Review

Novel insights into the management of rheumatoid arthritis: one year in review 2022

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ABSTRACT

New evidence for the treatment of rheumatoid arthritis (RA) has emerged during the last year. Specifically, updated guidelines on pharmacological and non-pharmacological management of RA have emphasised the necessity of global patient's care, and have shifted the role of some older drugs, such as glucocorticoids and methotrexate. In addition, the long-term safety of Janus kinase inhibitors was investigated and reinforced. With respect to the coronavirus-19 pandemic, reassuring data on the efficacy and safety of vaccinations in the RA population were acquired, as well as on the potential role of telemedicine in RA management. Machine learning prediction models and biomarkers development have emerged as promising innovations in the area of precision/personalised medicine, appearing to encourage future expansion. In this narrative review, the authors aim to give their specific point of view on the most relevant and potentially impacting novelties published during 2021 and early 2022 in the context of RA management.

Introduction

The current treatment options for the management of rheumatoid arthritis (RA) include a wide range of disease-modifying anti-rheumatic drugs (DMARDs), which are administered in a stepwise approach until remission or low disease activity (LDA) are achieved (treat-to-target strategy). However, given the absence of a hierarchy of efficacy or validated predictors of treatment response, the decision of which DMARD to choose is primarily based on safety concerns, economic issues, patient's preferences, comorbidities and other aspects of the disease. Thus, a percentage of patients fails one or more DMARDs, before achieving remission. This trial-and-error approach increases joint damage and economic burden, which is in contrast with efficient use of resources. So, one of the main challenges for rheumatologists is to choose the right drug for the right patient at the right time.

To help clinicians, updated guidelines for the pharmacological and non-pharmacological management of patients with RA have been published by the leading international rheumatology scientific societies in the last year (1-4). New information is now available on glucocorticoids (GCs) and conventional synthetic DMARDs (csDMARDs). Optimising the use of these first-line boundary drugs is crucial to control disease activity, preventing damage accrual and comorbidities. Moreover, a significant amount of data has been published on the safety of Janus kinase inhibitors (JAKis), an important issue in identifying patients eligible for this relatively new class of drugs. Despite this, additional efforts are necessary to achieve true personalised medicine in RA. In this area, machine learning (ML) prediction models and biomarkers adoption are emerging innovations, but still far from being applied in a routine clinical setting. Moreover, in the One Year in Review 2021 (5), limited data were available on the efficacy and safety of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) vaccines in the RA population and in patients treated with DMARDs. Nowadays, the safety of these vaccines has been proven through sufficient studies to encourage their administration in RA patients. Furthermore, since the outbreak of the Coronavirus disease-19 (COVID-19) pandemic, remote medi-

cal systems have gained more and more interest, although it remains uncertain how they should be integrated into the routine care of RA patients.

Therefore, this narrative review aims to summarise the most important innovations published in the field of the treatment of RA during 2021 and early 2022. Here, the authors chose the articles based on the degree of novelty and relevance, and provide their point of view on the most impacting novelties in the management of this systemic condition.

Novelties from international guidelines

New sets and updates of existing recommendations have been presented throughout the year, encompassing the pharmacological and non-pharmacological aspects of the management of RA. The most relevant update on the treatment of RA has been presented by the American College of Rheumatology (ACR) (1), with several novelties compared to the previous set. Methotrexate (MTX) is still the keystone of initial treatment, while hydroxychloroquine or sulfasalazine are recommended in patients presenting with low-disease activity. In this scenario, patient characteristics, such as autoantibody status or bone erosions, are not considered for the selection of the initial csDMARD. The administration of biologic or targeted synthetic (b/tsDMARDs) is still not supported as initial strategy. When starting MTX, oral administration is recommended, while subcutaneous injections are considered only in case of unsatisfactory response or intolerance to oral treatment. With regards to GCs, the ACR recommends their avoidance, even at short term, in the initial strategy, with the only possible placement as bridging therapy when rapid symptomatic relief is needed. Moreover, if the patient is unable to withdraw systemic or intra-articular GCs, a dose escalation or change of DMARD is recommended. The limited role of GCs is due to their detrimental effect on long term and cardiovascular (CV) outcomes. Regardless of the disease phase, a treat-to-target approach is suggested, with LDA as the initial desirable target, while clinical remission can be addressed at subsequent stages. In case of active disease despite csDMARDs, the combination with b/tsDMARDs is supported, while triple csDMARD therapy might be an option in case of contraindication to b/tsDMARDs or limited resources. When patients receiving second-line treatment miss disease control, the change of the mechanism of action is proposed. In patients with stable disease, the maintenance of the ongoing treatment is recommended, but in case of de-escalation dose reduction is advised over the abrupt interruption of DMARDs. Specific patient populations are also mentioned, such as those with stable subcutaneous nodules and lung disease, in which treatment with MTX is supported. Moreover, in active disease with a history of serious infection within 12 months, combination therapy with csDMARDs, rather than b/tsDMARDs, is recommended.

