Review

One year in review 2021: novelties in the treatment of rheumatoid arthritis

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ABSTRACT

Management of rheumatoid arthritis (RA) has evolved over the years as a result of better understanding of the role of different therapeutic strategies, as well as following an increasing availability of new disease-modifying anti-rheumatic drugs. However, the role of patients in sharing decisions, as well as the rules informing precision medicine or the principles to follow in case of specific comorbidities or extra-articular manifestations are still areas for improvement. Moreover, in 2020, the novel Coronavirus disease-19 outbreak has completely changed many attitudes in terms of assessment and treatment paradigms in most clinical diseases, including RA. In this narrative review, the authors report their specific point of view on the management of RA, based on a critical revision of literature published in 2020, focusing on relevant novelties and future research directions.

Introduction

Rheumatoid arthritis (RA) treatment schedules slightly change year by year, specifically in consideration of the growing knowledge on treatment strategies applicable to clinical practice, along with the availability of new disease-modifying anti-rheumatic drugs (DMARDs) and with the awareness of comparative efficacy and safety of already available medications. However, the impact of different therapeutic strategies on RA population health, as well as on the complex dimensions of care and adherence for individual patients, is far from being completely optimised. Moreover, given the increasing number of different drugs with multiple mechanisms of actions, rheumatologists should be conscious of the pros and cons of each individual therapeutic decision. Translational research studies defining biomarkers of treatment choice and response to specific drugs have been performed, but the approach to precision medicine is still incomplete, while the definition of specific clinical contexts in which to apply the recommendations might help in defining the rules of personalised and individualised treatment decisions. Finally, the novel Coronavirus disease 19 (COVID-19) pandemic has completely changed therapeutic algorithms and rules during the last year, with huge impact for patients and clinicians.

Starting from the last annual update on the topic (1), the authors give their specific point of view arising from a critical review of articles published in 2020 on the management of RA, aiming at resuming lessons learned, relevant novelties and future directions.

Rheumatoid arthritis population health: a clue still implementable

In recent decades many discoveries took place, both in terms of novel mechanisms of action of anti-rheumatic drugs, and of effective therapeutic strategies, such as early treatment, tight control, and treat-to-target (T2T). Despite the relevance of these innovations, the process of translational medicine still requires to be effectively translated into clinical practice, improving the health of the population.

Population-based studies, using administrative healthcare databases (AHDs), still report suboptimal indicators of early interventions and strict follow-up. A first paper from Canada, evaluating the frequency of treatment with DMARDs, showed that less than 40% of RA patients (2000-2014) were prescribed with any DMARD, with a significantly higher proportion for patients under rheuma-

tology care (around 60%), with about 60% of patients starting DMARDs within 1 months from the diagnosis (2). An Italian study confirmed these results, with more than 60% starting a DMARDs once diagnosed, of whom 62% within 1 month from the diagnosis (3). In both studies, the frequency of assessments was lower than recommended. The Italian study also developed a composite indicator of adherence to recommendations of early treatment, showing that patients more adherent to early DMARD treatment, with a short-time glucocorticoid (GC) trial and with earlier first re-assessment, carried a significantly lower risk of hospitalisation for RA, independently from demographic and comorbidities variables (3).

Beyond quality of care and clinical outcomes, the experience of care is another relevant dimension to consider. Patients' perception and preferences should be well known to fully understand the effectiveness of therapies. One of the most potentially effective treatment strategies, namely T2T, has a low feasibility in clinical practice. An international study showed that failure of adherence to T2T in patients with low-disease activity (LDA) was highlighted in about 40% of visits (4). The most relevant clinical barriers included high number of comorbidities and increased tender joints count, while seropositivity was a significant facilitator, suggesting that contraindication to treatment upgrade, or low confidence in the presence of synovitis, as well as prognostic-diagnostic uncertainty, led the clinical decision. Also, patient-related barriers do exist, such as patient medication risk aversion, poor patient-physician communication, limitations of disease activity measures, and sub-optimal treatment adherence (5). Patients' involvement in the treatment strategies might be a crucial tool in increasing awareness of T2T principles. An Australian initiative has developed and tested a patient-centred knowledge translation tool for T2T in RA, providing usable information to engage patients in the process of care (6). A Maximum Difference Scaling exercise including patients with inflammatory arthritis from the Netherlands showed that the main factors associated with adherence to treatment were related to reducing symptoms, maintaining independency and shared decision making, while practical issues were least important for RA patients to adhere to medications (7). Similarly, a discrete-choice experiment carried out on RA patients from Sweden compared the relative importance of different dimensions, including effectiveness, safety, and route of administration (8). Overall, effectiveness resulted the most important characteristic, along with safety, to a lesser extent. Notably, patients preferring effectiveness were more willing than others to accept higher risks of side effects. Oral route of administration was preferred over parenteral one, with daily frequency partially counterbalancing such effect. In a Spanish study, about a third of RA patients reported willingness to enter the treatment decision process at the time of the choice of biological (b)DMARDs, in a so-called 'shared decision' approach, although the majority of patients delegated this decision to the rheumatologist (9). Nonetheless, how to operationalise shared decisions in inflammatory arthritis and whether such approach might be favourable in terms of disease outcome along with better care experience is still matter of debate. Patient decision aids (*i.e.* information related to the disease and its treatment options to guide patients in the decision-making) are the most used tools to implement shared decisions making. A proof-of-concept study developed a decision-aid platform using a discrete choice-experiment for the identification of the best first-line treatment strategy (triple therapy *vs.* methotrexate, MTX) (10). The tool mainly helped in clarifying the individual preferences and it utilised a database of existing patient preferences to predict a given individual choice according to a preference profile, with a 72% of accuracy.

