Review

Novel insights into the management of rheumatoid arthritis: one year in review 2023

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ABSTRACT

New evidence from 2022 slightly changed some perspectives for rheumatoid arthritis (RA) management. Real-world data on the efficacy and safety of disease-modifying anti-rheumatic drugs strengthened the importance of tailoring treatment decisions based on patient characteristics. Moreover, the research of response biomarkers to therapy underlined the need for precision medicine and remote care applications showed an innovative outlook that supports a patient-centred approach. New developments in vaccinations led to the release of updated guidelines and to a consistent improvement in the prevention of vaccine-preventable infections. New literature data also reconsidered drug management in RA-associated interstitial lung disease and pregnancy. In this paper, the reviewers aim to present the most relevant studies published during the last year in the field of RA management.

Introduction

Novel insights that emerged in 2022 contributed to a slight shift in perspectives in the management of rheumatoid arthritis (RA), similar to the 2021 review (1). The 2022 update of the European Alliance of Associations for Rheumatology (EULAR) recommendations for the treatment of RA did not substantially change the current therapeutic strategy (2). Instead, real-world data on the efficacy, cycling and tapering of disease-modifying anti-rheumatic drugs (DMARDs) provided new important information. The safety of DMARDs continued to be a central focus for infectious, cardiovascular (CV) and malignant risks. Notably, the Janus kinase inhibitors (JAKis) safety profile remained in the spotlight as one of the most relevant issues. Moreover, new significant steps in the research of response biomarkers to DMARDs highlighted the advent of precision medicine in RA management. However, in this field, a breakthrough year is still expected. Vaccinations have become an important option for people with RA. American College of Rheumatology (ACR) guidelines for vaccination in patients with rheumatic conditions combined the experiences collected during the Coronavirus Disease-19 (COVID-19) pandemic and gave to rheumatologists a fundamental reference to optimise the vaccination plan of RA patients (3). Lastly, electronic patient-reported outcomes (ePROs) emerged as a promising tool in the management of RA. ePROs applications showed the potential to improve the accuracy and timeliness of PROs collection and to support new strategies for disease monitoring. Rheumatologists frequently have to deal with the management of RA-associated interstitial lung disease (RA-ILD) and pregnancy. In the past year, some advances regarding DMARD administration in these challenging conditions were published. In conclusion, in this narrative review, the authors aim to present their specific point of view on the most relevant novelties in the management of RA published in 2022.

Real world evidence for DMARD therapy

Conventional synthetic DMARDs

The 2022 EULAR recommendations for the treatment of RA confirmed the central role of methotrexate (MTX), which was defined as the anchor drug, and reiterated the utility of glucocorticoids (GCs) as bridging therapy under the condition that should be rapidly tapered and discontinued consistently

with the patient's response to treatment (2). An issue that was not specifically addressed in the recommendations was the route of MTX administration. A recent systematic literature review and meta-analysis demonstrated that even at higher dosages (between 15 and 25 mg weekly), there were no differences in efficacy and safety between the two administration routes (4). In addition, fewer flares were reported during oral MTX tapering than during subcutaneous MTX in patients in remission treated with MTX plus tumour necrosis factor alpha inhibitors (TNFi). Although the authors had no clear explanation of this, they suggested that the route of administration should be considered when reducing MTX (5). Finally, an observational study that was carried out in patients in the first year of treatment with MTX (98% of them on oral MTX at entry) found a prevalence of adverse events (AEs) similar to previous reports (6).

Regarding efficacy, in an early RA cohort of patients who did not reach the therapeutic target at six months of MTX monotherapy (68% oral), the same grades of improvement were achieved after optimisation of MTX (dose escalation and switch from oral to parenteral administration) and after the addition of a biological DMARD (bDMARD). Unfortunately, no specific analysis has been conducted on the effect of the route of administration alone on disease activity (7). Interestingly, the TREAT EARLIER study demonstrated that MTX was not able to prevent RA onset in a pre-arthritis cohort of patients presenting with arthralgia and a high risk of developing RA (8). However, patients receiving MTX had better magnetic resonance imaging (MRI) and clinical outcomes than those receiving placebo. Very important data emerged also for long-term outcomes from the ESPOIR study that highlighted the importance of early intervention (within 3 months from onset) with conventional synthetic DMARDs (csDMARDs) in 10 year clinical and radiological outcomes (9).

Although the safety and efficacy of MTX are now widely supported by evidence, optimisation of MTX treatment is not universally practiced. In the MITRA study, which included patients with recent diagnosis of RA who started csDMARD therapy, the maximum dose of MTX used was of 15 mg/weekly and was not optimised even in those patients (approximately one-third) that did not reach the target (low disease activity (LDA) or remission) at the end of the follow-up period (10).

