Novel insights into the management of rheumatoid arthritis: one year in review 2024

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ABSTRACT

New evidence from 2023 has slightly shifted some perspectives on rheumatoid arthritis (RA) management. Glucocorticoids have reaffirmed their role as bridging therapy, while novel studies on JAK inhibitors have examined efficacy, mechanism of action, and their potential in high-risk populations, bolstering our understanding with real-world data. Additionally, among treatment strategies, achieving low disease activity has emerged as comparable to achieving remission in the long term, and new insights have been gained regarding tapering both biological and conventional synthetic DMARDs. Furthermore, novel approaches have been proposed for managing difficult-to-treat RA and pre-RA. In this paper, the reviewers aim to present the most relevant studies published during the last year in the field of RA management.

Introduction

The treatment of rheumatoid arthritis (RA) remains a central topic of interest for rheumatologists. The development of recommendations and guidelines helps clinicians in the day-to-day management of patients to provide quality and appropriate care. However, there are still many areas of interest where there is not enough evidence to guide clinical decisions. For this reason, starting from the previous year *One Year in Reviews*, we updated the search in order to find new evidence able to answer to the open research questions raised by the European Alliance of Associations for Rheumatology (EULAR) recommendations (1, 2).

Therefore, we searched for novel insights on the role of glucocorticoids (GC); on the mechanism of action risks and use of Janus Kinase inhibitors (JAKi); on emergent indications in treatment strategy; on the management of difficult to treat RA and finally on the definition of pre-RA. To make it easier for readers, we have summarised the research agenda from the EULAR recommendations in Table I.

Glucocorticoids

Besides being one of the oldest available drugs for RA, GC are still far from being out-fashioned due to their ability to provide rapid symptomatic relief and have a long-lasting impact on radiographic progression. The debate on the best strategy of GC administration in RA is still vivid, since robust evidence has demonstrated a detrimental effect on cardiovascular and infectious risk and an overall increased mortality in patients receiving these drugs.

The latest update of the EULAR recommendations has taken the increasing concerns about the safety of GC into consideration. In fact, while the use of GC for bridging therapy in new-onset RA is still supported, the taskforce underlined that treatment should be at short-term, aiming at a rapid tapering and discontinuation (3).

To support this recommendation, a dedicated systematic literature review (SLR) on the efficacy, safety, and duration of GC treatment on background disease modifying anti-rheumatic drugs (DMARDs) was performed. The evidence retrieved made it possible to confirm the efficacy of GC as initial bridging therapy and the feasibility of GC withdrawal within 2 years. Interestingly, there were no studies evaluating GC courses shorter than 6 months. The results on the safety outcomes were conflicting, and this is in line with the difficulty to fully correct for confounding by indication in observational stud-

Table I. Research Agenda of the EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying anti-rheumatic drugs: 2022 update (adapted from Smolen *et al*. (3)).

	Research Agenda
1.	Glucocorticoids
-	Is the risk of glucocorticoids (GCs) different if a specific cumulative dose has been used within a relatively short period of time, such as up to 3 or 6 months, or chronically over a number of years?
-	What are the barriers and facilitators of GC cessation after induction therapy and how can a strategy for tapering and discontinuing be best implemented?
-	Does the concomitant use of GCs at very low doses (1–3 mg prednisone equivalent) increase therapeutic success without producing unacceptable side effects?
-	Can the chronic use of GCs be prevented by rapid (*i.e*. within 3–6 months) switching of disease-modifying anti-rheumatic drug (DMARDs) in patients who have active disease despite DMARDs of whatever kind?
-	How frequent is the chronic use of GCs among patients with rheumatoid arthritis (RA) followed in resource poor countries and how could such chronic use be mitigated or prevented?
-	What are the effectiveness and safety profiles of (repeated) intramuscular glucocorticoids, for example, methylprednisolone 120 mg or triamcinolone 80 mg 1–4 times yearly?
-	Are safety issues with chronic GC use related to pre-existing comorbidities and do patients with such comorbidities preferentially receive GCs rather than advancing to biological/ targeted synthetic (b/ts) DMARD therapies?
2.	Janus kinase (JAK)-inhibitors and bDMARDs
-	To which extent do in vitro selectivity and in vivo selectivity differ among JAK inhibitors (JAKi)?
-	Are the cardiovascular and malignancy risks of JAKi as seen in the ORAL-Surveillance study, different with JAK-1 or JAK- 1/2-selective agents than with pan-JAKi?
-	Which mechanisms lead to the cardiovascular events and the increase in malignancies seen with tofacitinib?
-	Which mechanisms lead to the increased risk of thromboembolic events with JAKi?
-	Is monotherapy of JAKi or combination of JAKi plus methotrexate (MTX) more efficacious than MTX+GC? Ideally, an active control arm using a TNF-inhibitor (TNFi) or tocilizumab (plus MTX) should be included in such a trial
-	How safe and efficacious is the use of a JAKi after another JAKi has failed?
-	How safe and efficacious is the combination of a JAKi with a bDMARD, such as a TNFi, in patients who have failed to respond to multiple drugs?
-	How safe and efficacious is the use of an IL-6 pathway inhibitor if a JAKi has failed?
-	How safe and efficacious are abatacept, tocilizumab and rituximab after any of the other non-TNFi bDMARDs or a tsDMARD has failed?
3.	Treatment strategy and risk stratification for DMARD use
-	Can we identify new biomarkers to stratify patients and to predict therapeutic response or lack of response?
-	Is tapering of bDMARD monotherapy possible?
-	Will randomised controlled trials on tapering of bDMARDs and tsDMARDs, designed to following predefined predictors for maintenance of good outcomes after their withdrawal, show success?
-	How good is patient adherence to a bDMARD or tsDMARD and can non-adherence explain secondary loss of efficacy?
-	How long should the duration of persistent remission be before conventional synthetic (cs)DMARDs can be tapered?
-	Can taxonomy of RA be improved to guide therapeutic decisions?
-	Can the identification of disease phenotypes inform tailored therapeutic use?
-	Will therapeutic drug monitoring improve disease course and outcome and support decisions about switching within or between drugs?
-	Is leflunomide equivalent to MTX as first line csDMARD therapy?
-	Is there true secondary loss of efficacy or is this due to non- adherence? And if the former, what is the reason for this loss of efficacy?
-	What is the optimal treatment target: remission or low disease activity?
-	What is the true frequency of undertreatment and that of overtreatment in RA clinical settings?
-	Does the risk stratification for bDMARD/tsDMARD initiation based on presence of good or bad prognostic factors as recommended by EULAR translate into improved outcomes for both prognosis groups?
-	Do patients who lack poor prognostic factors benefit as much from a switch to or addition of a csDMARD as from the additian of a bDMARD?
4.	Difficult-to-treat Rheumatoid Arthritis
-	What is the optimal treatment approach to refractory RA?
-	Which other factors (*e.g*. life-style characteristics, treatment history) allow the best possible therapeutic decisions to be made?
-	What is the optimal (therapeutic) approach to arthralgia suspicious for progression to RA?
5.	Pre-Rheumatoid Arthritis
-	What is the optimal (therapeutic) approach to arthralgia suspicious for progression to RA?

ies. In general, higher doses and higher cumulative doses were related to a worse safety profile, leading to higher risk of cardiovascular events and mortality. The use of GC was also related to an increased occurrence of infections, osteoporotic fractures, and diabetes (4). The safety of GC was investigated in a further SLR that included only data from randomised controlled trials (RCTs) on low-dose GC (≤7.5 mg/ of prednisone) with a follow-up of at least 2 years. The choice of RCTs was intended as a mean to avoid the biases caused by confounding by indication in observational studies, it should however be considered that the generalisability of the findings might be affected by the inclusion of fitter patients in RCTs and that such studies are underpowered to detect long-term and uncommon events. The SLR included 6 RCTs, the pooled results showed no significant increase in the overall occurrence of adverse events (incidence rate ratio, IRR, 1.08, 95% confidence interval (CI) 0.86,1.34) and mortality, although

a higher risk of infections was related to GC use (risk ratio, RR, 1.4, 95%CI 1.19,1.65). The efficacy of GC in terms of reduction of disease activity, radiographic progression and disability were also demonstrated (5).