Take home messages on RA population health

- The most recent data regarding the global health of RA population indicate that, despite the extensive scientific knowledge on the treatment of RA, the translation of these into the community of patients with RA has not yet took place (2-5) .
- The urgency of the emerging treatment of RA, rather than the availability of new drugs, appears to be to design and implement new treatment delivery strategies, with the involvement of patients to complete this process (6-10).

Targeted synthetic DMARDs: more than only "new drugs"

Janus kinase (JAK) inhibitors (JAKis) are oral targeted molecules (tsDMARDs) having recently emerged for the treatment of RA. In the last year, two new randomised controlled trials (RCTs), FINCH 3 and SELECT-EARLY, have investigated the efficacy and safety of selective JAK-1 inhibitors in patients with active RA with limited or no prior MTX exposure (11, 12). In both trials, JAK-1 inhibitors were superior to MTX in achieving the primary endpoint of American College of Rheumatology (ACR) response. In addition, in the SELECT-EARLY trial, upadacitinib (at 15 mg and 30 mg once daily - OD) was superior to MTX in all efficacy outcomes, including multiple definitions of clinical remission and patient-reported outcomes (PROs). Disease Activity Score at 28 joints - C Reactive Protein (DAS28-CRP) remission was achieved at week 24 in 48% and 50% of patients treated with upadacitinib 30 mg and 15 mg, respectively, compared with 19% in the MTX group (12). Through week 24, the frequency of adverse events (AEs) was slightly higher in the upadacitinib 30mg group than the other groups and three serious cardiac outcomes occurred in the upadacitinib groups (0.47%). In FINCH3 phase III RCT, instead, filgotinib in combination with MTX demonstrated to have a clinically meaningful benefit over MTX monotherapy. Significantly higher proportions of patients receiving filgotinib 200 mg OD plus MTX (54%) and filgotinib 100 mg OD plus MTX (43%) achieved a level of DAS28-CRP lower than 2.6 *versus* MTX (29%) at week 24. However, the proportion of patients achieving ACR20 at week 24

treated with filgotinib 200 mg OD monotherapy did not attain statistical significance *versus* MTX. Over 52 weeks, AEs rates were comparable among all treatments (11). These data, together with the results from the previous phase III studies of baricitinib and tofacitinib, provide further evidence of the clinically meaningful benefit of JAKis over MTX monotherapy in MTX-naïve patients with RA.

The most relevant current clinical question regarding JAKis refers to their long-term efficacy and safety data. Analysis of data from two completed phase III studies, RA-BEGIN (DMARD-naïve) and RA-BEAM (MTX-Insufficient Responders - IR), and one ongoing long-term extension (LTE) study (RA-BEYOND) evaluated the long-term efficacy of baricitinib 4 mg OD in patients with active RA (13). At week 148, Simple Disease Activity Index (SDAI) LDA was achieved in up to 61% of DMARDs-naïve patients and 59% of MTX-IR patients initially treated with baricitinib. After 3 years of treatment, only 3.6% and 10.7% of MTX-IR patients discontinued the treatment across all groups due to lack of efficacy or safety reasons (13). Using b/tsDMARDs as monotherapy in clinical settings is a common practice for patients with RA, and JAKis studies have tried to assess how this issue could be applied in RCTs and real-life studies contexts. In a recent analysis of RA-BEYOND trial, Fleischmann et al. evaluated the long-term efficacy and safety of maintaining baricitinib monotherapy in patients with RA originally treated with baricitinib monotherapy or switched from MTX or from the combination of baricitinib plus MTX to baricitinib monotherapy (14). Baricitinib monotherapy was maintained in 47% of patients through week 24, whereas the remaining patients had background MTX prescribed especially within the first 4 weeks of the study. Patients with lower disease activity at baseline generally continued to do well with baricitinib monotherapy as assessed by Clinical Disease Activity Index (CDAI), SDAI and Health Assessment Questionnaire Disability Index (HAQ-DI) scores. The groups of patients with lower rates of disease control on their original therapy showed sustained or improved disease control with the addition of MTX to baricitinib (14). Preliminary real-world evidence provided valuable insights into the efficacy and safety profiles of JAKis in patients with RA, used as monotherapy or combined with conventional synthetic (cs) DMARDs. A large, multicentre, national cohort (15) including bDMARDs-naïve and bDMARDs-IR patients, of whom 217 (49%) using baricitinib as monotherapy, demonstrated that, using DAS28-CRP as primary outcome, 51.6% of patients achieved remission at 6 months, while 15.9% reached LDA. At 12 months, 64% of patients were in remission and 17% in LDA. The use of concomitant MTX was not associated with significant difference in the frequency of remission or LDA in bDMARDs-naïve and bDMARDs-IR patients. Multivariate regression analysis showed that the hazard ratio (HR) for baricitinib withdrawal due to inefficacy was significantly lower in seropositive patients for both Rheumatoid factor (RF) and anti–citrullinated protein antibodies (ACPAs) or in bDMARDs-naïve. These *post-hoc* analyses and real-life data confirmed that many patients achieved acceptable disease control with baricitinib monotherapy (15).