Biological DMARDs

The 2022 EULAR recommendations confirmed the well-known role of bDMARDs in the management of RA without establishing a definite hierarchy of different mechanisms of action (MoA) (2). In the case of bDMARD failure, no preference was reported between switching to another MoA or cycling among drugs with the same MoA (2). On the other hand, points to consider in "difficult-to treat RA" (D2T-RA) management suggested to change MoA after the failure of a second or subsequent bDMARDs and particularly after two TNFi failures (11). However, data from randomised controlled trials (RCTs) are still lacking and will probably not be available in the future (12). Several studies, mainly based on national healthcare registries, attempted to address this issue by using real-world data. In an analysis by the British Society for Rheumatology Biologics Register for RA (BSRBR-RA), the first line of treatment with bDMARD, irrespective of the MoA, showed the best results in terms of efficacy, while the second to sixth lines were comparable (13). The TNFi were the most frequently used in the first- and second-line treatments (94% and 60 %, respectively). In addition, the probability of discontinuation, compared with line one, was higher for lines from two to six but was similar across them (13). In the RERCORD study, switching to a non-TNFi (nTNFi) was associated with a significantly lower risk of drug discontinuation, especially for abatacept (ABA), in TNFi-failure patients (14). Moreover, regardless of the use of MTX, the therapy survival rate for second-line TNFi was lower compared to nTNFi. However, the observed difference between the combination of MTX+TNFi and nTNFi was marginal and not statistically significant (14). On the other hand, the CERTAIN study failed to show differences in LDA achievement at 12 months between TNFi and nTNFi for non-responders to the first line of TNFi, while the patients were more likely to respond to nTNFi treatment after a second or further line failure. Furthermore, monotherapy patients were more likely to respond to nTNFi treatment (15). In contrast to 2019, the 2022 EULAR recommendations compared bDMARD and csDMARD tapering in sustained remission after GCs discontinuation. Moreover, the dose tapering or the interval increase ("spacing") were preferred to the withdrawal, as characterised by a lower risk of flare moment (2). A meta-analysis of 22 trials on inflammatory arthritis patients showed a higher risk of flares for either tapering or withdrawal b/targeted synthetic (ts) DMARDs compared to continuation, but an increased number of flares and a higher risk of persistent inflammation in case of withdrawal respect to the tapering (16). In the TapERA trial, patients in remission were randomised to continue etanercept (ETN) weekly or to taper to every two weeks. A decrease rate of remission was registered in the tapering group during the 12 months follow up. Although the number of patients relapsed in the two groups did not differ significantly. Furthermore, at least a third of the patients that re-escalated to the weekly ETN were not able to regain remission, which underlines the need for further evaluations to identify predictors of successful tapering (17). Successful tapering might be optimised offering this strategy to patients with a very low risk of flare, for example based on musculoskeletal ultrasonography combined with other clinical and laboratory markers (18).

JAK inhibitors

The 2022 update of the EULAR recommendations had re-evaluated JAKis in comparison to bDMARDs, highlighting the need for a careful assessment of CV and malignancy risk factors before choosing JAKis (2). Although the recommendations have downgraded the use of JAKis in certain patients, real-world evidence and long-term extension

of RCTs from the past year confirmed JAKis therapeutic effectiveness. A large observational study across 19 national registries evaluated the real-life effectiveness of TNFi, interleukin 6 inhibitors (IL-6i), ABA and JAKis (tofacitinib (TOFA) and baricitinib (BARI)) (19). After 1 year, TNFi, IL-6i and JAKis had a similar response rate in reducing Clinical Disease Activity Index (CDAI), while ABA had a slightly lower clinical response. Drug retention rates were similar across all treatments (19), and consistent with other studies (20). However, JAKis and IL-6i were less frequently discontinued for ineffectiveness compared with TNFi, but were more often discontinued for AEs (19). BARI demonstrated efficacy both in monotherapy in case of MTX intolerance or in combination with MTX (21), with high drug persistence rate and a higher retention rate compared to TNFi (21). Additionally, BARI was less frequently suspended due to reported ineffectiveness within the first year compared with any other drugs except rituximab (RTX) (21), with lower cumulative discontinuation incidence at 6 months in patients initiating BARI compared to those initiating any other tsDMARD or bDMARD (22). Three studies evaluated the efficacy of BARI, upadacitinib (UPA) and filgotinib in inhibiting radiographic progression. One study showed that BARI reduced the radiographic structural damage progression even in patients who continue to have moderate or high disease activity, which could have a high impact in clinical practice, as it could prevent disability regardless of disease activity state (23). Analysis of the SELECT-EARLY and SELECT-COMPARE studies demonstrated that UPA, alone or in combination with MTX, inhibited radiographic joint damage progression through one year (24). Additionally, a *post-hoc* analysis of the FINCH 1 and FINCH 3 trials revealed that filgotinib slowed radiographic progression in RA patients (25).

Another issue in clinical practice is whether to cycle to a second JAKis or switch to a bDMARD after a JAKis failure (26). At the time, there were no established recommendations for the best treatment strategy after JAKis failure (2). The JAK-pot collaboration registries conducted a study to address this issue and found that cycling and switching were equally effective in improving CDAI. However, cycling JAKis resulted in a slightly higher retention rate, even though cyclers were older and had failed more previous treatments. Moreover, cyclers who discontinued the first JAKis due to an AE, were more likely to have the second JAKis suspended for the same reason, whereas this was not observed for switchers (26). As previously noted, JAKis were mostly used in DT2T-RA patients, especially older patients with moderate to high disease activity and longer disease duration, after several treatment failures (27). The FIRST registry aimed to identify the best treatment option for D2T-RA patient and showed that JAKis (TOFA, BARI, peficitinib, and UPA) were associated with the highest proportion of rapid responders and the best outcomes in CDAI reduction, particularly in patients who were not treated with GCs or MTX, compared to TNFi, IL-6i and ABA (28).

Take-home messages

- Available evidence further strengthens the role of MTX as first line therapy in RA. In real life, optimisation of MTX treatment is not always carried out and combination therapy with other drugs is preferred (10).
- In real life, the TNFi are the most used as second line treatment in case of csDMARD failure, but most studies supported the use of nTNFi, particularly for D2T-RA patients (13).
- In case of sustained remission, the reduction of csDMARDs and/or bDMARDs is endorsed by the 2022 recommendations but a pragmatic approach is still lacking. Generally, the tapering or the spacing are considered safer approaches than the withdrawal, both characterised by a lower risk of flare (16).
- The real-world data about JAKis support their therapeutic effectiveness (19). However, beyond their proven efficacy in managing RA patients, the "better to be safe than sorry" approach should be taken into consideration.