While the ACR recommendations addressed the spectrum of pharmacological treatment, specific points to consider for the use of JAKis across immune-mediated diseases, including RA, have been developed by a multidisciplinary taskforce (6). The current indications of JAKis are confirmed, but in the specific setting of RA the combination with csDMARDs and the possible dose adjustment in case of persistent remission is proposed. Screening for eligibility and the follow-up are also addressed, underlining the unreliability of erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) as inflammatory markers during treatment. After defining difficult-to-treat RA, European Alliance of Associations for Rheumatology(EULAR) has recently released the points to consider for its management (3). The first step is to ascertain inflammatory activity; when this is not verifiable by clinical means, ultrasound is proposed as the instrument of choice. Once inflammation has been confirmed, alternative diagnoses should be considered. In fact, the diagnostic process in the early phases of arthritis might be unreliable, particularly in seronegative disease. Treatment adherence should also be discussed and verified. In presence of comorbidities, in particular fibromyalgia and obesity, which can affect the clinical assessment of the joints, composite measures of disease activity should be interpreted cautiously. When the second b/tsDMARD has failed to achieve disease control, a change in the mode of action and dose optimisation should be considered. Non-pharmacological measures to manage disability, pain and fatigue should be offered, as well as patient education and self-management tools. The increasing interest in the non-pharmacological management of RA is witnessed also by the development of specific recommendations, such as those by EULAR to support self-management strategies in patients with inflammatory arthritis, including RA (2). The aim of this work is to increase awareness among healthcare professionals, who are required to know the available resources, to strengthen the collaboration with patients and focus on patient education. Shared decision-making, self-efficacy and patient organisations are promoted, as well as the active involvement of patients in the pathway of care, with patient education as a cornerstone. Clinical practice throughout the course of the disease should include self-management interventions, digital tools, the promotion of physical activity and healthy lifestyle. Mental health and work-related aspects should also be assessed and addressed. Lifestyle habits and work participation have also been considered by EULAR in specific points to consider (4). These aspects are seen as equally important and complementary to pharmacological interventions to prevent the progression of rheumatic diseases, including RA. Exercise, alone or in groups, is strongly supported, while inactivity should be avoided. Keeping a healthy weight and quitting smoking should be promoted. Patients should also be aware of the increased risk of flares related to alcohol consumption.

Take home messages

- Recent ACR recommendations shift towards less extensive use of GCs with more interest in newer treat-

ments, and support a pivotal role of hydroxychloroquine in LDA RA (1).
- The main novelty is greater attention to the management of specific and difficult populations, and on non-pharmacological management of RA, implying a more active patient involvement. This reflects the will to address comprehensively RA, acknowledging its multidimensionality and aiming at goals that are more relevant to the patient than the simple absence of inflammation (2-4).

Old drugs, new insights

An interesting aspect of the 2021 ACR guidelines for the treatment of RA (1) is that to now, so many years from its approval for the use in RA (1989 in Italy), most of the recommendations on MTX are based on low level evidence or experts opinion and many important questions are still open. One of them is how to taper MTX in case of achievement of remission in combination therapy. In the 2019 EULAR recommendations (7), the task force recommended tapering of bDMARDs before tapering of MTX in contrast with 2021 ACR guidelines that conditionally suggested gradual discontinuation of MTX over gradual discontinuation of the bDMARD or tsDMARD (1). Two studies published in the last year tried to put some light on this issue. Curtis *et al*. (8) run a double-blind, three-arm longitudinal study trying to identify any differences in maintaining remission in patients on stable dose of etanercept (ETN) and MTX, where the first arm discontinued ETN, the second discontinued MTX and the third retained without interruption of any of the drugs. At 48 weeks, the second arm (ETN monotherapy) had a significantly higher percentage of patients without disease worsening than the first (MTX monotherapy). The third group also had significantly higher number of patients in remission than MTX monotherapy group, but not compared to ETN group. Emery *et al*. (9) explored the effect of 52 weeks of MTX withdrawal in patients in remission compared to those that continued with combination therapy of ETN plus MTX, in a *post-hoc* analysis of the COMET study. At the end of the observation period, rates of disease activity score (DAS)28 remission and normal Health Assessment Questionnaire-Disability Index (HAQ-DI) were similar in patients in combination therapy and ETN therapy. Thus, both studies suggest that MTX, rather than bDMARD, withdrawal is more effective to maintain remission. However, the effects of dose reduction or spacing MTX and/or bDMARD on remission maintenance, have still to be explored.

Further, in the ACR guidelines, a cornerstone of RA therapy has been questioned: GCs bridging therapy. According to the 2019 EULAR guidelines (7), short term GC therapy should be considered when initiating csDMARDs. On the other hand, ACR conditionally recommends to avoid short term (<3 months) GCs and strongly to avoid long term (>3 months) GCs in patients with moderate-high disease activity initiating DMARDs. Two studies in the last year aimed to assess the long-term outcomes of the use of GCs as bridging therapy. Stouten *et al*. (10), in the extension of the CareRA study, demonstrated that patients without markers of poor prognosis, who started MTX with bridging therapy, had better disease control and functionality over 5 years than patients in MTX monotherapy. On the contrary, Sapart *et al*. (11), in a retrospective study on patients with early rheumatoid arthritis, found no difference in clinical and functional outcomes at 5 years between patients that received GCs bridging therapy and those that did not. Further, in an analysis of the CorEvitas RA registry, Ocon *et al*. (12) highlighted that the relative CV risk of initiating GCs in a real world setting, in steroids-naïve patients, is associated with a threshold daily dose, cumulative dose and duration of use when analysed over short-term intervals. A daily dose ≥5mg of prednisone equivalents, elevated cumulative dose, and extended duration of use over the preceding 6 months to 1 year period are associated with increased risk of CV events. On the other hand, daily dose <4mg of prednisone equivalents, lower cumulative dose and short duration of administration appear to be safe regarding CV events.