The comprehensive evaluation of JAKis safety over time is also crucial to better characterise their risk-benefit profile. Winthrop *et al*. provided data on the risk of infection in patients with active RA from the global baricitinib clinical trial programme (16). The incidence rate (IR) was 3.0/100 person years (PYs) with no increased incidence over time, similar to that observed for other JAKis. The higher exposure-adjusted incidence rates of infection were attributed to the upper respiratory tract, herpes zoster (HZ) and herpes simplex (HS) infections. Advanced age (≥65 years), abnormal body mass index (BMI), region of enrolment (Asia, excluding Japan, and rest of world *versus* USA/Canada) and concomitant GCs regardless of dose, were independent factors associated with increased risk of serious infections in all groups. In the programmes there were 11 cases of tuberculosis; all occurred with 4 mg in endemic regions (16). An integrated analysis of tofacitinib with up to 9.5 years of follow-up in more than 7,000 RA patients reported cumulative safety data across 19 completed tofacitinib clinical trials and 2 open-label LTE studies (17). The most common treatment-emergent AEs (TEAEs) by Medical Dictionary for Regulatory Activities system organ class were infections and infestations (56.2% [3,970/7,061]). Overall, 782 (11.1%) patients developed HZ, with an IR of 3.6. IRs (95% Confidence Interval – 95%CI) for malignancies (excluding non-melanoma skin cancer - NMSC), NMSC and lymphomas were 0.8 (0.7–0.9), 0.6 (0.5–0.7) and 0.1 (0.0–0.1), respectively. Venous thromboembolism (VTE) was reported in 0.8% of patients with an IR of 0.3. Major adverse cardiovascular events (MACEs) including myocardial infarction (MI), stroke and/or cardiovascular (CV) death were reported in 85 (1.3%) patients, and IRs were similar for both tofacitinib dosages (17).

Take home messages on tsDMARDs

- Filgotinib and upadacitinib demonstrated efficacy over MTX monotherapy in RA patients with active RA with limited or no prior MTX exposure (11, 12).
- Efficacy outcomes for JAKis were confirmed in long-term extension studies and in real-life studies (13, 15).
- Except for HZ, rates of serious adverse events (SAEs) were generally similar between different JAKis, and globally comparable to bDMARDs (16, 17). HZ vaccination prior to initiation of JAKis, particularly in patients at high risk for infection, should be considered.

Comparative efficacy, safety and costs of different DMARDs: do we know enough?

Comparative efficacy among different drugs approved for RA remains one of the most crucial issues, particularly with the marketing of novel drugs with new therapeutic targets.

A systematic literature review (SLR) (18) investigated the efficacy of pharmacological interventions in RA, with the aim to inform the 2019 update of the EULAR recommendations for RA management (19). The SLR confirmed the high efficacy of csDMARDs (especially MTX) plus GCs in early RA (20), and, in parallel, it confirmed that, among csDMARDs-IR patients, the most efficient therapy is to combine csDMARDs with bDMARDs. The significance of switching among different bDMARDs needs to be evaluated in detail, yet, while a meta-analysis suggested that swapping to non-tumour necrosis factor inhibitors (TNFis) is more cost-effective than switching to TNFis (21).

A phase IV investigator-initiated, randomised, observer-blinded clinical trial, assessing benefits and harms of certolizumab pegol (CTZ), abatacept (ABT) or tocilizumab (TCZ) *versus* conventional treatment in patients with early RA, evaluated the longstanding question regarding whether it is efficacious to start a bDMARD in early treatment-naïve RA patients. Efficacy outcomes showed that adjusted CDAI remission rate at 24 weeks was 42.7% for patients in the active conventional treatment group, 46.5% for the CTZ group, 52.0% for the ABT and 42.1% for the TCZ groups. Conventional treatment reached the non-inferiority outcome compared to CTZ and TCZ, while ABT demonstrated higher CDAI remission rates (22). A large U.S. registry study evaluated comparative effectiveness of TNFis *versus* non-TNFis in b/tsDMARDs-naïve RA patients at 12 months (23). Between 2001 and 2018, 2,965 patients from the Corrona Register were eligible, of whom 2,372 treated with TNFis and 593 with non-TNFis. Despite similar demographic and disease-related characteristics at baseline, more patients in the TNFi group received concomitant csDMARDs. The final results demonstrated no significant differences in efficacy outcomes between TNFis and non-TNFis groups. Similarly, in a pan-European observational cohort of 11,505 bDMARDs-naïve patients (24), the effectiveness of TNFis and TCZ with and without csDMARDs was compared. Despite higher drug retention for TCZ group, CDAI assessment overlapped among groups. With the limitations intrinsic to an observational study, TCZ, both in monotherapy and in combination with csDMARDs is a suitable alternative to TNFis in bDMARDs-naïve patients. The concept of drug retention plays an important role to compare different pharmacological strategies, since it is considered a major index of both effectiveness and safety. A multicentre, retrospective analysis of the ANSWER cohort was designed to evaluate retention rates and reasons for discontinuation of seven bDMARDs and tofacitinib in bDMARDs-naïve and bDMARDs-experienced cases (4,415 treatment courses) (25). Considering bDMARDs-naïve patients, golimumab (GOL) had the highest retention rate among TNFis, while adalimumab (ADA) was superior to infliximab (IFX), CTZ and etanercept (ETA). With respect to TNFis, ABT and TCZ showed higher retention rates, and ABT was considered superior to TCZ. In bDMARDs-experienced RA subjects, instead, ETA was the TNFi with the highest retention rate, while TCZ, ABT and tofacitinib showed higher retention rates compared to TNFis, excluded ETA.