As the safety profile of GC remains the main concern limiting their use, some studies have investigated this area. An analysis based on a Swedish cohort of 9656 patients with new-onset RA evaluated the impact of GC on the occurrence of serious infections, taking into consideration time-varying confounders. Patients were categorised into GC non-users, low dosage GC (≤10 mg/day) or high dosage GC (>10 mg/day of prednisone) in separate periods of 90 days. This analysis showed a trend towards a dose-dependent effect, with current use at higher dosages and the cumulative exposure in the most recent year being related to higher risk of infections (6)

Cardiovascular safety is a further issue when prescribing GC. An administrative claim-based study held in Hong Kong on 12,233 RA patients, followed-up for a median follow-up of 8.7 years, demonstrated that 7% of patients experienced a major acute cardiovascular event (MACE). In a multivariable Cox analysis including concurrent treatment and C-reactive protein (CRP) levels to account for disease activity, a dose ≥5 mg of prednisone/day throughout the follow-up resulted in an increased risk, with a hazard ratio (HR) of 1.87 (95%CI 1.60, 2.18), while lower doses did not lead to a higher rate of events. These underline that even lower doses, when taken for long periods, can be detrimental (7).

A relevant clinical dilemma in everyday practice is represented by the difficulty in tapering GC, especially in patients with long-term GC treatment, and patients receiving biologic DMARDs (bDMARDs) are representative of such situation (8).

The aspect of GC tapering was also addressed by an analysis based on the TOcilizumab Collaboration of European Registries in RA (TOCERRA) and Paneuropean Registry collaboration for Abatacept (PANABA) observational collaborative studies, that integrate several RA registers comparing tocilizumab and abatacept to TNF inhibitors (TNFi), including 17,663 patients. The outcome was the proportion of patients receiving GC after 12 months of bDMARDs treatment and the survival on GC during the follow-up. A significant heterogeneity depending on the country was observed, with proportions of treated patients ranging from 30% to 85%. In all groups concurrent GC treatment decreased over time, with an OR of withdrawal (vs treatment start) of 2.19 (95% CI 1.58, 3.04) for TNFi, 2.46 (1.39, 4.35) for tocilizumab and 1.73 (1.35, 2.21) for abatacept. The median time of GC discontinuation was around 2 years in all groups, with a certain variability among countries, however not in line with current recommendations (9).

A meta-analysis of individual patient data from 7 RCTs assessed the risk of continuing GC after an initial bridging period. The overall risk was low after the up to 2 years of follow-up, however the risk was slightly higher with oral GC than parenteral administration. Higher cumulative dosages after the end of the bridging period were related to a higher initial dose and a slower tapering. (10)

A secondary analysis from the GLORIA (Glucocorticoid LOw-dose in RheumatoId Arthritis) trial, assessing the efficacy of 5 mg/day of prednisone add-on to the standard of care in patients aged more than 65 years, evaluated the impact of GC withdrawal after 2 years on disease activity, flares and adrenal insufficiency. There were no significant differences between patients on GC or placebo in terms of change of DAS28, while the RR of flare was 1.37 (95%CI 0.95,1.98), with a tendency toward a higher risk in patients on GC although not reaching statistical significance, taking into consideration that the analysis was based on 36 flares. There were no cases of adrenal insufficiency (11).

In the last year novel molecular mechanisms, exploiting GC-like effects, have also been tested. In a proof-of-concept phase II RCT, 48 patients with moderately active RA were randomised to receive either adalimumab or ABBV-3373, a novel antibody–drug conjugate composed by adalimumab and a proprietary glucocorticoid receptor modulator (GRM). The aim of this compound is to deliver GRM selectively to activated immune cells expressing TNF, thus minimising the systemic side effects of conventional GC. The primary endpoint of a change in DAS28 at 12 weeks was met by ABBV-3373, with a lower rate of adverse events compared to adalimumab (12).

The last year has seen a renewed research interest on the optimal placement of GC in the treatment strategy of RA, however there are still many unanswered questions in this area. In fact, there is no evidence on the impact of duration of GC treatment, of very low dosages and repeated parenteral administration. Moreover, there are no strategic studies on GC withdrawal, including switching DMARDs for this purpose. The information on the patterns of GC prescriptions in low-income countries are scarce, and, finally, it is still extremely hard to define whether the side effects of GC are determined by the drug itself or rather by the administration to a more fragile population.

Take-home messages

- Balancing side effects with therapeutic efficacy, GCs remain a valuable tool, and their effectiveness in reducing disease activity, radiographic progression, and disability has been demonstrated (3).
- The primary limitation of GC use is safety: a dose-dependent effect, with current usage at higher doses and cumulative exposure in the most recent year, has been associated with a higher risk of infections and the occurrence of major adverse cardiovascular events (4-7).
- Tapering GCs is still controversial, with trials showing varied results, but after 2 years of discontinuation, the number of flares does not significantly increase (10-11).
- The molecular mechanisms of GCs are still under study to synthesise new drugs with GC-like actions but without their side effects (12).

Janus kinase inhibitors

Janus kinase inhibitors are a class of targeted synthetic DMARDs (ts-DMARD) that currently includes five drugs ap-

proved for the treatment of RA: tofacitinib, baricitinib, peficitinib, upadacitinib, and filgotinib. The mechanism of action is based on the interaction with non-receptor tyrosine kinases (JAK1, JAK2, JAK3, and Tyk2), which transmit extracellular messages to the nucleus via the Janus kinase signal transducer and activator of transcription JAK/STAT pathway (13). Since we have limited head-to-head data on the selectivity and efficacy of JAKi, a Finnish study conducted an *in vitro* head-to-head comparison of the five JAKi approved for RA and five molecules under clinical evaluation (deucravacitinib, decernotinib, itacitinib, ritlecitinib, and brepocitinib). The analysis centered on the drugs' ability to inhibit catalytic activity, their capacity to bind to kinase and regulatory pseudokinase domains, the inhibition of cytokine signaling in peripheral blood from healthy volunteers, and the percentage of cytokine-induced STAT phosphorylation at clinically relevant concentrations of JAKi. These experiments were conducted *in vitro* using isolated peripheral blood mononuclear cells (PBMCs) obtained from patients with RA and from healthy donors. Pan-JAK inhibitors (tofacitinib, baricitinib, peficitinib) targeted JAK1, JAK2, and JAK3 with high potency (IC_{50}<10 n*M*) except baricitinib, which was less effective toward JAK3; on the other hand, JAK1-targeted inhibitors (upadacitinib, filgotinib, itacitinib) inhibited most potently JAK1, even only itacitinib was the only clearly JAK1-selective inhibitor (39-fold over JAK2), whereas filgotinib and upadacitinib also targeted JAK2 (2-fold selectivity for JAK1 over JAK2). Notably, JAK1-targeted inhibitors did not potently inhibit JAK3 and TYK2. Interestingly, the inhibition percentages of cytokine-induced STAT phosphorylation for clinically relevant concentrations of each JAKi did not demonstrate significant differences between pan-JAK and JAK-selective inhibitors. Moreover, this study revealed that JAKi inhibition of STAT phosphorylation was more pronounced in PBMCs from RA patients than in those from healthy individuals. As a result, the authors concluded that inhibiting JAK kinase activity did not directly translate into cellular inhibition of JAK/STAT signaling. Despite differences in JAK selectivity, the cytokine inhibition profiles of currently approved JAKi were highly similar, with a preference for JAK1-mediated cytokines. Novel types of JAKi exhibited a narrow cytokine inhibition profile specific for JAK3- or TYK2-mediated signaling. The necessity of understanding which pathway of the JAK-STAT transduction mechanism is inhibited has been underscored by the recent concern raised by the ORAL Surveillance trial about tofacitinib. Indeed, since this pan-JAK inhibitor blocks several intracellular signal pathways, it appears to increase cardiovascular risk in certain patients. The goal for the future is to identify which pathway is associated with cardiovascular damage and how each JAKi mechanism interacts with it (14).