Safety of DMARD therapy

Infections

As patients with RA carry a high risk of infections, which is further increased by immunomodulatory drugs, there is still a strong interest in investigating the safety profile of different drugs, with a focus on bDMARDs and tsDMARDs. Besides the overall risk of infections, research has focused on the risk related to specific agents, in particular Herpes Zoster (HZ), which represents a common clinical problem (29). An analysis based on 13,991 patients from the RABBIT register found that patients receiving tsDMARDs, monoclonal TNFi and B cell targeted therapy had higher exposure-adjusted event rate of HZ (respectively, hazard ratio (HR) 3.66 95% CI 2.38–5.63; HR 1.63, 95% CI 1.17–2.28; HR 1.57, 95% CI 1.03–2.40),compared to patients receiving csDMARDs (30). In a nested case-control study, risk factors for HZ infections in patients receiving JAKis were examined. Significant predictors of infections were the number of previous targeted therapies, with three or more determining an odds ratio (OR) of 5.29 (95%CI 1.45–19.31), as well as disease duration (OR 0.54, 95%CI 0.30–0.97). The type of treatment, including JAKis (OR 1.35, 95%CI 0.70–2.61) or GCs (OR, 95%CI 1.36, 0.76–2.45), was not associated with the occurrence of the infection (31).

Mycobacterial infections still represent a concern among opportunistic agents. A retrospective study based on administrative data, registered an incidence of 554/100,000 person-years (PY) of tuberculosis in RA patients treated with a first course of TNFi or tocilizumab (TCZ). Patients receiving infliximab showed a higher rate of tubercular infection (incident rate ratio (IRR) 3.06, 95%CI 1.22–7.69), while other treatments (adalimumab (ADA), golimumab or TCZ) were not related to an increased risk. Among patients who received latent tuberculosis treatment before initiating bDMARDs, no significant differences were observed between drugs, thus supporting the safety of treatment after the institution of a prophylaxis (32). Another analysis of 1,089 patients with RA showed

a similar incidence of non-tubercular and tubercular mycobacterial infection (328.1 and 340.9/100,000 PY, respectively) under TNFi. Compared to subjects not receiving TNFi, treatment with TNFi was significantly associated with an increased risk of non-tubercular mycobacterial infection (HR 1.75, 95% CI 1.11–2.77), with female gender, higher age (50–65 years) and lower charge of comorbidities as potential additional predictors (33).

A further relevant aspect was assessed in a recent analysis based on Japanese administrative databases that reported a higher incident rate of hospitalised infections in elderly patients (9,122 patients aged 65-74, and 6,419 aged more than 75) receiving bDMARDs or tsDMARDs. When analysing the impact of treatment, the OR for hospitalised infections compared to MTX in patients on bDMARDs/tsDMARDs was 1.33 (95%CI 1.04–1.70) in young patients, 0.79 (95%CI 0.61–1.03) in the elderly, and 0.73 (95%CI 0.56–0.94) in the older elderly. This result was confirmed in a secondary analysis on bDMARD users only, confirming the possibility to prescribe this treatment to older subjects (34).

While the greatest interest is raised by research on bDMARDs and tsDMARDs, the risk related to low dose GCs has yet to be fully uncovered. Concerning this, an association between low-dose GCs and infections requiring hospitalisation was detected in a recent analysis of 120,656 RA patients on stable immunomodulatory treatment, receiving low dosage GCs (≤5 mg/day) or no GCs (35).

Malignancy

One of the persistently unsolved problems related to DMARD safety refers to cancer risk, since patients with RA have a greater risk of malignancies *versus* the general population, but the risk carried by DMARDs remains under evaluation. This concern became topical again following the publication of the ORAL Surveillance trial in 2022, which turned on a light on JAKis safety (36). Recently, a *post-hoc* analysis of this open-label, RCT, focusing specifically on malignancy risk (37). Summarising, patients with moderate to severe RA, aged ≥50 years, with at least one additional CV risk factor were randomised to (i) TOFA 5 mg or (ii) 10 mg two times per day (BID) (until major protocol amendment in February 2019, when the TOFA 10 mg BID dose was reduced to 5 mg BID) or (iii) a subcutaneous TNFi. The specific risks of malignancies excluding non-melanoma skin cancer (NMSC) and NMSC were significantly higher for the individual and combined TOFA arms (with similar risks among the two doses) *versus* TNFi. Among TOFA-treated patients, the most frequent subtype was lung cancer, while the risk for breast cancer was similar for TOFA and TNFi. Older patients (≥65 years), ever-smokers, those with a history of chronic lung disease, atherosclerotic CV disease or with increasing CV risk scores were at increased risk of malignancies. Interestingly, the malignancy risk was similar among the study drugs during the first 18 months (HR for combined TOFA doses 0.93, 95%CI 0.53–1.62), and it significantly diverged from month 18 onwards (HR 1.93 95%CI 1.22–3.06), suggesting a time exposure-dependent risk profile.

Following the publication of this trial, an increasing number of real-life studies started focusing on the topic. The STAR-RA trial analysed two large cohorts of RA patients, taking advantage of U.S. insurance claims data (38). The "real-world evidence (RWE) cohort" included RA patients from routine care (83,295 patients), while the second one resembled the inclusion/exclusion criteria of the ORAL Surveillance trial (27,035). In both the cohorts, no significant differences were highlighted for malignancy risk between TOFA and TNFi users. However, mean follow up time was lower than 1 year, with only 10% of the patients followed for more than 2 years, thus a time exposure-dependent effect could not be excluded at all. Nonetheless, these reassuring data were confirmed in other datasets. In the Taiwan National Health Insurance Research Database, with over 3,000 RA patients followed for a mean follow up period of more than 2 years, TOFA carried a non-significantly higher risk of malignancies *versus* TNFi (HR 1.10, 95%CI 0.44–2.78) (39). Similar results were obtained from the Korean National Health Insurance database, with 4,929 RA patients (40). Among 1,064 starting JAKis, of whom 92.5% of the patients used TOFA, the HR for malignancies development was 0.69 (95%CI 0.30–1.56). The authors applied inverse probability of treatment weighting to balance characteristics between JAKis and TNFi groups, but the main result did not change significantly. A population-based cohort study from Sweden, with almost 70,000 RA patients followed for more than 3 years, did not highlight any significant issue with respect to malignancy risk for TNFi-treated with respect to b/tsDMARD-naive patients, as well as for nTNFi b/tsDMARD-treated patients (41). This effect did not change with increasing time spent on active treatment. However, in this study, the number of observed cancer events for JAKis (TOFA, BARI) was too low to allow for meaningful interpretations. As a point to consider, in this study, neoplasm risk with ABA was slightly increased with respect to b/tsDMARD-naive patients (HR 1.2, 95%CI 1.0–1.3).