Aside from efficacy outcomes, the establishment of the safety profile of the different classes of drugs is becoming more and more complete, with safety playing an increasingly important role in decisions-making.

A SLR was conducted to investigate the safety of synthetic and biological DMARDs and to inform the 2019 update of the EULAR recommendations for RA management (26). The SLR confirmed an increased serious infections (SIs) risk induced by bDMARDs and tsDMARDs compared to csDMARDs, with an almost overlapping risk between b- and tsDMARDs, apart from HZ, in particular in Japanese and Korean patients treated with tsDMARDs, while the risk of tuberculosis was greater with monoclonal TNFi antibodies. Overall, the risk of malignancies was not increased with b/tsDMARDs, except for NMSC, which was more prevalent with MTX *versus* general population (only one study at moderate risk of bias, with a standardised incidence rate (SIR) of 2.52) and with ABT compared with csDMARDs and TNFis in another study. IL-6 receptor inhibitors treatment confirmed an association with inferior intestinal perforations. MACEs were not increased with bDMARDs compared with csDMARDs, and no difference among bDMARDs was found. Regarding VTE, instead, the RCTs included in this SLR confirmed that tsDMARDs carried an increased risk. For baricitinib a dose-related effect is reported. The SLR also cited an interim analysis of an ongoing open-label study (A3921133); this analysis showed that patients with ≥1 CV risk factor treated with tofacitinib (5mg and 10mg twice daily) had increased chances of developing VTE, compared to TNFis-treated patients. In light of these data, the European Medicine Agency urged caution to use baricitinib and tofacitinib in RA patients with risk factors for VTE. The risk of MACEs and stroke/transient ischaemic attacks induced by cs/b/tsDMARDs in patients with RA, was compared in a SLR by Singh *et al*. (27). TCZ carried a lower risk of MACEs as compared with TNFis (OR 0.59), while csDMARDs demonstrated a higher risk (OR 1.58). Comparative risk of stroke/TIAs was comparable across TNFis and non-TNFis, whereas exposure to csDMARDs was associated with an increased risk, as compared to treatment with TNFis. It has to be underlined that concomitant non-steroidal anti-inflammatory drugs (NSAIDs) and GCs did not have a significant impact on the analysis.

While long-term treatment with DMARDs can be associated with AEs, there is still little evidence to drive the choice to taper or discontinuing treatments. Disease activity and imaging-detected inflammation could be risk factors for the occurrence of flares after ADA tapering or withdrawal. PREDICTRA was a phase IV, double-blind study that randomised 122 RA patients in clinical remission receiving ADA 40 mg every other week to double-blind adalimumab taper (every three weeks) or withdrawal (placebo) for 36 weeks (28). The primary endpoint was the association between the double-blind

baseline hand and wrist magnetic resonance imaging (MRI)-detected inflammation with flares occurrence. Approximately one-third of patients who tapered ADA *versus* half withdrawing it experienced a flare. Time to flare was numerically longer in the tapering *versus* withdrawal arm. Interestingly, baseline MRI inflammation was not associated with flares. None of the baseline disease characteristics or ADA concentration associated with flares after tapering. Moreover, approximately half of the flared patients regained clinical remission after 16 weeks of open-label rescue ADA. The combination of bDMARDs with MTX could improve the success of dose reduction attempts. In the UCLouvain Brussels cohort, relatively more patients receiving a tapered dose were treated with a combination of bDMARDs and MTX (86.7% *vs*. 73.8%) (29). Only 15 patients experienced a flare during follow-up. However, biases of observational design must be taken into account, as well the high proportion of patients receiving TNFis in this cohort (68%). It is also debated whether a clinician should discontinue the bDMARD or csDMARD first. The TARA study showed that DMARD-free remission was achievable in 15% of patients with established RA, and it was slightly more frequent in patients who first tapered csDMARDs (30). However, the order of tapering may not affect flare rates, disease activity or disability. This multicentre single-blinded RCT compared two strategies: the first one consisted of tapering the csDMARD first (mainly MTX), followed by TNFi, the second one consisted of tapering first the TNFi, followed by the csDMARD. 189 patients were randomly assigned to tapering their csDMARD (n=94) or TNF (n=95) first. The cumulative flare rate after 24 months was similar (61% and 62%, respectively), but the patients tapering their csDMARD first were more often able to go through the entire tapering protocol reaching drug-free remission more often than the other group. Similar results were obtained in an open-label RCT by Pope *et al*. (31). Among RA patients achieving a therapeutic response on combination therapy with CTZ and csDMARDs, withdrawing or maintaining csDMARDs led to sustained improvements in both groups at 18 months. However, the non-inferiority of csDMARDs discontinuation was not met. An important question is also whether it is possible to discontinue GCs in the long-term management of RA. The Steroid EliMination In Rheumatoid Arthritis (SEMIRA) trial, a 24-week double-blind, multicentre, two parallel-arm RCT assessed a tapering scheme for GCs in RA. In patients who achieved LDA with TCZ and with at least 24 weeks of GCs treatment, continuing GCs at 5 mg per day for 24 weeks provided safe and better disease control than tapering GCs. However, two-thirds of patients were able to taper their GC dose safely. SAEs were comparable between the two groups, and no patients had symptomatic adrenal insufficiency (32). Finally, gradually tapering either the TNFi or the csDMARD was equally cost-effective (33), but annual costs could be abated with a reduced dose of ADA, ETA and rituximab (RTX).