MTX and GCs seem to be under a repositioning process in the RA therapeutic strategy. However, in both cases there are still many grey zones. In real life, MTX is generally tapered and not interrupted in order to find the minimal dose to maintain remission balancing the potential side effects and future studies should aim to assess the best tapering strategy rather than withdrawal. Regarding GCs, in a real-life setting they are also used to provide immediate relief to patients' symptoms rather than to ensure optimal long-term outcomes as acknowledged also by the ACR taskforce (1). Probably the "old but gold" will be still applicable in the near future for these therapeutic options.

Take home messages

- MTX and GCs seem to be under a repositioning process in the RA therapeutic strategy (1).
- In the case of achievement of remission, MTX rather than bDMARD withdrawal appears to guarantee longer persistence of remission (8, 9).
- GCs bridging therapy might not provide additional advantage over csDMARD therapy alone in long-term clinical outcomes, with impact on increased risk of CV events (11, 12).

JAKis safety concerns

Cardiovascular safety

One of the most relevant current clinical questions in the treatment of RA refers to the long-term safety profile of different JAKis. One major highlight concerning the safety profile of JAKis was the publication of the post-marketing phase IIIb-IV study ORAL Surveillance (ORALSURV) (13). This trial was mandated by the Food and Drug Administration (FDA) to better explore a potential increased risk of cancer, CV disease (CVD) events and serious infections observed in the developmental programme in patients who received tofacitinib (TOFA) at 10 mg twice daily. Previously, concerns about an increased risk of venous thromboembolism (VTE) have been raised for baricitinib (BARI) at the dose of 4 mg daily. ORALSURV enrolled 4,362 patients with RA more than 50 years old and at

high CVD risk, who were inadequate responders to MTX. This trial compared TOFA at a dose of 5 mg or 10 mg twice daily with tumour necrosis factor alpha (TNF-α) inhibitors (TNFis) (ETN or adalimumab, depending on the region). The trial primary endpoints were major adverse CV events (MACEs) and malignancies, and the trial was designed as an event-driven, non-inferiority study with regard to these two outcomes (hazard ratio [HR] upper confidence limit ≤1.8). ORALSURV demonstrated an increased risk of VTE with TOFA 10 mg twice daily compared to TNFis (HR 3.52, 95% confidence interval [CI] 1.74; 7.12), while TOFA 5 mg and TNFis were associated with a similar risk of VTE. Moreover, TOFA at both the 5 mg and the 10 mg twice-daily doses failed to demonstrate non-inferiority for MACEs compared to TNFis. The incidence rate (IR) for TOFA 5 mg was 0.91 per 100 patient-years (PY) and for TNFis was 0.73 per 100 PY (HR 1.24; 95% CI 0.81–1.91). Whilst the ORALSURV results will probably affect RA management recommendations, some considerations are mandatory. First, the IR for MACEs in RA patients receiving TNFis in ORALSURV was markedly lower than that seen in prior studies of TNFis, suggesting lower overall CVD risk owing to improved CVD outcomes in RA patients compared to a decade ago. Second, the interpretation of dose-effect on VTE is complicated because all patients on TOFA 10 mg were moved to the 5 mg dosage during the trial; still, their data continued to be analysed as part of the 10 mg cohort. Third, a population-based study of 20,374 RA patients identified from MarketScan, Medicare, and Optum databases and exposed to TOFA did not show an increased risk of VTE compared to TNFis (HR 1.13, 95% CI 0.77–1.65) and VTE events infrequently occurred (<1 per 100 RA patients) (14). Moreover, in a retrospective observational pharmacovigilance study, the analysis of 126,815 Individual Case Safety Reports extracted from VigiBase, the World Health Organisation (WHO) database of adverse drug reactions reporting, documented no significant risk of MACEs associated with TOFA or BARI with respect to the risk in the full database or for other drugs under disproportionality analysis (15). Over-reported "embolism and thrombosis" adverse events (AEs) were ranked the highest for BARI, then TOFA. Fourth, the hypothetical biological pathway by which JAKis could lead to an increased VTE, MACEs or cancer events is uncertain. And fifth, MACEs and VTE occurred primarily in those RA patients sharing traditional risk factors for such CVD events (*e.g.* smoking, obesity). Finally, are CVD issues (MACEs and VTE) a class-mediated effect of JAKis? Might greater selectivity for one or more kinases (*e.g.* those relatively sparing JAK2) improve CVD safety? Concerning the increased risk of VTE, this is unlikely to be substantially increased in those receiving JAKis (TOFA, BARI, upadacitinib [UPA], filgotinib) compared to those receiving placebo (16). One meta-analysis of phase II-III RCTs (n=42; 6,542 JAKis patient exposure years [PEYs] compared to 1,578 placebo PEYs) found that incidence rate ratios (IRRs) of VTE, pulmonary embolism, and deep venous thrombosis in patients receiving JAKis were 0.68 (95%CI 0.36–1.29), 0.44 (95%CI 0.28–0.70), and 0.59 (95%CI 0.31–1.15), respectively, thus not providing evidence that supports the current warnings of VTE risk for JAKis (16). Reassuringly, no signals for increased VTE or MACEs were detected in long-term, open-label extension studies of BARI (17), UPA (18), and filgotinib (19), as well as in a real-world cohort of more than 400 Italian patients treated with BARI (20).