Cardiovascular disease

One of the most relevant current clinical questions in the treatment of RA refers to the CV safety profile of different JAKis, after the U.S. FDA issued a boxed warning regarding the increased risk of blood clots and death with the use of TOFA. Similarly, on 23 January 2023, European Medicines Agency's human medicines committee endorsed the measures recommended by the Pharmacovigilance Risk Assessment Committee to minimise the risk of serious side effects, including CV events and blood clots, with JAKis (42). These pronouncements were released following the publication of the results of the ORAL Surveillance trial mentioned above. A *post-hoc* analysis from the same trial further evaluated the risk of major adverse cardiovascular events (MACE) in patients with or without a history of atherosclerotic CV disease (ASCVD) (43). In patients with a history of ASCVD (14.7%; 640/4,362), MACE incidence was higher with TOFA 5 mg two times per day (8.3%;

17/204) and 10 mg two times per day (7.7%; 17/222) *versus* TNFi (4.2%; 9/214). MACE HRs were 1.96 (95% CI, 0.87, 4.40) for TOFA 5 mg two times per day *versus* TNFi, 2.01 (95%CI, 0.89, 4.50) for TOFA 10 mg two times per day *versus* TNFi and 1.98 (95%CI 0.95, 4.14) for combined TOFA doses *versus* TNFi. In patients without previous ASCVD, MACE risk did not appear different with TOFA 5 mg two times per day *versus* TNFi (43). A second exploratory *post-hoc* analysis from the same trial examined potential mechanistic biomarkers and pharmacogenomic associations with venous thromboembolism (VTE) (44). None of the selected biomarkers (including levels of antiphospholipid antibodies) was conclusively linked to VTE. Interestingly, difference between the baseline and the 12-month D dimer level was associated with VTE and pulmonary embolism (PE). Notwithstanding this observation, the authors have rightfully exercised caution in interpreting the results, given the low specificity of the test and the inevitable influence exerted by the systemic inflammatory condition.

More recently, in a population-based study including 102,263 RA, patients initiating treatment with TOFA or with TNFi was subdivided into two cohorts: a "real-world evidence cohort" consisting of routine care patients and a "RCT-duplicate cohort" mimicking inclusion and exclusion criteria of the ORAL Surveillance trial (45). The pooled weighted HR for CV events, when comparing TOFA with TNFi was 1.01 (95%CI, 0.83, 1.23) in "real-world evidence cohort" and 1.24 (95%CI, 0.90, 1.69) in RCT-duplicate cohort (45).

At the time of the FDA's boxed warning release, there were no comparable safety studies of other JAKis except for TOFA. This underscored the imperative to scrutinise the safety profiles, especially CV, of individual JAKis in relation to their diverse selectivity. A nationwide population-based cohort study of the French national health data system included RA patients at their first dispensation of a JAKis or ADA (46). Among 15,835 patients, 8,481 were exposed to JAKis and 7,354 were exposed to ADA and the risk of MACEs and VTEs did not significantly differ between initiating a JAKis and initiating ADA. These risks did not significantly differ stratifying the analysis by type of JAKis, TOFA or BARI neither in patients with at least one CV risk factor who were 50 years or older and 65 years or older (46). A second nationwide study assessed the incidence of VTE in patients with RA treated with JAKis (here BARI and TOFA) or bDMARDs (47). In this case, the analysis was performed on 32,737 b/tsDMARD new users between 1 January 2010 and 31 December 2020. The fully adjusted HR with JAKis *versus* TNFi was 1.73 (95%CI, 1.24, 2.42) for VTE, 3.21 (95%CI, 2.11, 4.88) for PE and 0.83 (95%CI, 0.47, 1.45) for deep vein thrombosis (47). Beyond the safety profile of JAKs, over the past year, greater attention has been given to the CV safety profile of bDMARDs. A wide observational cohort study compared the 1-year, 2-year and 5-year incidences of the acute coronary syndrome (ACS) in patients with RA initiating bDMARDs. Comparing the bDMARDs to each other, little differences were observed in ACS rates in the short and intermediate terms. At the 5-year follow-up, initiation of infliximab (HR 1.49, 95%CI 1.08, 2.05) was associated with a moderately increased rate of ACS, while for the other bDMARDs, HRs were close to 1 (48). This reassuring data was also confirmed by similar, or even decreased, risk of MACEs with bDMARDs compared with csDMARDs reported in the systematic review informing the 2022 EULAR recommendations for the management of RA (49).

Take-home messages

- HZ infection was more frequent in patients receiving more intensive immunosuppression, with some patient-related features being associated with a higher risk (30, 31). Mycobacterial infections remain an issue to keep in mind during treatment with TNFi (33).
- Second-line treatment for RA appears to be safe also in the elderly, while an increased risk related to treatment with GCs, even at low dose, should be taken into account (34, 35).
- *Post-hoc* analyses of the ORAL Surveillance trial suggest that the risk of malignancies is higher for TOFA *versus* TNFi. Survival curves specifically diverged following month 18 onwards, while the cancer risk remained similar within that time (37). This time exposure-dependent effect could explain, at least partially, the reasons for non-confirmatory results in real-life studies with JAKis, which usually share shorter follow up periods (38).
- Further monitoring of the malignancy safety of TOFA is warranted, as well as specific safety data regarding the other members of the JAKis family.
- The ORAL Surveillance trial has raised concerns regarding the CV safety of JAKis, however, observational studies conducted in real-life settings over the past year appear to mitigate this risk by providing reassuring data (45, 46).
- The risk of VTE was confirmed to be significantly higher in RA patients exposed to JAKis, even in the context of clinical practice, beyond RCTs (47).