Take home messages on comparative efficacy and safety of DMARDs

- In csDMARDs-IR patients, an overlapping effectiveness between TNFis and non-TNFis was confirmed, particularly maintaining background csDMARDs therapy. In bDMARDs-experienced RA subjects, especially in case of primary TNFi treatment failure, swapping to another class seems to be more effective, also from a purely economic point of view (18, 21).
- Safety outcomes emerged in recent years are overlapping across DMARDs, but supported by more complete data (26, 27). Regarding CV risk, no major differences emerged among bDMARDs, while more robust data are expected on the correlation between tsDMARDs and VTE.
- Tapering the bDMARD, with or without withdrawing the concomitant csDMARD, is confirmed feasible, even if the specific features (*e.g*. clinical, imaging, biomarkers) of the patients suitable to undergo this tapering have not been univocally depicted so far (28-31). Again, weaning from GCs, particularly for experienced patients, is still difficult for rheumatologists (33).

Precision medicine: a window open to the future

The issue of '*the right drug for the right patient at the right time*' is one the most challenging clues in RA management (19). For several years it has been suggested that the identification of disease phenotypes, or eventually surrogate biomarkers of specific disease clusters, could inform tailored therapeutic use of available DMARDs. At present, however, biomarkers have not fully entered clinical practice in therapeutic decisions making, and there are still great obstacles in reaching precision medicine in RA. The great questions regarding the role of synovial membrane analysis in driving treatment decisions, as well as the possibility to stratify *a priori* the responsiveness to first line 'anchor' drug MTX, and the exact role of biomarkers from serum, remain substantially unanswered.

For the first time in RA, Humby and colleagues (34) have tried to demonstrate the role of synovial membrane evaluation in informing treatment decisions in a biopsy-driven RCT. In this 48-week, stratified, multicentre, open-label, phase IV RCT, 164 TNFis-IR RA patients, after a synovial biopsy in a clinically active joint, were stratified depending on synovial B-cell status (immune-histochemical (IHC) analysis) to receive RTX or TCZ infusions. The hypothesis of the authors was that patients without baseline enrichment in B-cells might have been less responsive to RTX. This trial demonstrated that baseline IHC evaluation of B-cells is not useful to predict clinical response to bDMARDs, since the primary outcome was not reached. In fact, CDAI-50% response at 16 weeks was similar between RTX and TCZ groups. However, if RNA sequencing was performed as adjunctive procedure, patients classified as B-cells poor responded better to TCZ as compared to RTX (RTX 12 of 33 patients; TCZ 20 of 32 patients; difference 26% (95%CI 2–50), p=0.035).

This trial is fore-runner in the application of a precision medicine approach to RA management since, for the first time, it demonstrates in a multi-centre trial the utility of a synovial biopsy-driven approach, and, in particular, an RNA sequencing-based stratification, to justify treatment decisions in refractory RA. These results should be confirmed in independent cohorts, but enter overwhelmingly among the most promising ones to change clinical practice in the future. In fact, despite peripheral blood leukocytes phenotyping could inform on whether a patient will respond or not to TNFis, as demonstrated in a prospective observational pilot study including 98 RA patients starting TNFis (35), the trial by Humby *et al*. (34) further suggests a cautious information on the type of drug the patient is more likely to respond, moving away from the approach common to many studies aimed at identifying biomarkers of non-response to a targeted mechanism (or biomarkers of response to a single mode of action). Again, other studies have tried to depict to which TNFi a patient is more likely to respond, as assessed exploiting a machine learning model to describe 6-months response to ADA or ETA after gene expression and/or DNA methylation profiling on peripheral blood mononuclear cells (PBMCs), monocytes, and $CD4^+$ T cells (36). The adoption of a biopsy-driven approach, however, approximates the most-inner location to depict the inflammatory changes in RA. This is in line with the demonstration that peripheral blood and synovial transcriptomic data significantly differ, as demonstrated by a meta-analysis of gene expression microarray data from synovium, whole blood cells, PBMCs, and $CD4^+$ T cells from patients with RA and healthy controls (37). This dichotomy, with little overlap between compartments, significantly complicates the search for biomarkers of response in peripheral blood, and corroborates the utility of synovial membrane analysis, possibly with a simultaneous evaluation of peripheral blood and synovial cells.