Other safety alerts

Beyond the CV events, JAKis have been associated with several safety risks, including herpes zoster (HZ), serious and opportunistic infections and malignancies. The special attention on this topic is testified by the publication over the past year of three safety integrated analyses and one randomised, open-label, non-inferiority, safety endpoint trial (ORALSURV) with JAKis (13). During a median follow-up of 4.0 years, the incidences of cancer were higher with combined TOFA doses than with a TNFi (4.2% *vs.* 2.9%, HR 1.48 [95%CI 1.04–2.09]). Over a period of 5.5 years, the estimated cumulative probability of cancers was 6.1% with the combined TOFA doses and 3.8% with a TNFi (13). A safety signal was more evident for lung cancer, lymphoma and non-melanoma skin cancer (NMSC), particularly among RA patients who were older, exposed to tobacco smoke and living in North America. Taylor *et al.* described the long-term safety of BARI in RA patients over 14,000 patient-years of exposure in a final integrated analysis including 9 RCTs and one completed long term extension trial (17). The analysis estimated the standardised incidence ratio (SIR) for malignancies (excluding NMSC) and standardised mortality ratio (SMR) up to 9.3 years of treatment. The SIR for malignancies excluding NMSC was 1.07 (95%CI 0.90, 1.26), similar to that expected in the general United States population, and the SMR was 0.74 (95%CI 0.59, 0.92) (17). A second integrated analysis characterised the safety of filgotinib in RA from seven clinical trials that included 3,691 patients, 19% of whom aged ≥65 years, treated for a median of 1.6 years (maximum exposure, 5.6 years in <3% of patients) (21). Infections were more frequent in filgotinib groups versus placebo and the most reported ones were upper respiratory tract infections, nasopharyngitis and urinary tract infections. In the placebo-controlled period, HZ occurred in 5 patients, while in the long-term analysis HZ was higher for filgotinib 200 *versus* 100 mg, especially in the Asian population, and remained stable over-time. Malignancies were uncommon, and exposure adjusted incidence rates (EAIRs) did not increase with time exposed to filgotinib (21). A third integrated analysis evaluated the safety profile of UPA in patients with RA enrolled in five pivotal phase III RCTs (22). Across studies, 3,834 patients received one or more doses of UPA for a mean duration of approximately one year and with a maximum exposure of 2.5 years for a total of 4,020 PY of exposure (22). The most common treatment-emergent AEs

(TEAEs), (≥10 event/100 PY) were upper respiratory tract infection, nasopharyngitis, and urinary tract infections for UPA 30 mg only. Pneumonia was the most common serious adverse event (SAE) reported with both UPA doses. Rates of serious infection were similar between UPA 15 mg and adalimumab but higher compared with MTX (22). Rates of active/latent tuberculosis as well as rates of malignancies and NMSC were generally comparable across treatment groups. UPA 30 mg had higher rates of gastrointestinal perforations, although this was based on a limited number of events (22). In this analysis, the rates of HZ were greater with UPA versus placebo, adalimumab and MTX. A further analysis corroborated the previous observation (23). A total of 5,306 patients were included in this study, the incidence rate of HZ/100 PY (95%CI) was 0.8 (0.3–1.9) in the MTX monotherapy, 1.1 (0.5–1.9) in the adalimumab + MTX group, 3.0 (2.6–3.5) and 5.3 (4.5–6.2), in UPA 15 mg and UPA 30 mg groups, respectively. Disseminated HZ occurred in 12 (5.9%) and 11 (7.3%) patients in the UPA 15 mg and 30 mg groups, respectively. In patients treated with UPA, the Asian region and prior history of HZ increased by more than three times the risk of HZ infection (23). Again on the topic of HZ, a *post-hoc* analysis provides the first detailed description of the outcomes and management using data from TOFA RA and psoriatic arthritis clinical studies (24). HZ was experienced by 11.1% of 7,061 patients with RA who received TOFA with an IR of 3.6 (95%CI 3.4–3.9) per 100 PY, recurrence of HZ was observed in 8.0% of patients with RA. Most of the patients received antiviral treatment within 3 days of onset, 42.8% of the patients temporarily discontinued TOFA treatment (24). Post-herpetic neuralgia developed in 6.9% and 3.2% of patients with RA with first and second events, respectively.

Take home messages

- The ORAL Surveillance study has shown increased risks of heart-related severe events, cancer, blood clots and death with TOFA compared to TNFis (13).
- The reasons why treatment with JAKis could cause venous thromboembolism or major CV events are unclear. Reassuringly, neither observational data from real-life cohorts (14) nor long-term extension studies of randomised controlled trials detected safety signals with JAKis (17).
- JAK inhibitors have been linked to an increased risk of HZ in patients with RA (17, 22, 23). Asian region and prior history of HZ may be associated with an increased risk of HZ infection (23, 24).