Precision medicine in rheumatology

Predicting through synovial pathology, molecular patterns, and lymphocyte phenotyping

The R4RA, a biopsy-based precision-medicine RCT, has shown convincingly that RA patients with low/absent synovial B cell molecular signature had a lower response to RTX compared with that to TCZ. In the last year, a novel report from this study illustrated in-depth humoral immune response gene signatures in synovium associated with response to RTX and TCZ (50). Post-treatment changes in synovial gene expression and cell infiltration highlighted that RTX responses were associated with antigen presentation, lymphocyte activation and interferon signalling, while in TCZ responders, the myeloid cell cytokine module was upregulated together with peroxisome proliferator-activated receptor (PPAR) signalling and metabolic pathways. Furthermore, a signature involving mainly stromal cells and fibroblasts (*i.e.* a fibroid pau-

ci-immune pathotype) was able to identify multi-drug (TNFi, RTX and TCZ) refractory RA patients. This study provided strong evidence for the notion of 'RA endotypes': diverse molecular pathology pathways in the diseased tissue determine specific clinical and treatment–response phenotypes.

Molecular signatures of response to TNFi were evidenced from repeat synovial biopsies in 46 RA patients before and 12 weeks after treatment with a TNFi. RA patients with robust ACR/EULAR responses to TNFi were characterised at baseline by immune pathway activation, which decreased following TNFi treatment (51). Another clinical trial explored B-cells subsets of RA patients undergoing TNFi therapy with ETN (n=43) or ADA (n=20) for 24 weeks. Interestingly, peripheral blood B cell subsets remained remarkably stable under TNFi and not differentially impacted by ETN or ADA, whilst activated B cells did associate with a less robust response (52). One small open-label study (n=34) aimed to fill the gap of prediction of treatment response to nTNFi bDMARDs. in bDMARD-naive RA patients initiating CTLA4-Ig therapy, baseline IL-6 serum levels ≤8.4 pg/ml and peripheral blood-derived $CD4^+$ subpopulations ($CD4^+CD25^+FoxP3^+$ cell rate ≥6.0) were prognostic biomarkers of more likely DAS remission at 6 months (53). Other data showed a significant reduction of the serum levels of C-X-C motif chemokine 13 (CXCL-13) in a cohort of RA patients treated with ABA, while this variation was not predictive of clinical response (54).

Emerging applications of machine learning to predict treatment-response

The interest in the field of rheumatology in the potentiality of machine learning (ML) algorithms to ease treatment decision-making in the next future is growing exponentially. Combining DAS28 and genomic data comprising 160 single-nucleotide polymorphisms (SNPs) previously associated with RA or MTX metabolism, researchers found intergenic SNPs rs12446816, rs13385025, rs113798271, and ATIC (rs2372536) along with baseline DAS28 scores among the top predictors of MTX response (55). One study developed and externally validated through ML a prediction model for response to MTX within 24 weeks in DMARD-naive patients with RA, using conventional outcome measures data from 775 patients from 4 RCTs. The model provided cut-offs for DAS28-Erythrocyte Sedimentation Rate (ESR) (>7.4) and Health Assessment Questionnaire (HAQ) (>2), along with anti-citrullinated protein antibodies (ACPA) status for clinical decision-making (56). One major limitation was that the study population included only RA patients with very high disease activity (mean DAS28-ESR: 6.5 to 7.6). Again from the R4RA study, the authors developed ML algorithms predictive of response to RTX (AUC=0.74) and TCZ (AUC=0.68). Importantly, the authors could also accurately predict multidrug resistance to several bDMARD classes (AUC=0.69) (50).

Gender, early treatment and therapeutic drug monitoring for more precision

Sex may be an independent predictor of response to RA therapies, with men responding overall better than women with early RA. The NORD-STAR trial was a RCT comparing four treat-to-target (T2T) strategies (MTX+GCs, MTX +hydroxychloroquine+sulfasalazin, certolizumab+MTX, TCZ+MTX and ABA+MTX) in csDMARD-naive early RA patients. A *post-hoc* analysis of the NORD-STAR trial observed numerically higher remission rates in men than in women in all four treatment groups at week 24, suggesting that this generalised sex difference was unrelated to the treatment. The difference between men and women was significantly greater with TCZ than with active conventional treatment that included MTX and GCs, suggesting a possible additional sex-based effect specific to IL-6 blockade (57). Results were replicated by an independent group albeit better outcomes in men were limited to ACPA-negative early RA patients (58).

One study showed that treatment-related factors in the early management of RA could predict drug-refractoriness in the course of the disease. Initiating MTX within 3 months from diagnosis of RA compared to >6 months was associated with significantly reduced risk of D2T-RA (OR 0.3; 95% CI 0.1-0.9), specifically for the persistent inflammatory type. Long-term GCs therapy (*i.e.* given beyond six months) was significantly associated with both inflammatory and non-inflammatory D2T-RA (59). Remarkably, therapeutic drug monitoring has entered the armamentarium of precision medicine in RA with the recently published EULAR points to consider for therapeutic drug monitoring of biopharmaceuticals in inflammatory rheumatic and musculoskeletal diseases (60). According to EULAR, measurement of anti-drug antibodies (ADAs) alongside biopharmaceuticals blood concentrations should be considered in cases of tapering or clinical non-response or drug reactions.

Take-home messages

- Novel reports from the R4RA trial revealed different molecular pathways in the synovial tissue associated with RTX and TCZ response, underlining the notion of 'RA endotypes' (50). ACR/EULAR response to TNFi associated with baseline immune pathway activation in synovial tissue, which decreased after TNFi treatment (51).
- Combining genetic, clinical and immunological data, ML applications showed a potential advantage in response prediction to DMARDs (50, 56).
- Female sex, delay in MTX therapy institution and long-term GCs therapy might help to identify patients refractory to treatment (57, 59).

Latest novelties in the field of vaccinations

COVID-19 vaccines for RA patients with compromised immunity

Vaccination against COVID-19 largely proved to be effective and safe in the general population, while the body of evidence in disease-specific subpopulations like RA is still limited, but consistently growing (61).