Similarly, given the broadly recommended adoption of MTX as first-line treatment boundary, the possibility to predict clinical response to this drug has been fascinating for many years, in order to define *a priori* which patients are the most likely to proceed to more advanced therapeutic approaches. A recent SLR, aimed at identifying available biomarkers of clinical response to MTX at 3–6 months (38), retrieved 100 different predictors, among which clinical characteristics, genetic predictors, other laboratory markers, and differently-combined predictive models, were enlisted. Only a small proportion of these markers was evaluated in more than one cohort, and external validation of proposed predictive models was performed only in two cases, with low-quality evidence. The results of this SLR highlight that none of proposed biomarkers are presently able to reliably predict clinical response to MTX at individual patient level. Recently, an external validation study on the U-Act-Early trial by Gosselt *et al*. (39), not included in the SLR, suggested that a multivariable model based on clinical, genetic, and biochemical parameters reached similar sensitivity to the validation dataset in predicting clinical response at 3 and 6 months to MTX. Disease activity and functional parameters counted for the most relevant part of the predictive ability of the model. Application of this algorithm in the context of a clinical trial is expected to enable its clinical application. Moreover, it has been confirmed that the adoption of a machine-learning approach is not able to overcome the ability of multivariable logistic regression to predict insufficient clinical response to MTX. In a *post-hoc* analysis of the Rotterdam Early Arthritis Cohort and the U-Act-Early trial, in fact, 355 RA patients starting MTX were evaluated for DAS28 response at 3 months (40), and sensitivity, specificity, positive and negative predictive values were similar between multivariable logistic models and machine learning-derived algorithms using a predictive model mainly composed of clinical variables.

Serum biomarkers are easily obtainable and, therefore, widely studied in search of a precision-medicine approach. These biomarkers should ideally reflect systemic and local disease activity. However, apart from prognosis stratification markers like RF, ACPAs, and acute phase reactant levels, none of them is actually endorsed by international recommendations to make significant changes in treatment schedules (19). The multi-biomarker disease activity (MBDA) score, in the context of a tight-control, T2T-based trial, performed as well as DAS28 in resembling clinical response to MTX when assessed longitudinally (41), while the same score performed poorly in a 16-week, open-label study, either when assessed at baseline and in its longitudinal modifications (42). These studies confirm that MBDA score might not be useful as a baseline predictive index to define treatment response before initiating csDMARDs. Apart from MBDA, other biomarkers from serum were evaluated. In a diagnostic test accuracy retrospective cohort study of RA patients starting ADA and then withdrawing it due to inefficacy or side effects, starting another TNFi or a non-TNFi, anti-ADA antibodies and ADA serum levels were not useful in differentiating responders and non-responders to the subsequent drug (43). Among 1,193 patients in the MOBILITY trial population and 300 patients in the MONARCH trial, baseline serum IL-6 levels were predictive of a greater response to sarilumab at 24 weeks compared to ADA or placebo plus MTX (44). These results, nonetheless, should be confirmed in independent cohort studies.

Take home message on precision medicine

- The results of the presented studies suggest it is time to reconsider biomarkers discovery studies design, focusing on tissue-specific markers in combination with systemic ones. Despite more difficult to retrieve, the former might reflect in a more intimate way the inflammatory burden occurring in the most affected joints of the patient, giving information on the active pathway suitable to be targeted by available drugs. A precision medicine approach in RA, expected since many years, is now believed to be less unreachable than before (34).

Challenging conditions in RA: what clinicians need to know

Despite the great advances having led to a revolution in the level of control of the disease and functional outcomes, there are some situations in different phases of its natural history in which the management of RA remains challenging even for the most expert clinicians (45). First, patients can exhibit specific comorbidities, with possible impact on disease activity, limiting therapeutic options (46). In addition, a subset of patients might be refractory even to advanced treatment strategies, but there is the need to consider the net weight of pain and depression on disease activity outcomes. Again, extra-articular manifestations can complicate RA, while surgery might be necessary, complicating treatment balances difficultly achieved. Many of these issues are still not solved, representing a stimulating field of debate.

Elderly patients

Elderly subjects might be affected because of elderly-onset RA or due to a long-standing disease, diagnosed at a younger age. In both cases, the need to weight the intensity of the treatment against frailty and an increased burden of comorbidities constitutes one main difficulty. Both under-treatment and over-treatment can occur under these circumstances.