Vaccines and RA management

SARS-CoV-2 vaccines

The novel COVID-19 has dramatically affected RA management rules and algorithms during the different waves of the pandemic. The most important novelty in 2021 refers to the availability of vaccines, which heavily influenced the course of the disease and the socio-demographic advertisements. Notwithstanding, people with rheumatic musculoskeletal diseases (RMDs) are often treated with several drugs, which could theoretically put them at risk of either more severe forms of COVID-19 (25), as well as less effective rates of vaccination. Apart from the risk connected to GCs use, as an example, the COVID-19 Global Rheumatology Alliance physician registry has underlined that, in patients with RA treated with b/tsDMARDs, rituximab (RTX) and JAKis are associated with a higher burden of COVID-19 severity and mortality (26). On the other hand, TNFis carry a lower risk of adverse outcomes of COVID-19, in particular when administered as monotherapy (27). Therefore, prioritisation of COVID-19 mitigating strategies during the course of 2021 was endorsed by EULAR as one of the most important strategies to reduce the risk of severe forms of COVID-19 in frail patients (28). First, patients with RMDs should be strongly advised to receive a SARS-CoV-2 vaccination with any of the vaccines approved in their country. Despite a general fear and certain expectations, patient-reported AEs following SARS-CoV-2 vaccination were comparable to those reported in the general population, with rheumatic disease flares requiring medication changes occurring in less than 5% (29), and with no specific concerns regarding a third vaccination with respect to the second one (30). Second, patients with RMDs not using immunomodulatory or immunosuppressive treatment should receive SARS-CoV-2 vaccination preceding a treatment start with such therapy if clinically feasible, in particular before a course of B-cells depleting therapy. However, this second point faces the relevant problem of the optimal immune response in patients already treated with immunosuppressants and, despite an unambiguous clarification has not been provided yet, some literature data provide relevant points to consider related to the interruption, the postposition or the continuation of the ongoing immunosuppressive therapy around the vaccination period.

Pfizer-BioNTech BNT162b2 (BNT162b2) has been the most utilised vaccine in Europe and the first one approved against severe SARS-CoV-2. Since immunosuppressive therapy was an exclusion criterion in the phase 3 trial of BNT162b2, in the mid-2021 clinicians started receiving the first robust real-life data regarding antibody response to vaccines in patients with RMDs. 134 patients from the COPANARD cohort, Denmark, of whom 73 with RA, were included in a prospective study (31) and blood samples for antibodies against SARS-CoV-2 were collected prior to vaccination and 1 week after the second vaccination with BNT162b2. Globally, 23% of the patients had undetectable antibodies against SARS-CoV-2, with similar levels between systemic lupus erythematosus and RA. Specifically, only 4 of 17 (24%) patients on RTX had detectable antibodies levels, suggesting this category of patients should deserve a specific focus on preventive strategies. This was confirmed by a sub-analysis from two prospective cohort studies in The Netherlands including 3,682 RMDs patients, of whom 260 (41%) with RA (32); seroconversion after two doses of SARS-CoV-2 vaccine was lower for individuals treated with RTX with respect to other immunosuppressive treatments

(43% *vs*. >80%). The timespan between last RTX infusion and vaccination, as well as the dosage of RTX (200 mg *vs*. 1000 mg), impacted humoral response, as demonstrated by Van der Togt *et al*. in a large cohort of RA patients using RTX (n=196) (33). This suggests that lower dosages and vaccination delay since last RTX infusion should be encouraged (when clinically feasible). Moreover, a third dose, despite not affecting antibodies levels, can enhance T cells response in RTX-treated RA patients, as measured by the level of anti-wild-type Spike protein $CD4^+$ and $CD8^+$ T-cell responses following a third dose of a SARS-CoV-2 vaccine (34). Although the exact role of T-cell immunity in protection against SARS-CoV-2 infection is rather unclear, it is worth noting that more than half of RTX-treated patients could build T-cell-mediated immunity following vaccination, as demonstrated analysing SARS-CoV-2-specific T-cell responses quantified by interferon-gamma (IFN-γ) enzyme-linked immunosorbent spot assays, and this was independent of peripheral B cells response (35).

Apart from RTX, relevant concerns relate to the combination therapy of biologics with csDMARDs, like MTX. The DECODIR prospective cohort study assessed SARS-CoV-2 antibody levels at baseline and after six weeks following BNT162b2 or mRNA-1273 vaccine (Moderna) vaccines in 243 RMDs patients, of whom 142 (58%) with RA (36). Median immunoglobulin G (IgG) levels in patients on cs/bDMARD combination therapy were significantly lower compared to patients without any DMARD treatment ($p<0.01$), and numerically lower than patients on bDMARD monotherapy. This was a confirmation of a previous report from two independent cohorts of patients with RMDs, which demonstrated that MTX negatively affected either humoral (anti-SARS-CoV-2 IgG levels after second dose) and cellular (activated $CD8^+$ T cells) immune response to BNT162b2 vaccine (37). Moreover, in line with the previously published American College of Rheumatology indications (Version 1 – now updated) (38), in a prospective study enrolling 35 RA patients (none on RTX) following a modification/discontinuation in the ongoing therapeutic regimen during the vaccination period, Picchianti-Diamanti *et al*. demonstrated that antibodies levels after 2 weeks following BNT162b2 vaccination were present in almost all (97.1%) RA patients (39). These data support the notion that temporary discontinuation of MTX can enhance immune response in patients receiving SARS-CoV-2 vaccines. However, clinicians should be aware of the risk of disease flare following even transient interruption of concomitant immunosuppressive treatments, which is possible in particular in case of COVID-19 cases or vaccines administration (40). Second, the entity of seroconversion is different in RA Vs controls, even if a temporary withdrawal of the drug is undertaken. Cytotoxic T-lymphocyte antigen (CTLA)-4 inhibitors and interleukin (IL)-6 inhibitors negatively influenced the titre of anti-region-binding-domain (RBD)-antibodies and T-cell specific responses against spike protein ($p<0.001$) with respect to controls (39), while TNFis impacted mostly on cellular response, suggesting different immunosuppressive treatments differently modulate B and T cell responses to COVID-19 mRNA vaccines.