The ORAL Surveillance trial, a randomised, open-label, non-inferiority study requested by the Food and Drug Administration (FDA), aimed to compare the risk of developing MACE and malignancies in patients aged over 50 with cardiovascular risk factors who were treated with either tofacitinib or a TNFi for RA. This trial, which has been subject of debate, revealed that tofacitinib may expose patients to a higher risk of these adverse events. Thus, both FDA and the European Medicine Agency strictly regulated the possibility to prescribe tofacitinib and all the other JAKi and these decisions were received in the 2022 EULAR recommendations of RA treatment (3).

During the past year, there has been widespread discussion regarding the true extent of the risk of major adverse cardiovascular events (MACE) and malignancies associated with Janus kinase inhibitors (JAKi), with re-analysis of data from principal RCTs and new studies on real-world populations. Wei *et al*. conducted a SLR and network meta-analysis, which included a collection of RCTs focusing on the incidence of MACE and all-cause mortality associated with JAKi. After selecting and analysing 14 RCTs, the difference in the risk of MACE between JAKi and tumour necrosis factor inhibitors (TNFi) and abatacept did not reach statistical significance. Conversely, the risk of all-cause mortality for tofacitinib was notably increased compared to adalimumab (odds ratio (OR) 1.9, 95%CI: 1.12–3.23). Interestingly, baricitinib had the lowest risk of all-cause mortality among JAKi. Moreover, both baricitinib and upadacitinib showed an incidence of all-cause mortality lower than adalimumab (15).

These findings were corroborated in real-world settings: in a national cohort study from Sweden, researchers compared the incidence of MACE in patients with RA treated with tofacitinib, baricitinib, and upadacitinib against both TNFi and other bDMARDs, as well as against the general population. Patients were recruited from 2016 to 2022 in the national Swedish Rheumatology Quality Register for a total of more than 13,000 persons, 3,037 of them starting a JAKi. After a median follow-up of 1.62, 1.6 and 1.7 years for patients treated with JAKi, non-TNFi and TNFi respectively, the authors highlighted that among patients in JAKi therapy, only 59 had a MACE (mainly in patients assuming baricitinib) and the sex and age-standardised incidence ratios were similar in the JAKi (0.88) and TNFi (0.91) cohorts. Moreover, when comparing the occurrence of MACE and myocardial infarctions in JAKi-treated against TNFi-treated populations with cardiovascular risk factors, the adjusted hazard ratios (HR) were 0.71 (95%CI 0.52–0.99) and 0.65 (95%CI 0.41–1.02) respectively. Consequently, this study suggests that in the short-term follow-up period (in comparison to the ORAL Surveillance trial where the median follow-up was approximately 4 years) and with different inhibition pathways of JAK, there is no difference in the incidence of MACE in patients treated with JAKi or TNFi (16.)

A favourable safety profile under cardiovascular risk was also demonstrated in an Italian real-world study on filgotinib: both bDMARDs naive and bDMARDs-inadequate responders did not exhibit a higher incidence of MACE after 2 years of follow-up (17).

The second warning raised from the ORAL Surveillance trial was the higher incidence of malignancies in patients

treated with tofacitinib. This issue has been investigated in patients treated with other JAKi, and data were synthesised in a meta-analysis by Russell *et al*. The authors analysed 62 RCTs and 16 long-term extension studies involving all JAKi approved for RA. Each JAKi (tofacitinib, baricitinib, upadacitinib, filgotinib, peficitinib) showed no significant differences in malignancy incidence compared with placebo or MTX (IRR 1.06; 95%CI 0.58–1.94), while when comparing JAKi to TNFi, the incidence of all malignancies was significantly higher in the JAKi group (IRR 1.63; 95% CI 1.27–2.09). Since the ORAL Surveillance trial was included in the RCTs, the authors conducted an influence analysis excluding this study. While the effect remained in the direction of a higher malignancy incidence with JAKi compared with TNFi, it was not statistically significant. Consequently, the authors suggested that JAKi are not associated with a higher incidence of malignancies but are not as protective as TNFi in patients with RA (18) However, the potential mechanisms associated with an increased risk of MACE and malignancies have not yet been fully elucidated.

Currently, it is known that tofacitinib can lead to dose-dependent increases in lipid levels, including total cholesterol, low-density lipoprotein (LDL) cholesterol, and high-density lipoprotein (HDL) cholesterol. These alterations in lipid profiles might play a role in the development of atherosclerosis and subsequent cardiovascular events. However, the exact mechanism behind these effects needs further quantification and investigation (18). Additionally, the immunosuppressive effects of tofacitinib may hinder leukocyte's ability to detect and eliminate malignant cells, potentially increasing the risk of cancer development. Research has demonstrated that tofacitinib inhibits the proliferation of natural killer cells, which could diminish the ability to regulate tumour growth and prevent metastasis (19).

Furthermore, JAKi could potentially disrupt the balance between prothrombotic and antithrombotic factors, influencing platelet production and function, and thus contributing to thrombogenicity. For example, inhibiting JAK2 might impact thrombopoietin receptor signal transduction, which plays a role in platelet activation. However, the precise role of JAK2 in platelet activation remains uncertain. Additionally, other pathways not directly linked to the JAK/STAT pathway may be affected, leading to unintended prothrombotic outcomes. Moreover, the pre-existing conditions of patients exposed to JAKi often entail an increased risk of thromboembolic events (such as RA itself, as well as factors like age and obesity). Nonetheless, the exact mechanism by which JAKi elevate thromboembolic events remains incompletely clarified at present (20).