In a Danish nationwide cohort study the incidence of COVID-19 hospitalisation

Table I. Medications management and timing considerations for immunosuppressive therapy of interest for RA at the time of vaccine administration according to ACR guidelines (3, 63).

Medication(s)	Vaccinations			
	COVID-19	Influenza	Other non-live attenuated†	Live attenuated^
csDMARDs Methotrexate	Withhold for 1-2 weeks after each vaccine dose	Withhold for 2 weeks after vaccine dose	Continue	Withhold 4 weeks before and 4 weeks after vaccine dose
Leflunomide	Withhold for 1-2 weeks after each vaccine dose	Continue	Continue	Withhold 4 weeks before and 4 weeks after vaccine dose
bDMARDs TNFi, IL-6i	Recommendations were not given	Continue	Continue	Withhold 1 dosing interval before and 4 weeks after vaccine dose
Abatacept	Withold abatacept SC for 1-2 weeks after each vaccine dose. The next dose of IV abatacept should be administered 1 week after each vaccine dose.	Continue	Continue	Withhold 1 dosing interval before and 4 weeks after vaccine dose
Rituximab	The next dose should be administered 2-4 weeks after vaccine dose*	Continue°	Withhold for at least 2 weeks after vaccine dose	Withhold 6 months before and 4 weeks after vaccine dose
tsDMARDs JAK inhibitors	Withhold for 1-2 weeks after each vaccine dose	Continue	Continue	Withhold 1 week before and 4 weeks after vaccine dose

csDMARDs, conventional synthetic disease-modifying antirheumatic drugs; HCQ, Hydroxychloroquine; bDMARDs, biologic disease-modifying antirheumatic drugs; tsDMARDs, targeted synthetic disease-modifying antirheumatic drugs; IV, intravenous; SC, subcutaneous; TNFi, tumor necrosis factor inhibitors; IL-6i, interleukin-6 receptor inhibitor; †Pneumococcal, Hemophilus influenza b, Hepatitis A, Hepatitis B, Human papillomavirus, Inactivated polio, Meningococcus B, Meningococcus ACWY, Tetanus toxoid, Typhoid (injectable), Zoster subunit; ^Influenza intranasal, Measles-Mumps-Rubella, rotavirus, Typhoid oral, Varicella, Zoster, and Yellow fever; *in patients being administered rituximab every 6 months, vaccine dose should be provided before next dose at month 5.0 or 5.5; °give influenza vaccination on schedule and, if disease activity allows, postpone rituximab for at least after 2 weeks after vaccination

for RA was lower in vaccinated compared to unvaccinated patients (vaccinated IR 0.9; unvaccinated IR 10.4) and such decreasing risk suggested a benefit of vaccination in most patients. However, this risk was steadily increased regardless of vaccination status in RA compared to matched controls (62). These epidemiologic data strengthen the well-established practice to encourage unvaccinated RA patients to receive COVID-19 vaccination and patient engagement should be on charge of rheumatology health care provider as it was restated in the newest version of the ACR guidance for COVID-19 vaccination in rheumatic and musculoskeletal diseases (RMDs) patients published in January 2023 (63). Since no additional contraindications to COVID-19 vaccination are known for RA patients and the response to vaccine for those receiving immunosuppressive therapies is expected to be blunted in its magnitude and duration, patients who completed the primary COVID-19 vaccine series of 3 doses should receive supplemental doses (*e.g.* ≥2 additional boosters, for a total of 5 doses) regardless of whether patients have ever experienced natural COVID-19 infection. Then, immunity to COVID-19 postvaccination should not be tested to guide clinical decisions about the need for vaccination. Finally, disease activity and severity should not be considered a limitation to receive COVID-19 vaccination, although the setting of well-controlled RA is advisable. Indications about the use and timing of immunosuppressive therapies in relation to COVID-19 vaccination administration in RMD patients were detailed and a focus on drugs currently used for RA is shown in Table I. Particularly, the need to carefully plan the timing of COVID-19 vaccine administration in relation to the treatment with MTX and RTX was confirmed by the following publications. In an open-label RCT, the antibody responses against the S1 receptor-binding domain (S1-RBD) of the SARS-CoV-2 spike protein was increased in patients who suspend MTX treatment for 2 weeks immediately after their COVID-19 booster compared to patients who continued MTX (64). However, a self-reported disease flare-up was recorded more frequently in patients who suspended MTX compared to who did not both in the first 4 weeks (OR 3.10, 95%CI 1.78–5.40) and after 12 weeks (OR 2.83, 95%CI 1.64–4.88), even though most cases were self-managed and difference in seeking health-care were not significant across the two groups. Further, a cohort study investigated the serological and T-cell responses to spike peptides following two and three doses of SARS-CoV-2 vaccines in 90 RTX-treated RA patients (65). After two doses, a serological response was observed in 22%, $CD4^+$ T-cell response in 53% and $CD8^+$ T-cell response in 74% RA patients. Longer time since last RTX treatment was observed to be associated with serological responses. Finally, the third vaccine did not induce serological response (16%), but boosted the cellular immune response (100%).

Vaccinations other than those against COVID-19

New recommendations on non-COVID-19 vaccinations in patients with RMDs were recently issued by ACR (3). High-dose or adjuvanted influenza vaccination, pneumococcal and recombinant varicella-zoster virus vaccinations were recommended in adult patients taking immunosuppressive medications. The administration of any non-live vaccinations was recommended regardless of patient's disease activity, whilst live attenuated vaccinations should be deferred to avoid vaccine-associated illness. Unambiguous indications were also given about whether to hold immunosuppressive medication at the time of non-live attenuated vaccination to maximise vaccine immunogenicity. The management of timing for the immunosuppressive treatments of interest for RA patients is shown in Table I. Specific recommendations were given conditionally to GCs dosage. In case of equivalent prednisone ≤20 mg daily, administering any non-live vaccinations is recommended, but for a dosage >20 mg daily only influenza vaccination is still recommended while vaccines other than influenza should be deferred until GCs are tapered <20 mg daily.