Other vaccinations

The COVID-19 pandemic has focused attention on the vaccinations in general in immunocompromised with autoimmune diseases, like patients with RA. An important interest was already emerging for vaccinations for influenza, pneumococcus, and varicella zoster (VZV), the latter motivated by the increase in cases of HZ in patients treated with JAKis. New evidence supports the efficacy of 13-valent conjugated pneumococcal vaccine (PCV-13) and HZ vaccines in RA. An open label extension of a phase 2 trial of UPA demonstrated the efficacy 13-valent conjugated pneumococcal vaccine (PCV-13) on seroconversion in the majority (67.5%) of patients treated with the combination of UPA 15mg and MTX, similarly to what already known for other JAKis (41). The combination with MTX appears to be a strong determinant of the decrease in seroconversion, leading to decrease from about 90–95% for patients treated with MTX alone or JAKis alone compared to about 52.5% in patients treated with their combination, while low dose GCs do not affect humoral response (42, 43). The adjuvanted recombinant zoster vaccine (RZV) confirmed its efficacy in a *post-hoc* analysis of >50 and >70 years aged patients with pre-existing immune-mediated diseases, including RA, showing an average vaccine efficacy against HZ of 90% in the mixed population. Given the *post-hoc* nature of the analysis and that immunosuppression was an exclusion criterion of the trials, the real effect in actively treated patients is not yet clarified (44). Conversely the live attenuated zoster vaccine (ZVL) was tested in a RCT including >50 years aged patients on stable disease on TNFis, including a majority (57.6%) of RA (VERVE trial). This large pragmatic trial (617 patients) demonstrated the safety of the ZVL vaccine in patients on TNFis, without an increase of flare in the subgroup of RA, and good humoral response (58.8% at 1 year) over a non-sustained the T-cell response, indicating a potential need of a booster vaccination (45).

Take home messages

- SARS-CoV-2 vaccines should be strongly encouraged in patients with RMDs not yet vaccinated against COVID-19, in particular before starting a new course of b/tsDMARDs, since safety and tolerability of these vaccines in rheumatic patients have been confirmed in observational studies (28).
- RTX hampers humoral response to SARS-CoV-2 vaccination, and lower dosages, as well as delay between RTX infusion and vaccine administration should be encouraged; a third dose of the vaccine appears to particularly enhance cellular response to vaccines in RTX-treated patients (33-35).
- MTX, especially in combination with bDMARDs, impacts as well on humoral and cellular response to SARS-CoV-2 vaccines (37), but un-

ambiguous rules regarding DMARDs postposition or continuation in the context of vaccination lack, specifically considering the risk of flares carried out by treatments discontinuation (40).
- JAKis exposed patients have a satisfactory humoral response to the PCV-13, which is affected by concomitant MTX, but not by low dose GCs (41, 42).
- HZ vaccination by the RZV is a safe and effective vaccine for patients with immune-mediated diseases, but also ZVL may be an option in TNFis-treated patients with stable disease in the absence of an alternative vaccine (43, 44).

Innovations towards the near future

Emerging evidence on telemedicine in rheumatoid arthritis

More than two years of COVID-19 pandemic boosted technological innovation in health services and telemedicine went from a special interest to a matter of fact among RA patients. Although telemedicine entered current daily clinical practice to improve healthcare access, emerging publications on RA management have been still sparse since our last review in 2021 (5). New evidence mainly consisted of observational studies, whilst only one *post-hoc* analysis from a RCT was found. In the Danish pragmatic non-inferiority RCT named Telehealth RA (TeRA), the effectiveness of telehealth strategies for monitoring was tested in 294 RA with LDA or in remission in 2014 and additional analyses on cost-effectiveness have been recently published (45). Patients were randomised into patient-reported outcome (PRO)-based telehealth follow-up by either a nurse or a rheumatologist (interventions) compared to conventional outpatient follow-up (controls). Cost-effectiveness was evaluated using costs per quality-adjusted life-year (QALY) gained and health-related quality of life (HRQoL), indicated by the 5-level EuroQol 5 Dimensions questionnaire, equalised to QALY for a 1-year period. The difference in total costs during the intervention year compared with the year before was lower in the interventions compared to the control, and the difference was statistically significant in the rheumatologist-based group (p=0.047), yet not in the nurse-based group (p=0.7). Moreover, interventions led to lower HRQoL and, when the comparisons were performed as incremental cost-effectiveness ratios, the results of lower costs and a negative effect were interpreted as the cost saved when losing a QALY. However, neither statistical nor clinically relevant difference in disease activity (DAS28) was found between the groups. A limited number of small observational studies consistently reported no apparent differences with regard to PROs when RA patients were followed by telehealth strategies compared to usual care. Prior to COVID-19 pandemic, a cohort of 122 RA patients in Alaska (USA) was prospectively observed over 12 months (46). No significant differences were reported in the proportions of patients in low disease activity or remission as measured by Routine Assessment of Patient Index Data 3 (RAPID3) between those who incorporated telemedicine follow-up (52%) and in-person only (odds ratio [OR] 0.41, 95%CI 0.17–1.04, p=0.06). During COVID-19 pandemic, in a Colombian centre, 218 RA patients were prospectively monitored by following three models based on telemedicine, face-to-face usual care, and a mixed care allowing transitions between the other models (47). No significant differences were observed in the groups regarding functional status (HAQ) and other PROs (patient activity score [PAS], patient general assessment [PGA]). Finally, disease monitoring of 197 RA on stable treatment with a bDMARD or a tsDMARD by telemedicine over a 3-month period was retrospectively analysed in a monocentric study in Italy during the very first outburst of the COVID-19 pandemic (48). No substantial differences between those followed by telemedicine only (n=121) and those who performed at least one in-person visit (n=76) were observed when multiple PROs (general health [GH], visual analogue scale [VAS] pain, functional assessment of chronic illness therapy [FACIT], rheumatoid arthritis disease activity index [RA-DAI], recent onset arthritis disability [ROAD], and PRO-CLinical ARthritis Activity [PROCLARA]) were considered. While awaiting for evidence to accumulate, a list of points to consider on remote care has been recently published by the EULAR to guide the implementation of telehealth for people with rheumatic diseases (49). Tailored care combining remote and face-to-face attendance on the basis of shared decision-making and patient preference was stated as the first overarching principle. Then, telehealth was indicated to be considered as preassessment in the referral process, for disease and drug monitoring, education and in some non-pharmacological interventions including advice on physical activity and psychological treatment. However, diagnosis and disease-modifying drug commencement were suggested to be made in a face-to-face visit. In conclusion, a guidance is now available to improve quality of telehealth and increase healthcare access within rheumatology, but there is still little evidence about the role of telemedicine in the management of RA. If, on the one hand, findings on effectiveness of telehealth strategies on RA are still far from being conclusive, in particular with regard to disease activity control, on the other, telemedicine interventions were consistently not associated with worse PROs or harm to patients with comparison to usual in-person care.