Since the recent introduction of multiple JAKi, the effectiveness of intraclass cycling is not fully understood. An interesting study aimed to compare the efficacy of switching to another JAKi *versus* switching to a bDMARD in patients with RA after failure of the first JAKi. The observation period started from the failure of the first JAKi up to the failure of the second b/tsDMARD. Two thousand patients were enrolled from 17 different registries worldwide: 365 were treated with a second JAKi, while 1635 received another bDMARD. Disease activity was assessed using the clinical disease activity index (CDAI) over time and was estimated using a linear regression model, adjusting for confounders. Patients initiating a second JAKi were found to be older, more often seropositive, had longer disease duration, received a higher number of previous bDMARDs, had longer exposure to the first JAKi treatment, and more often were on monotherapy compared to those switching to a bDMARD. After two years of treatment, cycling to another JAKi was associated with a higher retention rate than switching to a bDMARD (hazard ratio for withdrawal 0.82, 95%CI 0.68–0.99). Adverse events were the most frequent cause of discontinuation in both groups. CDAI showed similar improvement in both groups after 12 months of follow-up (mean CDAI improvement 8 [95%CI 3.4–18.2] for the JAKi cycling group *vs*. 10.4 [95% CI 3.1–17.7] for the bDMARD group; p=0.79). In addition, after the failure of the first JAKi, both the use of a second JAKi and switching to a bDMARD demonstrate similar efficacy in reducing disease activity. However, when discontinuation of the first JAKi occurs due to adverse events, it is more likely that the second JAKi will also be discontinued for the same reason, suggesting that switching to a bDMARD might be a more reasonable alternative in this scenario (21).

Among different mechanisms of action (MOA), both JAKi and b-DMARDs (sarilumab and tocilizumab) directly interfere with the interleukin 6 pathway. An interesting study compared clinical responses in patients with RA who switched from an interleukin 6 receptor inhibitor (IL-6Ri) to a JAKi and *vice versa*. The primary outcome was the CDAI after six months of therapy. In both groups, the improvement was clinically significant, and even the adjusted comparison of CDAI at the beginning of the treatment and after 6 months between IL-6Ri initiators and JAKi initiators showed no significant differences. Secondary outcomes such as the Health Assessment Questionnaire, patient-reported pain, and fatigue also improved in both groups without significant differences. The only notable result highlighted by the authors was that IL-6Ri initiators (with moderate-to-severe disease) had higher odds of achieving CDAI low disease activity (LDA) compared to JAKi initiators (adjusted OR [95% CI]: 3.30 [1.01, 10.78]), suggesting that switching from IL-6Ri to JAKi and *vice versa* appears to yield comparable responses in a short-term observation period (22).

It would be intriguing to conduct a comparison between JAKi as a first-line treatment against MTX plus GC to explore the potential of blocking the dysregulated JAK/STAT pathway in the early phases of RA. Such a study could demonstrate whether an aggressive initial therapy can induce and sustain remission more effectively than the usual standard of care, potentially preventing structural damage in patients with rheumatoid arthritis.

Take-home messages

- JAK inhibitors interfere with the JAK-STAT pathway at various steps

and with differing selectivity, yet their cytokine inhibition profiles are highly similar, showing a preference for JAK1-mediated cytokines (14).

- Despite this similarity, pan-JAKi and more selective JAKi may have different risk profiles concerning malignancies and all-cause mortality (15, 18).
- In a very short-term observation period, the risk of MACE for JAKi is not statistically different from that of TNFi. However, long-term studies are needed to confirm this data (16-17).
- The exact mechanism underlying both MACE and malignancies in JAKi therapy is still partly understood (19-20).
- Further studies are needed on cycling and switching of targeted synthetic/biologic DMARDs after JAKi failure, and robust data on JAKi as first-line therapy are lacking (21-22).

Treatment strategy and risk stratification

In the treatment landscape of RA, emphasis has shifted from singular medication approaches to comprehensive therapeutic strategies.

One of the remaining frontiers in the treatment of RA is the personalisation of therapies. While we recognise certain patient profiles that respond better to treatments, we are not yet able to select therapies based on individual characteristics. For patients achieving good disease control, treatment reduction strategies can be applied, although optimal schemes are still unknown. While the available therapies have proven efficacy, their acceptability and adherence are often suboptimal. New challenges include transferring accumulated knowledge into clinical practice fully and finding new ways to personalise treatments.

Biomarkers

Current RA treatment guidelines lack recommendations for selecting personalised b/tsDMARD therapies. This gap results in trial-and-error b/tsDMARD prescription until an effective class of drug is found, highlighting the need for predictive biomarkers to promote optimal treatment decisions.

The potential benefits of utilising a hypothetical biomarker to predict response to treatment for RA has been formally evaluated through a Markov model comparing a standard treat-to-target (T2T) strategy with a biomarker-guided approach, in terms of time spent in remission or LDA and associated costs. Findings suggest that the biomarker strategy may lead to an additional 2.9 months in LDA or remission over 48 months compared to usual care. While total costs were slightly higher for the biomarker strategy, cost-effectiveness was influenced more by early and proactive tapering of medication and drug costs rather than biomarker characteristics (23).

Unfortunately, an approach based on individual biomarkers has not yet identified useful tools for precise identification of patients responsive to specific treatments. More pragmatically, several studies agree on identifying markers of inflammatory activity as useful factors for identifying patients more likely to respond, combining diagnostic potential with predictive potential.

An UK study aimed to identify proteomic biomarkers associated with clinical outcomes in RA patients starting etanercept, the study identified ten individual proteins (including T-complex protein 1 subunit eta) related to acute phase and inflammatory responses that were significantly associated with RA clinical outcomes (24).

The predictivity of synovial inflammation as potential biomarker of treatment response has been investigated by different modalities, so far. New evidence further strengthens the concept that patients with objective signs of synovitis are more likely to respond to DMARD treatments. For example a study reported a significantly higher uptake of [68 Ga]Ga-FAPI-04 in synovial tissue compared to non-responders (25). A synovial biopsy study assessed 53 inflammatory arthritis patients including 34 RA: in the follow-up study high-grade synovitis were significantly associated with DAS28 remission, ACR20/50 response, and Boolean 2.0 remission (26).

Disease phenotypes

In the management of the delicate balance between therapeutic efficacy and pharmacological safety profile, the identification of distinct phenotypes of RA and their impact on treatment response represents a key element in the RA research agenda. Recognising early onset RA and promptly initiating appropriate tapering strategies has significantly improved patients' outcomes over the past year. This improvement has resulted in enhanced quality of life and increased life expectancy, particularly when compared to cases of late-diagnosed RA (27). Moreover, differentiating patients with RA according to their autoantibody status, including both rheumatoid factor (RF) and anti-citrullinated proteins antibodies (ACPA), is known to have relevant implications in terms of both clinical response and prognosis. A recent SLR with meta-analysis, incorporating data solely from RCTs (n=23), aimed to investigate the role of rheumatoid factor (RF) and anti-citrullinated protein antibodies (ACPA) in predicting clinical response to bDMARDs in RA. The findings from the meta-analysis suggest that bDMARDs demonstrate comparable efficacy in patients with both autoantibody-positive and autoantibody-negative RA, regardless of the specific pharmacological mechanism of action. Moreover, in patients who are refractory to TNFi, the available evidence tends to suggest a higher response rate for bDMARDs in those who are seropositive. However, due to the limited number of studies, definitive conclusions cannot be drawn at this time (28). In a recent prospective observational study, Aripova and colleagues investigated the predictive role of an expanded antigen-specific ACPA profile compared to the commercially available anti-cyclic citrullinated peptide (CCP)-3 assay in 1092 patients with RA initiating bDMARDs. Two out the three expanded ACPA profiles, identified by a principal component analysis and explaining ≃ 70% of the variability in ACPA expression, demonstrated a significant superiority to predict positive treatment response to bDMARDs compared to conventional anti-CCP-3 assay (29). The impact of the expanded antigen specific ACPA profile was independent of the mechanism of action of the bDMARD. In the hypothesis that

RF may potentially reduce therapeutic drug levels through the interaction with the fragment crystallisable (Fc) portion of TNFi, a recent Spanish study retrospectively compared the retention rate of certolizumab pegol (CZP), the only TNFi lacking an Fc portion in its structure, with other TNF-i according to baseline RF titre in 638 patients with RA. After matching by using a propensity score technique, patients with very high RF levels (≥200 IU/mL) exhibited longer drug survival with CZP than with any anti-TNF monoclonal antibodies [HR 2.3 (95% CI 1.2, 4.3)] or etanercept [HR 2.8 (95% CI 1.5, 5.2)], irrespective of age, co-medication with MTX and previous exposure to b/tsDMARDs. No differences between groups were found when considering only patients with RF levels <200 UI/mL (30).