Take-home messages

- The risk of COVID-19 hospitalisation for RA was decreased in vaccinated compared to unvaccinated patients, but it was steadily increased regardless of vaccination status in RA compared to matched controls (63).
- The hampering effect of treatment with MTX and RTX on immune response to COVID-19 vaccination was confirmed. A 2-week interruption of MTX resulted in enhanced antibody responses after COVID-19 vaccination compared to treatment continuation (64). RTX showed to induce a blunted serological response to COVID-19 vaccination and time since last treatment was associated with the chance of an increased response (65).
- Up-to-date clinical practice guidelines both on COVID-19 and on other vaccinations for RMDs patients were issued by the American College of Rheumatology, providing expanded indications to optimise vaccination strategies (3, 63).

Electronic patient-reported outcomes

Since the COVID-19 pandemic outbreak, remote care has become one of the most discussed topics in rheumatology. The general term "telemedicine" includes not only video or telephone consultation, but also remote disease monitoring with ePROs. Studies using smartphone apps or webpages to register ePROs between in-person visits are expected to increase after the recent publications of EULAR points to consider for remote care in rheumatic and musculoskeletal diseases (66). ePROs could enhance patient engagement and improve efficiency in the healthcare system. In a randomised crossover trial, ePROs [HAQ-Disability Index, visual analogue scale (VAS) -pain, VAS-global health, VAS-fatigue, Patient Acceptable Symptom State (PASS)] collected with a smartphone app were equivalent to those obtained with outpatient touchscreen devices (67). Moreover, 78.3% of the patients preferred the use of the smartphone app to outpatient touchscreens. The data derived from experience during the COVID-19 pandemic in a large cohort of patients with inflammatory arthritis (21,742 RA patients) showed a good percentage of use (nearly 70% during the first 1.5 years) of an online webpage for ePROs entry (VAS-pain, VAS-fatigue, HAQ, PASS) (68).

ePROs can provide rheumatologists with accurate and real-time data on symptoms, disease activity and health-related quality of life outcomes. This information may be useful in defining the follow-up and treatment plan, increasing the effectiveness and personalisation of care. A randomised trial proposed a patient-initiated approach combined with the self-assessment Routine Assessment of Patient Index Data 3 (RAPID3) to monitor RA patients with LDA (69). In the intervention group, patients registered weekly RAPID3 on a smartphone app with a single scheduled outpatient visit at 12 months. Patients were also taught to contact the rheumatologist if necessary and in case of worsening of RAPID3. At 12 months, the combination of patient-initiated care and ePROs self-monitoring was non-inferior to usual care in terms of disease activity (DAS28-ERS) and led to a significant reduction in outpatient visits. A similar approach was adopted in a randomised trial with the addition of a cost-effectiveness analysis (70). RA patients with indication to start DMARD therapy and with DAS28-ERS equal or greater than 3.2 were randomised to receive usual monitoring or smartphone-assisted monitoring with the weekly registration of ePROs (auto-DAS28, RAPID3). In case of RAPID3 greater than 12 for two consecutive weeks, an outpatient visit was scheduled at 3 months and, if necessary, the rheumatologist could schedule an in-person or telephone visit. At 6 months, the smartphone-assisted strategy resulted in lower costs and no significant difference in health status outcomes (quality-adjusted life-years assessed using the EuroQol-5D questionnaire) compared to usual care. A retrospective study evaluated ePROs collected before in-person visits to predict RA patients who did not receive intensification of DMARD or GC therapy in the following two weeks (71). The combination low RAPID3 and negative flare question ("Are you having a flare of your RA at this time?") was found to have a high predictive positive value (PPV 100%) for the identification of stable patients who could skip the subsequent outpatient visit.

While these applications of ePROs seem promising, some issues need to be clarified. First, PROs assessed by the COSMIN guidelines cannot be recommended as outcome measures of RA disease activity, especially due to the lack of evidence in content validity (72). It is therefore necessary to be careful when using ePROs to monitor disease activity. Second, the impact on treatment decisions of the reduction of in-person visits and their potential substitutions with patient self-assessed physical examinations is still unclear (73, 74). Third, long-term adherence and low technological knowledge could be barriers to ePROs use in clinical settings (69, 75, 76).

Take-home messages

- ePROs appears to be comparable and preferable to PROs collected in outpatient clinics and are promising innovations for a new patient-centred approach in the management of RA (67, 69).
- ePRO-guided referral for remote or in-person consultation reported positive results in term cost- effectiveness (70).
- Further studies are needed to assess the validity and efficacy of ePROs in clinical practice.

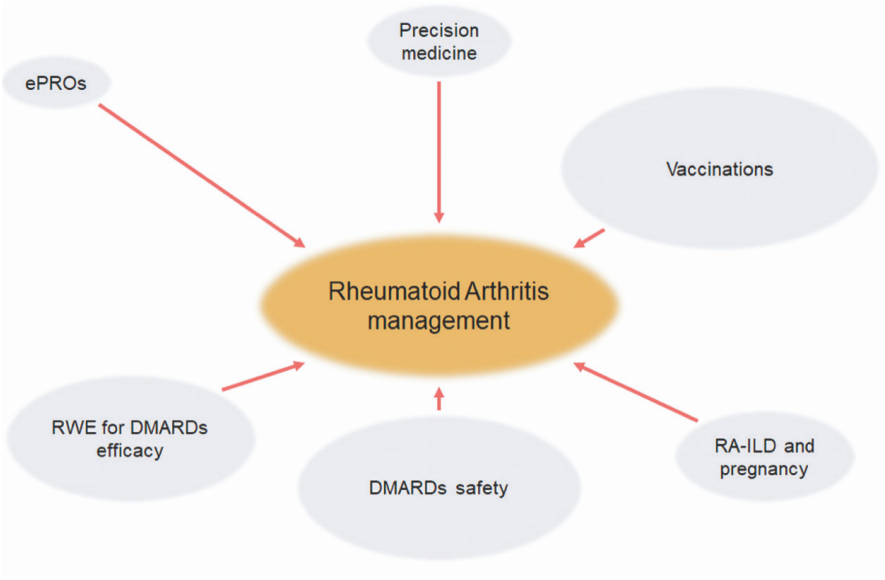

Fig. 1. Graphical synthesis of novelties into management of rheumatoid arthritis (RA).
The relevance is represented by the size of the box, while the actual translational potential is indicated by the distance from the central box.
RWE: real-world evidence; DMARDs: disease-modifying anti-rheumatic drugs; RA-ILD: rheumatoid arthritis associated interstitial lung disease; ePROs: electronic patient-reported outcomes.