Machine learning prediction models

An increasing number of ML applications have been proposed in recent years for the rheumatology field. The overall enthusiasm for this new computerised analytical technique arises from the benefits it brings to the biomedical field. Indeed, ML algorithms allow to discover associations within huge quantity of data and to use them to make decisions. In this way, ML can classify or cluster patients into labelled or unlabelled groups, respectively, or predict a specific outcome. This technique has been employed in rheumatology for the analysis of electronic health record (EHR), imaging and transcriptomic data, as well as for the investigation of biomarkers and

predictors of treatment response (50). Despite the limitations resulting from its application often in small samples and the use of models not adequately optimised, the ML represents an important innovation in improving RA treatment and personalised medicine. In a retrospective study, the accuracy of different ML-based models was evaluated in predicting the persistence of MTX therapy in RA patients (51). As an exception to the above, a large sample (n=5,475) of RA patients who started MTX monotherapy at the time of RA diagnosis was obtained by combining six different databases with over 4,000 covariates collected. In this cohort, approximately two thirds of patients (70%) retained MTX at one year. In preselected covariates set (n=20), manual logistic regression model and ML models were compared for the accuracy to predict MTX persistence with similar results. Indeed, area under the receiver operating characteristic (AUROC) was 0.66 (95% CI 0.64–0.68) from manual approach and AUROC 0.67 (95% CI 0.62–0.71) from Lasso regression or elastic net, as best performing ML algorithms from the total of five tested. Only ML models were employed in full set of variables and new predictors were identified without significant improvement (AUROC 0.66 95% CI 0.62–0.71). In summary, this article shows the potential of ML in the analysis of big data in RA populations, however this does not actually translate in more accurate prediction with respect to manual logistic regression models. Instead, different use of ML was proposed by Vondecaveric *et al*. to predict the risk of flare in 41 patients with RA who discontinued DMARDs therapy (52). This study employed 4 ML models (logistic regression, naive Bayes, k-nearest neighbours, random-forest) and stacking model, a logistic regression method in which input variables were the results of the other 4 algorithms. The best predictive results were achieved with stacking model (AUC 0.81). The sample size of the RCT was the main limitation of these results, which should be validated in a larger real-life cohort. Another interesting approach was tested by Lim *et al*. to predict MTX therapy response using single nucleotide polymorphisms (SNPs) (53). Out of a total of 53,452 SNPs, 56 potentially-functional SNP (pfSNP) were identified through ML features selection from the exome sequencing of 349 RA patients. Using the same method, five non-genetic features were selected and integrated with pfSNPs in ML prediction models, which were carried out with six different algorithms. Again, the good predictive performance provided by ML models (AUC 0.751–0.826) needs to be validated in a larger sample.

Precision and personalised medicine: myth or reality?

The management of RA is progressively improving over-time and one of the main goals is "to target" as much as possible the therapeutic approach for every single patient. The main prerequisite for this approach is the identification of characteristics linked to a favourable outcome of a certain treatment. These characteristics of interest might be clinical aspects or molecular biomarkers, as well as identified through imaging, allowing for stratification of patients, prediction of response and even for the follow-up of the disease.