The STRAP and STRAP-EU trials are two open-label, biopsy-driven, phase-3 randomised controlled trials conducted in the UK and Europe, respectively. These trials aimed to evaluate the efficacy of rituximab, tocilizumab, and etanercept in 226 biologic disease-modifying anti-rheumatic drugs (bDMARDs)-naïve patients with rheumatoid arthritis (RA), categorised into B cell-rich and B cell-poor synovial histopathology groups. The results showed no significant difference in terms of ACR20 response between the tocilizumab/etanercept group and rituximab group in either histopathology group. However, radiological progression was more frequent in B cell-rich patients treated with rituximab (31). Although the classification based on synovial pathotypes did not predict a better response to rituximab compared to alternative strategies, further studies are needed to explore the role of synovial pathotypes in guiding therapeutic decisions for patients with RA.

Despite the progress in therapeutic outcomes for RA, managing patients diagnosed with RA after the age of 65, known as late-onset RA (LORA), can be challenging due to a relatively higher disease burden and concerns about serious adverse events. A recent retrospective study examined the therapeutic management of 33,373 LORA patients using Medicare data. Despite recommendations emphasising the early introduction of DMARDs in RA, DMARDs were initiated in less than one third of LORA patients (28.9%). This initiation was less likely in those receiving long-term GC or with a history of severe infections. Remarkably, about ten percent of patients not treated with DMARDs were undergoing prolonged GC monotherapy. Factors positively associated with the use of DMARDs included younger age, fewer comorbidities, and higher income (32).

Therapeutic management of obese or overweight patients with RA remains controversial, with some studies suggesting lower treatment responses and worse outcomes in this population. Three recent studies examined the clinical effects of various bDMARDs and tsDMARDs in patients with RA, categorised by individual body mass index (BMI). A first study, a retrospective analysis involving 2,515 RA patients (443 overweight and 829 obese) from the Swiss Clinical Quality Management in Rheumatic Diseases registry, demonstrated comparable effects among etanercept, infliximab, abatacept, and adalimumab in terms of achieving Disease Activity Score on 28 joints (DAS28) remission within 12 months, regardless of BMI (33) In a second study, a *post-hoc* analysis of the FINCH 1-3 RCTs, it was found that treatment with filgotinib at doses of 100 or 200 mg/day did not affect the likelihood of achieving a clinical response based on baseline BMI. Interestingly, treatment with filgotinib did not lead to significant changes in BMI throughout the study period (34). Lastly, a secondary analysis of the RACAT and TEAR RCTs explored whether BMI and adipokine levels could significantly impact treatment response in RA patients receiving either triple therapy with MTX, sulfasalazine, and hydroxychloroquine or an early combination of MTX and etanercept. The analysis revealed that underweight or normal-weight patients and those with lower adipokine scores were more likely to respond to the early introduction of etanercept compared to triple therapy. In contrast, no significant difference was observed among obese or overweight patients and those with higher adiposity findings. These findings suggest an increased probability of achieving therapeutic goals through the early initiation of TNF inhibitors in patients with lower BMI (35).

Adherence

Adherence to treatment is a well-known determinant of the efficacy of DMARDs in RA. With the wide availability of highly effective oral tsDMARDs, questions arise about the acceptability and adherence to this new class of drugs. Recent industry-funded analyses have focused on comparing adherence rates among bDMARDs and tsDMARDs. In a study assessing adherence to tofacitinib and self-injectable TNFi therapies in RA patients using the Medication Event Monitoring System, 112 patients were included, with 76% initiating tofacitinib and the remaining receiving other TNFi. Tofacitinib demonstrated marginally better adherence compared to TNFi (36).

Another study comparatively assessed adherence to different tsDMARDs, demonstrating better adherence for upadacitinib compared to TNFi and other licensed JAKi. However, a substantial level of non-adherence ranging from 40% to 60% was observed for all investigated drugs, indicating that non-adherence is still an unresolved issue in RA regardless of the administration route (37).

Tapering

DMARD tapering is a relevant point to consider when treating patients with RA achieving remission or LDA, while the optimal individual strategy is far to be fully elucidated.

In the last year, trials investigating disease activity-driven tapering strategies for TNFi treatment, such as the Arctic Rewind trial, failed to demonstrate noninferiority in terms of flare occurrence, with flares observed in a significant proportion of patients tapering TNFi compared to those maintaining bDMARDs at a full dose. In this trial, patients with RA in remission for at least one year on stable TNFi dosages were randomised to tapering or maintaining TNFi therapy, with most patients also receiving csDMARDs.

At 12 months, 63% of patients in the tapering group experienced a disease flare compared to 5% in the stable TNFi group. Notably, 19% of flares in the tapered group occurred when patients were receiving TNFi half-doses. Since csDMARD dosages remained unchanged, it remains uncertain whether reducing csDMARDs first might have yielded better outcomes than tapering TNFi first. The trial demonstrated that despite maintaining remission for one year, most patients still required continuous therapy with TNFi (38, 39).

Conversely, the Dose Reduction Strategy of Subcutaneous TNFi Study (DRESS) trial showed noninferiority for tapering compared to maintenance strategy for major flares but not short-term flares. This study involved patients with RA who had achieved LDA while on stable treatment with adalimumab or etanercept, compared with continuation over an 18-month period. Despite slightly higher radiographic progression in the dose optimisation group, no significant differences were observed in major flare incidences, disease activity, or radiographic progression in the extended 3-year study. A follow-up study of the DRESS trial demonstrates that over a decade, disease activity–guided dose optimisation of TNFi in RA leads to significant dose reduction while maintaining disease control, including a discontinuation attempt after 2.5 years. Adhering to a strict treat-to-target approach is crucial for mitigating radiographic progression. These findings offer valuable insights for refining dose optimisation recommendations in RA management, highlighting the importance of optimising dosing strategies and monitoring outcomes to ensure patient safety (40).

The amount of evidence on the potential benefit of non- TNFi bDMARD tapering is more limited. The DREAM study showed that tocilizumab discontinuation resulted in high flare rates, with only 13.4% of patients in sustained remission at 1 year (43) Another study, the Study on Abatacept and Tocilizumab Attenuation (SONATA), found that tapering tocilizumab or abatacept was possible in only a minority of patients with RA, with complete discontinuation achieved in a small percentage (10%).