An analysis from the British Society of Rheumatology Biologic Registry assessed the efficacy and safety of a first bDMARD line of TNFi, stratifying patients according to the age (< or ≥75 years). Out of 15,700 subjects, 5% were older than 75. While TNFis without background MTX resulted in an increased risk of treatment failure in younger patients, this was not the case in the older population. Moreover, older patients were more likely to discontinue treatment due to AEs, rather than inefficacy, compared to younger subjects (47). Recently, a study based on the Korean KO-BIO registry included 355 patients aged 65 or older, treated with ts/bDMARDs, and a control population of 104 patients receiving csDMARDs, followed for 1 year to evaluate response. The median age was 70 years, and the median disease duration 6.6 years. The proportion of patients achieving LDA or remission was similar in patients receiving ts/bDMARDs compared to those on csDMARDs, however the higher rates of response were seen in patients treated with ABT. Treatments with ABT or TCZ were more frequently related to a good EULAR response (61 and 68%, respectively) compared to TNFis and tofacitinib (43 and 45%). The OR for achieving a good EULAR response at one year was 2.51 for ABT and 3.11 for TCZ, with TNFis as reference. While retention rate at 3 years was 51.6% and AEs represented the cause of one third of discontinuations, there was no significant association between the type of DMARD and AEs (48).

These observational studies support the feasibility of ts/bDMARD therapy in elderly patients, still with a greater awareness of AEs.

Cancer

RA is burdened by a high risk of malignancies, and when cancer or history of cancer are present as comorbid conditions, the choice of treatment, especially the second-line, can be challenging. While data from long-term observational studies do not suggest a relevant increase of the risk of malignancies related to treatment, there is still scarce information on the safety of ts/bDMARDs in patients with a history of cancer. A recent SLR of recommendations has highlighted the relevance of this gap of knowledge. The topic of cancer was touched by 79% of the 39 included recommendations, and although the increased risk of malignancies was mentioned in all papers, the recommended approaches were extremely discordant. In fact, while TNFis were contraindicated in case of lymphoma in all the sets, there was a great heterogeneity in case of solid neoplasms, depending on timing, type of malignancy and treatment (49). De Germay *et al*. evaluated the risk of malignancy during treatment with ABT in a large international pharmacovigilance database. The reference group was constituted by patients on TNFis, without a control group not receiving bDMARDs. ABT was not associated with overall cancer occurrence, although a higher incidence of melanoma was found (50).

Despite the recognised relevance of this topic, the evidences to support treatment decisions are still extremely limited, and do not suggest any safer approach.

Pulmonary comorbidities

The role of the lung at the onset of the disease and as a potential target in the course of RA has been lately under the spotlight. A source of further controversy, however, is also represented by the management of RA in patients with pulmonary comorbidities. In fact, some of these patients carry a higher risk of infection, moreover in clinical trials ABT had been associated with an increased risk of chronic obstructive pulmonary disease (COPD) exacerbation.

A study based on the Marketscan database included patients with RA and comorbid COPD and RA, starting ts/bDMARDs (including ABT) and matched by propensity scores with users of csDMARDs. Adverse respiratory events were defined as severe COPD exacerbation requiring hospitalisation, bronchitis or pneumonia or influenza. 7,424 patients starting a b/tsDMARDs and the same number of matched controls were included. The overall incidence rate of respiratory AEs was not greater in patients receiving ts/bDMARDs compared to those on csDMARDs (51). Kang *et al*. compared the impact of ABT and TNFis in determining severe exacerbation of pulmonary comorbidities (interstitial lung disease - ILD, COPD and asthma) through Medicare and Marketscan. The outcome of interest was the access to the emergency department due to clinical worsening of the pulmonary picture. A large sample of 3,295 patients with ILD, 7,161 with COPD, and 5,613 with asthma was included. IR of exacerbation was higher in COPD than in ILD or asthma. Incident rate ratio (IRR) in patients starting ABT *versus* TNFis was 0.44 for ILD exacerbation, 0.91 for COPD exacerbation, and 0.81 for asthma exacerbation (52).

Although these results support the possibility to use ts/bDMARDs in subjects with pulmonary comorbidities,

the occurrence of exacerbation of the preexisting diseases should be kept in mind. Based on the available data, different profiles for different drugs do not seem to emerge.

Lung involvement - interstitial lung disease

Since the capability of managing joint manifestations has improved, RA-related ILD is emerging as a new difficulty, also taking into account its perceived poor prognosis and the scarce availability of effective treatments. A further aspect is represented by the possible negative impact of drugs on this manifestation.

A cohort study, based on AHDs of a large population of newly-diagnosed RA receiving MTX or sulfasalazine (SSZ), assessed the occurrence of ILD or respiratory failure at 1, 5 and 10 years. Of the 30,512 RA patients identified, 60% received MTX and 109 experienced respiratory failure after 1 year, while 359 after 5. ILD was found in 127 patients at 1 year and 285 at 5 years. There was no association between MTX use and ILD at all time points. Interestingly, MTX associated with a reduced risk of respiratory failure at 1 year and at 5 years (53). Besides the investigation of csDMARDs toxicity, a number of studies have evaluated the impact of some RA-specific drugs on the course of existing ILD. All of these were observational studies, including two studies with retrospective design. A single study included a control group of untreated patients. The compounds of interest were ABT and TCZ (one study each), RTX in two studies, and nintedanib in a small series of 7 patients. All these studies were likely to report positive results of the treatment, however solid conclusions are hardly drawn because of the study design itself. These studies are summarised in Table I.