Special topics

RA-interstitial lung disease

The role of the rheumatologist in the management of patients with interstitial lung disease (ILD) in the context of multidisciplinary teams is increasingly recognised (77). Despite the paucity of solid evidence, recommendations have been issued on the management of patients with ILD in RA (78). The Spanish inter-society recommendations advise caution in the introduction of MTX in patients with RA-ILD due to the risk of drug-induced acute pneumonia, while support the continuation of treatment in patients already on therapy and with good response to treatment. They also indicate the use of RTX or ABA as preferred second-line drugs, and alternatively IL6-i or JAKis. The use of immunosuppressive therapies for RA-ILD is not recommended, although it may be considered in relation to the radiological pattern. Patients with inflammatory forms [non-specific interstitial pneumonia (NSIP), organising pneumonia (OP)] can be treated with GCs therapy and/or immunosuppressive treatments [mycophenolate mofetil (MMF), ABA, RTX], while antifibrotic drugs (nintedanib) should be added to the DMARD treatment in progressive fibrosing phenotypes.

New evidence is emerging to support the role of immunosuppressive therapy in the treatment of RA-ILD. In particular, a retrospective study included 212 patients with RA-ILD, treated with azathioprine (92), MMF (77), or RTX (43), reports a reduction in 12-month functional progression compared to expected both for forced vital capacity (FVC) (+3.90%) and diffusing capacity of the lungs for carbon monoxide (DLCO) (+4.53%) (79).

Additional evidence supports the safe use of MTX, with also some efficacy data in preventing functional progression of ILD (80). Other drugs of interest such as TOFA confirm their safety in patients with ILD (81), while leflunomide would appear to be associated with a risk of progression in patients with moderate-severe ILD (82). However, the strength of this evidence is weak as it derives from retrospective studies.

Finally, regarding the research of diagnostic and prognostic biomarkers for RA-ILD, the Human epididymis protein 4 (HE4), measured in serum and bronchoalveolar lavage, was found associated with the presence and severity of RA-ILD (83).

Take home messages

- The efficacy of immunosuppressive treatments in RA-ILD is not yet defined, while the use of anti-fibrotic drugs (nintedanib) is recommended in progressive fibrosing forms (78).
- Safety data support the use of cs-DMARDs (MTX) and some b/ts-DMARDs (RTX; ABA; IL-6i; JAK-is) in patients with RA-ILD (80).

Pregnancy

Optimising the treatment of RA in women of childbearing age remains a fundamental theme of patient-centred disease management. Although MTX is the therapy of choice for all RA patients, its use in women of childbearing potential should be carefully considered due to its teratogenic effects but also its potential impact on fertility and pregnancy outcome. A large retrospective analysis on healthcare databases including 3,564 RA patients and 14,256 age matched controls, showed a two-fold excess of pregnancy losses attributable to MTX use (OR 2.22, 95%CI 1.40–3.45) (84). The same study also reported an increased frequency of elective termination of pregnancy (OR 4.77, 95%CI 1.08–19.40) in women exposed to MTX during the conception period.

Over the last year, evidence has also accumulated to support the safety and efficacy of treatment with bDMARDs during pregnancy. A matched cohort study from Sweden and Denmark linking RA data with pregnancy outcomes (1,739 RA pregnancies) compared to the general population (17,390 controls), showed a two-fold excess of preterm birth and small for gestational age. The main determinant of such outcomes related to disease activity (high *vs*. low disease

activity adjusted OR 3.38, 95%CI 1.52–7.55) rather than bDMARD therapy (adjusted OR 1.38, 95%CI 0.66–2.89), being drug-related risk residually confounded by disease activity or severity (85). Another study focused on the relationship between bDMARD discontinuation at the beginning of pregnancy, flare and pre-term delivery analysing the course of 73 women who had a live birth (86). Discontinuation of bDMARDs at positive pregnancy test increased the risk of flare (OR 2.86, 95%CI 1.11–8.3) and flaring associated with an even higher risk of pre-term delivery (OR 4.62, 95%CI 1.03–20.83).
Additional safety data of nTNFi biologics comes from a pharmacovigilance analysis of mixed populations, including RA (87). No special safety signal was identified regarding the occurrence of congenital malformations after exposure to ABA (n=64), RTX (n=57), and TCZ (n=124).

Take home messages

- MTX exposure should always be monitored in patients with RA of childbearing age (84).
- Optimal control of disease activity appears to have some priority over limiting the use of bDMARDs during pregnancy (85, 86) .

Conclusions

In 2022, the most important novelties from real-world data confirmed the primary role of MTX and TNFi in the management of RA. Information on the strategy for switching or cycling DMARDs, although not conclusive, suggested a better efficacy of non TNFi in multidrug-failure patients. However, safety profile is one of the main drivers of DMARD selection and in this regard the JAKis saga is expected to continue over the next few years. Significant findings on response biomarkers to DMARDs, in particular to TCZ, RTX and TNFi, approached the horizon of precision medicine for RA treatment. Additional efforts are required for the validation of ePROs and for the management of RA-ILD. Finally, optimal vaccine coverage for patients with RA is now more achievable thanks to updated vaccination guidelines.

Competing interests

A. Adinolfi has declared fees for consulting from AbbVie, Roche, Janssen outside the submitted work.
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N. Ughi has declared fees for consulting and advisory boards from AbbVie outside the submitted work.
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The other authors have declared no competing interests.

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