The ToLEDo trial aimed to assess the non-inferiority of progressively spacing tocilizumab or abatacept driven by Disease Activity Score on 28 joints (DAS28) versus maintenance at full dose on disease activity, relapse, structural lesion progression, and function in patients with established RA in sustained remission. In this open-label RCT, 60% of patients in the spacing arm were able to space or discontinue their treatment by the end of the 2-year follow-up. However, the study could not demonstrate non-inferiority between the two arms for the main or any of the secondary study outcomes. While guidelines suggest tapering biologic or targeted synthetic disease-modifying anti-rheumatic drugs (b/tsDMARDs) as a viable strategy for patients in sustained remission, the ToLEDo trial indicates no discernible benefit when this approach is applied to patients receiving TCZ or ABA (41).

Despite previous efforts to identify predictors for successful discontinuation of b- and ts-DMARDs, there remains a lack of consensus on when or in whom these medications should be discontinued. Some authors have attempted to develop tests to predict RA relapse after tapering TNFi, but these efforts have not been successful so far (44) Indeed, the concept of "deep remission" has emerged as a significant predictor for successful discontinuation of b- and ts-DMARDs. Studies define deep remission based on various criteria, often involving DAS measurements of sustained remission or sustained LDA. Physical function, as measured by the Health Assessment Questionnaire (HAQ), has also been identified as a significant predictor. Lower HAQ scores at baseline are associated with successful bDMARD discontinuation, which is often linked to shorter disease duration and less radiographic progression. Serological markers such as RF and ACPA are additional predictors. Seronegative patients are more likely to maintain LDA or remission after discontinuation. Furthermore, low levels of acute phase reactants like CRP, ESR, and IL-6 also predict successful bDMARD discontinuation. Certain demographic factors also play a role, with smoking identified as an independent predictor for restarting infliximab, and women tending to experience more disease exacerbation than men. Understanding these predictors can assist clinicians in selecting appropriate candidates for tapering strategies, ultimately optimising treatment outcomes while minimising the risk of disease flares or worsening symptoms (43).

Discontinuation of csDMARDs in RA management is a matter of debate, especially regarding the duration of remission needed before tapering. ACR guidelines suggest a minimum 6-month remission period, but individual factors like disease severity, treatment response, and comorbidities can influence this decision. Patients with severe disease may require longer remission for stability, while those with milder disease could taper sooner. Decisions should be tailored to each patient, considering disease status and monitoring closely for signs of relapse during tapering (3).

Furthermore, it is crucial to carefully consider the risk of flare when tapering or discontinuing csDMARDs. In this regard, an insightful letter by Lillegraven and colleagues provided reassurance (44). The authors enrolled 56 RA patients from the Arctic Rewind trial who were taking csDMARDs (not b/tsDMARDs) and had previously tapered to half-dose, remaining flare-free for at least 12 months. They divided these patients into two groups and assessed the superiority of discontinuing csDMARDs (26 patients) versus maintaining a stable half-dose (30 patients) regarding disease flare over an additional 12-month follow-up. During the observation period, 10 out of 26 (38.5%) patients discontinuing csDMARDs experienced a flare, compared to 5 out of 30 (16.7%) continuing a half-dose regimen. Importantly, after the flare, a significant proportion of patients in both groups regained remission as defined by DAS28 parameters (80.0% and 66.7%, respectively). Additionally, no significant differences in radiographic bone damage progression, as defined by the Sharp-van der Heijde score, were detected between the two groups, suggesting that discontinuation of csDMARDs

might be feasible for some patients, and structured follow-up of DMARD treatment-free patients is advisable, but further studies are needed (44).

Therapeutic drug monitoring

While bDMARDs have notably transformed the treatment landscape and long-term prognosis for RA patients, a considerable subset still struggles with refractory disease or fail to sustain adequate control over time. Therapeutic drug monitoring (TDM), potentially coupled with the detection of anti-drug antibodies (ADAs), emerges as a promising precision medicine strategy aimed at optimising therapeutic outcomes in immune-mediated disorders. A recent study conducted in Norway examined the association between serum adalimumab levels after three months, treatment response, and drug discontinuation in a cohort of 340 patients with inflammatory joint diseases (97 with RA, 69 with psoriatic arthritis (PsA), and 174 with axial spondyloarthritis) (45). In patients with both RA and PsA, therapeutic response and drug persistence were significantly associated with adalimumab levels ≥6.0 mg/l [OR 2.2 (95% CI 1.0–4.4) and HR 0.49 (95% CI 0.27–0.80), respectively]. ADAs were detected in about 10% of patients, with a negative impact on treatment response and drug survival. Previous bDMARD use, non-combination with MTX, and the use of adalimumab originator compared to GP2017 were significantly associated with the development of ADAs. To explore how identifying serum trough levels of TNFi outside therapeutic intervals may impact clinical decision-making, Pfeiffer-Jensen and colleagues conducted an open RCT comparing the effect of a TDM approach on reducing drug prescription versus a conventional strategy in 239 patients with chronic inflammatory arthritis (99 with RA, 48 with PsA, 92 with SpA) receiving infliximab, adalimumab, and etanercept (46). Compared to standard approach, TDM allowed a significant dose decrease of infliximab [-12% (95% CI -20, -3); $p<0.001$] and etanercept [-15% (95% CI -29, -1); $p<0.001$], as well as a prolonged interdosing interval of etanercept [+235% (95% CI 38, 432); $p=0.03$] and adalimumab [+28% (95% CI 6, 51); $p=0.03$]. Moreover, in non-responsive patients, TDM resulted in an earlier switch to other bDMARDs compared to conventional approach (11 *vs*. 2 participants for all three drugs; $p=0.036$). Although the TDM approach did not reduce the occurrence of adverse events, similar or even better clinical outcomes were observed in comparison to the conventional arm. The potential negative impact of ADAs on RA clinical outcomes was confirmed by the recent ABI-RA multicenter prospective study, which included 230 patients with RA treated with different classes of bDMARDs (68 TNFi monoclonal antibodies, 82 etanercept, 50 tocilizumab, 30 rituximab). ADAs were detected within 12 months in 38.2%, 6.1%, 20%, and 50% of patients receiving TNFi monoclonal antibodies, etanercept, tocilizumab, and rituximab, respectively. An inverse correlation between the detection of ADAs and EULAR response at 12 months and at each time point was observed in all groups of bDMARDs (OR 0.19; 95% CI, 0.09, 0.38; $p<0.001$). Notably, a significantly lower concentration of infliximab and adalimumab was documented in patients with ADA positivity compared to those with ADA negativity. Likewise, non-responder patients exhibited lower drug levels of etanercept and adalimumab compared to responders (47). Consistent with earlier findings, there was a negative association between concomitant use of MTX at baseline and the development of ADAs. Additionally, an intriguing study by Martínez-Feito *et al*. investigated the impact of baseline RF and ACPA levels on serum drug levels of infliximab, adalimumab, and certolizumab pegol in 170 patients with RA. They observed that patients with high RF levels at baseline had lower levels of infliximab and adalimumab serum levels, and secondary non-response was more common in these patients compared to those with low serum RF levels (48). These findings underscore the importance of implementing therapeutic drug monitoring (TDM) algorithms to customise treatment decisions and optimise drug exposure in patients with RA.

