patients, revealing that there was no lasting benefit of ABA over other bDMARDs in this population. Findings on GCs from the 2022 SLR were also confirmed, with the 2022 CORRA study reinforcing the fact that high-dose GCs do not provide meaningful benefits to justify their side effects compared with moderate- or low-dose GCs, which still play a relevant role as bridging therapies in the initial treatment algorithm.

Clinically relevant novel conclusions can be drawn from the tapering and withdrawal trials. Although several studies showed that tapering and even sustained withdrawal of DMARDs are feasible in a subset of patients, flare rates were such that DMARD discontinuation cannot be broadly recommended, while careful dose reduction or interval spacing remains an acceptable strategy in selected patients with deep and sustained REM and/or higher risks of DMARD-associated adverse events.

In RA ILD, promising results were seen with 2 antifibrotic agents, whereas the lack of lung-related data from RCTs on currently used bDMARDs or tsDMARDs still constitutes an important research gap. It also remains uncertain how changes in pulmonary function tests or lung imaging commonly seen in patients with RA, as well as their improvement with novel drugs, impact patient outcomes and long-term disease prognosis. Care is needed to avoid overdiagnosis and treatment of asymptomatic individuals.

In this context, the potential of DMARDs to prevent RA in at-risk individuals is attractive, given the lifelong burden of the disease. Yet, most trials failed to demonstrate preventive benefits; there were a few studies that appeared to delay the onset of clinically manifest RA according to classification criteria, but a catch-up effect was observed in the control groups after treatment discontinuation. This impairs inference from survival analyses in all trials (violation of the proportional hazard assumption) and poses the fundamental problem of potentially not really preventing RA, but rather showing a therapeutic effect in very early or subclinical RA, hence attenuating signs and symptoms and consequently delaying the evolution to classifiable RA. Currently, early diagnosis, fast referral, and effective treatment of clinically manifest RA remain the most effective and safest option for our patients.

In summary, this SLR, along with the SLR on safety, provides evidence to further refine the EULAR recommendations for the management of RA with DMARDs, but also strongly supports the key principles and foundational concepts on which these recommendations are built.

Competing interests

JSS and CJE report that financial support, administrative support, article publishing charges, and travel were provided by the European Alliance of Associations for Rheumatology. VK received speaker's or consultancy fees from Eli Lilly, AbbVie, and AstraZeneca. FL received speaker fees from Alfasigma. JSS received honoraria for consultancies and/or speaking engagements from Abbott, AbbVie, Anaptys, Ananda, AstraZeneca, Celltrion, Chugai, Immunovant, Lilly, R-Pharma, Samsung, Sandoz, Shattuck Labs, and UCB. CJE received honoraria, advisory boards, speaker's bureau, research support from AbbVie, Alphasigma, AstraZeneca, BMS, Biogen, Boehringer Ingelheim, Celgene, Celltrion, Fresenius, Gilead, GSK, Janssen, Lilly, Pfizer, MSD, Novartis, Roche, Samsung, Sanofi, and UCB. DA received honoraria from Advanz, Janssen/Johnsen & Johnsen, Sanofi, Mitsubishi Tanabe, UCB, and AstraZeneca, and grants to his institution from Lilly and Johnson & Johnson. DvdH received consulting fees from AbbVie, Alfasigma, ArgenX, BMS, Eli Lilly, Grey-Wolf Therapeutics, Janssen, Novartis, Pfizer, Takeda, and UCB Pharma, and is associate editor of *Annals of the Rheumatic Diseases*, editorial board member of the *Journal of Rheumatology*, and director of Imaging Rheumatology. KLW received honoraria for consulting from AbbVie, AstraZeneca, BMS, Eli Lilly, Galapagos, Gilead, GlaxoSmithKline (GSK), Moderna, Novartis, Roche, Sanofi, Union Chimique Belge (UCB), Zurabio, Takeda, Ouros, and Otsuka. TT received speaker's or consultancy fees from AbbVie GK, Chugai, Eli Lilly Japan, Eisai, Gilead Sciences Inc, Pfizer Japan Inc, Mitsubishi Tanabe, and Taisho Pharma. RC received consultancy and speaker fees from AbbVie, Alfasigma, AstraZeneca, GSK, Eli Lilly, Galapagos, Janssen, Novartis, Pfizer, and UCB. PV received research grants from Alfasigma and Pfizer, speaker or consultancy fees from Alfasigma, AbbVie, Galapagos, Eli Lilly, Cytrill, and Boehringer Ingelheim, and support for attending meetings from Fresenius Kabi and AbbVie. JEP received research grants from BMS, Mallinckrodt/Therakos, and Pfizer (Seattle Genetics), consultancy fees from AbbVie, Amgen,

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Contributors

All authors contributed and finally approved the current manuscript. VK is the guarantor of the study. The guarantor accepts full responsibility for the finished work and the conduct of the study, had access to the data, and controlled the decision to publish the manuscript together with the methodologists (AK and RL) and the convenors of the taskforce (JSS and CE).

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Patient consent for publication

Due to the nature of the analyses, this is not applicable for the current work. All patients gave informed consent to participation in the studies included and publication of study results. One Patient Research Partner (SdS) participated in the steering group, and 2 patients contributed to the task force that developed the guidelines. Patients and/or the public were otherwise not involved in the design, conduct, reporting, or dissemination plans of this research. Details are provided in the methods section.

Ethics approval

Due to the nature of the analyses performed here, this is not applicable to the current project. All studies included in this work were approved by the respective ethics committees.

Provenance and peer review

Not commissioned; externally peer reviewed.

Data availability statement

Not applicable, as no datasets were generated for this study. All data relevant to the study are available in public and are included in the article or uploaded as online supplemental information.

Declaration of generative AI and AI-assisted technologies in the writing process

During the preparation of this work, the authors used DeepL (DeepL SE) and ChatGPT (OpenAI) for spelling, grammar, and text-fluency editing before finalising the manuscript. After using these tools, the authors reviewed and edited the content as needed and take full responsibility for the content of the published article. Research and data synthesis were performed without the use of artificial intelligence tools, and the interpretations and opinions presented are solely those of the authors.

Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.ard.2026.03.020.

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