A large systematic literature review (SLR) by Law-Wan *et al*. (54) pooled the individual patients' data from 29 RCTs evaluating the effect of clinical and biochemical factors on the TNFis efficacy (compared to the placebo) according to the ΔDAS28(CRP) from baseline to 6 months. This study demonstrated that only the body mass index (BMI) was significantly associated with a higher risk of non-response, while the multivariate models indicated that disease duration and baseline DAS28CPR positively modified the final DAS28CRP, respectively decreasing by 0.02 for each year of disease duration ($p<0.001$) and by 0.21 for patients with a baseline DAS28CRP>5.1 ($p=0.05$) (results confirmed only in one database included). These data are quite surprising as showing that long-standing disease could not be a poor prognostic factor for therapy response. These results contrast with most of the data from the literature and should be further verified in clinical practice. In the attempt to better define the RA therapeutic strategies, the role of the seropositivity for rheumatoid factor (RF) and/or anticitrullinated protein antibody (ACPA) is commonly evaluated. Courvoisier *et al*. (55) pooled the data from sixteen observational RA registries with 26,555 subjects enrolled starting treatment with TNFis, RTX, abatacept (ABA) and tocilizumab (TCZ) to assess the effect of seropositivity for each bDMARD. Seropositivity was mainly associated with reduced discontinuation of ABA and RTX, and remission and LDA rates were higher in seropositive patients than seronegative for RTX, ABA and TCZ. No differences emerged for TNFis. The serological status, furthermore, is a milestone to differentiate clusters of RA patients. Although it is commonly assumed that ACPA-positive and ACPA-negative are different RA subgroups and that ACPA-negative RA is a milder disease, a variable percentage of ACPA-negative patients do not achieve DMARDs-free remission. Verstappen *et al*., retrospectively collecting data from the cohort of Leiden Early Arthritis Clinic, aimed to assess which variables could act in the achievement of DMARDs-free remission for ACPA-negative patients, identifying that a stronger decline of the matrix metalloproteinase-3 (MMP-3), the Serum Amyloid A (SAA) and CRP associated to a sustained remission, while the decline of other biomarkers did not change the outcome. Clinically, baseline higher CRP levels and earlier DAS28 remission significantly correlated with a sustained drug-free remission (56).

Beyond biomarkers, imaging, particularly ultrasound, could help to personalise RA management. Geng *et al*. (57) included ultrasound in the RA follow up, using either a classical treat-to-target (T2T) strategy (target: DAS28 (ESR)≤3.2) or an ultrasound-targeted method (target: power Doppler score equal to 0). This study enrolled 194 RA patients, divided into two groups according to T2T strategy adopted and pointed to identifying the main factors associated to the risk or relapse.

The authors observed that a DAS 28 (ESR)>2.29 and the presence of ultrasound subclinical synovitis correlated with RA flares occurrence, suggesting that a step-down therapeutic strategy should be attempted carefully in these patients. This datum was confirmed in a recent SLR assessing the role of ultrasound when compared to clinical examination in a T2T strategy in RA (58). Ultrasound better predicted disease relapses with respect to clinical examination in patients in remission, while its role in the context of moderately-to-highly active disease is still largely unverified.

Take home messages

- New studies on telemedicine in RA were boosted by COVID pandemic, but the number is still limited and high-quality trials are needed to clarify the effectiveness of telehealth strategies in RA management. A telehealth approach for the management of RA in LDA or remission proved to be cost-effective, but health related quality of life may be negatively affected in these patients as showed in the *post-hoc* analysis of a randomised clinical trial (45).
- Small observational studies consistently showed that telemedicine interventions were not associated with worse PROs compared to usual care or harm to patients, but interventions were heterogeneous as well as the measured outcomes. A guidance on remote care in rheumatic diseases has been published by the EULAR and telemedicine may assist pre-diagnostic processes, monitoring, and some non-pharmacological interventions (49).
- ML applications in the field of rheumatology are growing and it is important to gain confidence with this powerful new analytics tool. While not yet robust enough, results of cited studies suggest a promising contribution of ML in the treatment of RA and personalised medicine (50).
- A "precision medicine model" for RA is still in progress, but it is reasonable that it should include clinical, biological and imaging markers to be feasibly applied in the clinical practice. The identification of new molecular targets remains a priority to improve short and long-time outcomes of RA therapy.

Conclusions

The most important RA management novelties in 2021 and early 2022 referred to new repositioning of old drugs in the context of T2T, as well as in new safety information regarding JAK inhibitors. Further real-life studies will assess the role and the position of GCs, MTX and JAKis in the management rules of RA. Moreover, new data are expected regarding efficacy and safety of SARS-COV2 vaccines in the context of immune system diseases, and in relationship with cs/b/tsDMARDs administration, while whether telemedicine, ML-based algorithms and precision/personalised medicine approaches could dramatically change our clinical paradigms in the treatment of the disease has not yet been demonstrated.

Competing interests

A. Adinolfi received consulting and/or speaker's fees from Janssen Roche, BMS. A. Bortoluzzi received consulting and/or speaker's fees from GSK. A. Giollo received consulting and/or speaker's fees from Galapagos, Novartis, Lilly. G. Sakellariou received consulting and/or speaker's fees from AbbVie, Galapagos, Novartis, Bristol Myers Squibb and SOBI. N. Ughi received consulting and/or speaker's fees from Abbvie, Galapagos, Janssen, Roche. C.A. Scirè received research support form AbbVie, Lilly, and consulting and/or speaker's fees from AbbVie and BMS. E. Silvagni received research support from AbbVie and consulting and/or/speaker's fees from AbbVie, Galapagos, Novartis, Pfizer.
The other authors have declared no competing interests.

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