Treatment target in rheumatoid arthritis

Our literature review from the past year did not yield any articles examining whether achieving clinical remission in RA leads to better outcomes compared to LDA. However, there has been recent criticism of the Boolean definition of remission in RA, particularly regarding the stringent requirement for a patient global assessment (PtGA) score of ≤1. Many patients with RA may not achieve this threshold despite the absence of swollen or tender joints and normal CRP levels, often due to factors unrelated to inflammatory activity. To address this issue, a revised version of the Boolean definition (Boolean 2.0) with a PtGA threshold of 2 was externally validated and endorsed by the ACR/EULAR. This revision aims to improve agreement between the Boolean definition and index-based criteria for remission (49, 50). Adopting the Boolean 2.0 definition allows for a broader classification of RA patients as achieving remission, resulting in increased agreement with index-based definitions. This expanded definition does not sacrifice the correlation with structural and functional outcomes, providing a more inclusive approach to assessing remission in RA management.

Take-home messages

- Biomarker-guided strategies show promise in predicting treatment response and optimising outcomes in RA, especially by assessing objective synovial inflammation (23, 26, 28, 29, 31).
- Adherence to DMARD treatment remains a critical issue, even with the introduction of oral ts-DMARDs (36-37).
- Tapering bDMARDs monotherapy in RA patients in sustained remission often results in flares, indicating inconsistent success in this approach (38, 40).
- Studies have not shown non-inferiority when tapering or discontinuing bDMARD therapy compared to maintaining full-dose treatment in preventing disease flares or joint damage progression (45, 47).
- It is commonly recommended to wait

for at least six months to one year of sustained remission or LDA before considering tapering DMARDs (43-44).

- Adopting an individualised tapering approach may be an attractive addition to daily practice for effectively managing RA for both patients and rheumatologists (45-47).
- Achieving "remission at the lowest efficacious dose" is an important goal in RA management, with therapeutic drug monitoring potentially more beneficial than fixed-dose injection spacing strategies (49-50).

Difficult-to-treat rheumatoid arthritis

Refractory cases of RA, also known as difficult-to-treat RA (D2T-RA), are recognised clinical challenges in RA management. Since 2020 a consensus-based definition of D2T-RA has widespread for clinical practice and trials purposes and the following was agreed upon to classify patients as D2T-RA within the framework of the EULAR recommendations: the failure of ≥2 b/tsDMARDs with different mechanisms of action after failing csDMARDs along with the finding(s) of either active disease, disease progression, impact on quality on life, or inability to taper GCs (51).

In the last year, very little but noteworthy evidence has come to light and might help to answer the latest research questions about the optimal treatment approach to refractory RA and about the factors which allow the best possible therapeutic decisions to be made on D2T-RA.

It is not yet possible to give a solid answer to the critical question about the optimal treatment of D2T-RA and scarce data were published on pharmacological and non-pharmacological treatments which may be beneficial for such patients.

In 2023, only one study described the response to targeted therapies in a French retrospective cohort of 320 RA patients, where 76 were D2T-RA and 244 were non-D2TRA, and a higher percentage of remission (DAS28-ESR <2.6) was observed with anti-CD20 antibody (7/26, 27%) and with JAKi (3/11, 27%) compared with other targeted therapies with a similar number of prior targeted therapies (<20%) (52) When patients not fulfilling the EULAR definition due to the failure of at least two targeted therapies but without regard to the mechanism of action were classified as "alternative" D2T-RA (n=120 *vs*. 200 non-DT2-RA), equivalent percentages of remission and treatment escalation were observed with an equivalent number of therapy lines, notably with a similar pattern of response to anti-CD20 and JAKi. Moreover, in this subgroup the absence of combination with MTX was associated with D2T-RA (63/120, 53% and non-DT2-RA 128/200, 64%, p=0.046), but the inclusion of RA who failed two TNF inhibitors with low proportion of patients receiving MTX may explain this finding.

With regard to non-pharmacological treatments, the effectiveness of physical exercise for RA patients including D2T-RA was proved in a randomised controlled trial on 217 people (90% female, mean age 59 years old) (53) In this trial, 104 patients received a personalised, supervised and longstanding (≥52 weeks) active exercise therapy according to a standardised protocol to be delivered by a trained primary care physical therapist as intervention in comparison with 98 patients treated as per usual care. The change in the highest-ranked Patient-Specific Complaints Numerical Rating Scale score (0: easy; 10: impossible to do) for the most limited activities at 52 weeks was the primary outcome and a significant improvement was shown in the intervention group (mean difference and 95%CI -1.7 and -2.4,-1.0) overall. Significantly larger improvements favouring the intervention were also shown for the secondary outcomes (the Patient Reported Outcome Measurement Information System Physical Function-10, the HAQ-Disability Index, the Rheumatoid Arthritis Quality of Life Questionnaire, the 36-Item Short-Form Health Survey (SF-36) Physical Component Summary Scales and the 6-minute walk test) except for the SF-36 Mental Component. A large proportion of these patients were classified as EULAR D2T-RA (intervention 44/101, 43.6% and usual care 46/90, 51.1%) and even though specific sub-analyses were not provided, these results were arguably reflective of a population of RA and considerable functional disability like D2T-RA. Probably, the best treatment strategy for D2T-RA could be the prevention of its development. In an Italian retrospective multicentre cohort study conducted between 2021 and 2022, 48 D2T-RA patients were compared to 145 non-D2T-RA controls and a failure to start MTX within 3 months since diagnosis was associated with features of D2T-RA (OR 0.3, 95%CI 0.1–0.7, p=0.007; adjusted OR 0.3, 95%CI 0.1–0.9, p=0.031 for at least 6 months of MTX, GC >6 months). Moreover, persistent GC therapy (*i.e*. >6 months) was also observed to be associated with D2T-RA (OR 4.8, 95%CI 2.3-9.7, p<0.001; adjusted OR 4.6, 95%CI 2.2–9.5, p<0.001 for at least 6 months of MTX and MTX delay) and these findings support the hypothesis that an unsuccessful early RA management due to treatment delay with MTX and inability to discontinue GCs may lead to a D2T-RA status (54). Likewise, the potential role of MTX against the development of D2T-RA was confirmed by the data from the Korean College of Rheumatology Biologics registry. Out of 2321 RA treated with b/tsDMARDs, 271 patients were classified as D2T-RA and the prior use of MTX was protective against D2T-RA (OR 0.36, 95%CI 0.23–0.57, p<0.001; adjusted OR 0.44, 95%CI 0.24–0.81, p=0.008 for age, body mass index, smoke, and use of GCs), as well as the history of use of other csDMARDs (sulfasalazine, OR 0.65, 95%CI 0.47-0.90, p=0.008; adjusted OR 0.59, 95%CI 0.42–0.83, p=0.003; leflunomide, OR 0.76, 95%CI 0.57-1.02, p=.061; adjusted OR 0.67, 95%CI 0.49–0.92, p=0.013) (55).

Unfortunately, it is unclear which factors allow to predict the development of D2T-RA and to guide the best possible therapeutic decisions in these patients.

Data on sociodemographic and clinical features as predictors of D2T-RA are sparse and inconsistent. Young age, elevated initial disability, long-standing disease, concomitant interstitial lung disease, low socioeconomic status, and

diabetes were found to be associated with D2T-RA. On the other hand, results on disease activity, smoking and female sex were conflicting. Interestingly, the proportions of RF and ACPA positivity did not differ consistently between D2T-RA and non-D2TRA in multiple studies except for a lower proportion of RF in D2T-RA in one study (52, 55-57).

A subset of patients was observed to have a non-inflammatory refractory RA (NIRRA) in opposition to persistent inflammatory phenotype (PIRRA) with elevated DAS-28-CRP, swollen joint counts, CRP levels and synovitis detected by ultrasound examination. In a cross-sectional study in the United Kingdom, among 247 D2T-RA, a substantial proportion of patients had no objective signs of inflammation (46/107, 43% NIRRA) and similar findings were observed when D2T-RA patients were subclassified in polyrefractory (*i.e.* failed at least 5 b/tsDMARD classes, 11/34, 32% NIRRA) with no differences in terms of age, sex, time of disease, and time on biologics between PIRRA and NIRRA (57) Likewise, the proportion of NIRRA was substantial in another Italian study on DT2-RA (17/48, 35%) and treatment delay with MTX was found to be associated with PIRRA (<3 months *vs.* >12 months, OR, 95%CI, 0.2, 0.1–0.8, p=0.015) (54) Moreover, NIRRA was observed to have high proportion of obesity and fibromyalgia compared to PIRRA (n=24, 55% *vs.* n=15, 26%, p=0.004; n=7, 15% *vs.* n=2, 3%, p=0.037, respectively) (57). These findings could have implications for management.

Thus, it is widely accepted that a definition of D2T-RA is necessary, but a data-driven update was also proposed.

The importance of defining D2T-RA on the basis of drug failures in opposition to other reasons for drug change (*e.g.* safety or compliance) was confirmed in a Spain prospective study on 253 patients (131 non-D2TRA and 86/122, 71% D2TRA-inefficacy and 36/122, 29% D2TRA-other) where the absence of differences was observed between non-D2TRA patients and D2TRA-other with regards to sociodemographic characteristics and disease activity, unlike what occurs in patients with D2TRA-inefficacy (58). However, RA patients failing two TNF inhibitors showed similarities with D2T-RA who failed ≥2 b/tsDMARDs with different mechanisms of action and this suggest that future updates of the EULAR definition of D2TRA might reconsider the role of the mechanism of action further to the number of failures (52) Finally, it was proposed to consider the inflammatory phenotype since PIRRA and NIRRA may benefit from different treatment approaches (57).

Take-home messages

- The optimal treatment for D2T-RA has still to be defined and first data suggest that JAKi and rituximab might be considered based on higher remission rate than with other targeted therapies (52, 54, 57, 58).
- A comprehensive strategy including also non-pharmacological treatments like physical exercise programs should be implemented in the management of D2T-RA (53).
- Predictors of D2T-RA development and outcomes are yet to be identified, but unsuccessful early treatment due to delay in MTX commencement and GCs discontinuation and noninflammatory disease phenotypes might have a role in D2T-RA patients (54, 57).

Pre-rheumatoid arthritis

The concept of pre-clinical RA is not yet fully established but is characterised by inflammatory arthralgia, positivity for ACPA and/or RF, and subclinical signs of joint involvement on imaging modalities like ultrasound (US) or magnetic resonance imaging (MRI). This pre-phase presents an opportunity to intervene early and potentially prevent the progression to established RA, although the appropriate treatment approach remains controversial.

Many questions surround the early treatment of pre-RA. A survey conducted among healthcare professionals and patients enrolled in the TREAT EARLIER trial revealed that only a small percentage of healthcare professionals strongly agreed with initiating treatment in pre-RA patients for one year. Additionally, only half of the doctors who agreed with treatment actually treated pre-RA patients in their clinical practice, citing concerns about potential side effects as their main reason for hesitancy. However, among patients, most respondents were satisfied with the treatment, although satisfaction decreased among those who progressed to confirmed RA (59).

The Abatacept in individuals at high risk of rheumatoid arthritis (APIPPRA) and Abatacept Reversing subclinical inflammation as measured by MRI in ACPA positive Arthralgia (ARIAA) trials investigated the effects of abatacept in patients with pre-clinical rheumatoid arthritis (RA), focusing on clinical and imaging outcomes (60, 61).

The APIPPRA study was a phase 2b RCT that included patients at risk of RA, positive for both ACPA and RF, and experiencing inflammatory joint pain. Participants were treated with either abatacept or placebo for 12 months and followed for an additional 12 months. The primary endpoint was the time to the development of clinical synovitis in three or more joints or a diagnosis of RA according to ACR criteria. Secondary outcomes included changes in patient-reported outcomes (PROs) and US findings, such as synovial hypertrophy and power Doppler signal. The analysis of primary outcomes showed that at 12 months, 6% of participants in the abatacept group and 29% in the placebo group met the primary endpoint. These proportions increased further at the 24-month follow-up to 25% and 37% for the abatacept and placebo groups, respectively. Kaplan-Meier analysis demonstrated differences between the groups favouring abatacept at 24 months. Additionally, at 12 months, the proportion of participants with swollen joints was higher in the placebo group than in the abatacept group, although this difference was less substantial at 24 months. Similarly, improvements in PROs were observed in the abatacept group at 12 months but were not sustained at 24 months. Regarding serial US assessments, abatacept was found to reduce the progression of subclinical disease, with some effects sustained at the 24-month follow-up (62).

In the ARIAA trial, the primary objective was to assess the proportion of patients experiencing any reduction in inflammatory MRI findings at 6 months among those with arthralgia, ACPA positivity, and evidence of synovitis, tenosynovitis, or osteitis on baseline MRI scans. Participants were randomised to receive either abatacept or placebo. After 6 months, 57% of patients in the abatacept arm and 31% in the placebo arm showed improvement in inflammatory signs on MRI. Tenosynovitis exhibited the highest improvement rate, followed by a slight improvement in synovitis seen only in the treatment group. Furthermore, after 18 months, the difference in improvement rates between the two groups remained consistent. In terms of the onset of RA, the proportion of patients progressing to RA was significantly higher in the placebo group at both the 6-month and 18-month marks. However, the proportion also increased in the treatment group over time. These findings suggest a potential benefit of abatacept in reducing inflammatory MRI findings and delaying the onset of RA compared to placebo (63).

The study by Krijbolder *et al*. further supports the significance of tenosynovitis in the early phases of rheumatoid arthritis (RA). They evaluated serial MRI examinations conducted in the placebo arm of the TREAT EARLIER trial. Their findings revealed that the reduction in tenosynovitis occurred before decreases in synovitis and osteitis among patients who did not develop RA. This suggests that tenosynovitis may serve as an early indicator or precursor to the development of RA, highlighting its potential role in identifying individuals at risk of progressing to overt disease (64).

Take-home messages

- Pre-RA presents a potential opportunity for intervention to prevent progression to established disease, but the optimal therapeutic approach remains controversial (59).
- Abatacept is promising in preventing progression to RA and resolving subclinical inflammatory signs in pre-RA patients (60, 61).
- The long-term benefits of treating pre-RA patients are not fully understood, as progression to RA may increase even after treatment withdrawal (63).

Conclusions

In our 2023 review of RA treatment, we followed the research agenda outlined in the latest EULAR recommendations for RA management. Throughout our review, certain topics garnered continued interest, such as the use of GCs, the potential risks of cardiovascular events and malignancies associated with JAK inhibitors, the exploration of new biomarkers, and the optimal strategy for tapering and discontinuing DMARDs. However, there are still areas that require further investigation, including switching between different types of DMARDs, patient adherence to therapy, understanding the molecular mechanisms of JAK inhibitors, refining RA classification, and discerning differences between remission and low disease activity over the long term. In conclusion, our review underscores the enduring importance of RA research and encourages continued focus on both clinical and laboratory investigations for the benefit of our patients.

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