Increasing data, in line with those published this year, are reassuring regarding the safety profile of csDMARDs and MTX, in particular over the risk of RA-related ILD. Despite an increasing interest on treatment options for these conditions, the strength of the available evidence is limited to support a specific approach. So far, no study has assessed the impact of early diagnosis or intensive management on the occurrence of RA-related ILD.

Refractory RA and unmet needs

Despite timely and intensive treatment, a proportion of patients with RA does not respond to multiple courses of therapy. Considering this point, in 2020 EULAR defined difficult-to-treat RA through a process of consensus as the first step towards the development of recommendations on the management of this condition. Patients are defined as difficult-to-treat when they fail at least 2 ts/bDMARDs after csDMARDs, have signs of active and/or progressive disease (moderate disease activity, clinical, imaging or laboratory signs of active disease, GCs-dependence, radiographic progression, reduction of the quality of life), and if the management of the disease is perceived as problematic by the patient or by the treating physician (54). The identification of patients not responding to standard treatment constitutes a central step in planning further research, however also patients meeting treatment targets may still experience the consequences of RA in different domains. A SLR on the unmet needs in RA included studies applying a T2T strategy and investigated residual symptoms, such as pain, fatigue and functioning in patients meeting the target. The review included 53 studies that applied strategies based on different targets. Patients achieving the target still reported significant functional disability in several studies, as well as residual pain and fatigue. All these symptoms, however, were less relevant in patients achieving clinical remission. Very few studies assessed different symptoms, such as anxiety and depression (55).

The emerging challenge for the next years seems, therefore, to be double: from one side there is a need to optimise treatment by performing strategic studies in refractory patients, but from the other side it seems relevant to address a group of symptoms that are partially unresponsive to pharmacological management and have a relevant impact for patients.

Mood disorders and chronic pain

The reliability of PROs included in disease activity outcomes may be affected by comorbid mental health disorders and chronic non-inflammatory pain, leading physicians to unnecessarily upscale of treatment. The link between mood disorders and inflammation seems to be bidirectional: high disease activity, as well as the distortion of PROs, may have an influence on disease management.

In a retrospective study, an association between bDMARDs initiation or switching and the use of antidepressant and anxiolytic medications was observed during a 2-year period (56). Among 12,002 RA treated with a bDMARD, the proportion of switchers from one bDMARD to another was 13%, and the prescription of antidepressants and anxiolytic medications was documented in 24% and 43% of patients, especially in older age. The introduction and switching of a bDMARD was associated with the prescription of antidepressants or anxiolytics. Similarly, the prescription of antidepressants and benzodiazepine-related hypnotics showed to be increased among 11,693 RA patients before initiation of either a TNFi or a csDMARD in a register-based crossover study in Sweden (57).

The management of residual pain is challenging in the long-term treatment of RA, and it is a major component of remaining unmet needs for RA patients. In a *post-hoc* analysis of the multicentre SWEFOT trial (58), almost one third of 258 MTX-IR RA patients experienced a residual amount of unacceptable pain (VAS>40 mm) despite early treatment. The addition of IFX as compared to the addition of SSZ and hydroxychloroquine (HCQ) resulted in significantly less unacceptable pain up-to 21 months of follow-up. However, the proportion of patients with refractory non-inflammatory pain (*i.e.* unacceptable pain with 28 swollen joint count≤1 in absence of high levels of CRP) was not significantly lower in the IFX group (23% *vs.* 28% in the SSZ+HCQ group) and counted for 82% of unacceptable pain. Thus, the effect of biological treatment with IFX proved to be better than triple therapy

Table I. Relevant studies on the treatment of RA-related ILD.

Study	Study type	Population	Duration of observation	Treatment	Outcome	Results
Fernandez-Diaz (86)	Longitudinal cohort	263 patients with RA-related ILD Median disease duration 9.74 (8.47) years	Median follow-up 12 months	Abatacept i.v. or s.c. (at least one dose)	Pulmonary efficacy and safety Modified Medical Research Council (MMRC) scale, lung function tests and chest HRCT	Clinical assessment: 71.2% stable, 20.7% improvement point on the MMRC scale Lung function test: FVC remained stable or improved >10% in 87.7% of patients HRCT: improvement in 24 cases (18.8%), worsening in 30 (23.4%)
Narvaez (87)	Retrospective cohort	31 RA-related ILD Median disease duration 48 (19-116) months	12 months	Rituximab (1000 mg x 2, every 6 months)	Changes in FVC and DLCO Distance at 6MWT Improvement at HRCT	Lung function test: reverse of the decline of PFTs parameters: Δ%pFVC +8.06%, p<0.001 and Δ%pDLCO +12.7% *p*<0.001 6MWT: increase in the distance covered (from 393 to 4146 m; *p*=0.376). HRCT: 6/18 patients (33%) worsened, 2/18 Improved, 10/18 (56%) were stable.
Vadillo (88)	Longitudinal cohort	68 RA-related ILD, 31 treated with rituximab	Maximum follow-up of 11 years	Rituximab according to clinical practice for RA	Functional respiratory impairment (decline of >5% in the predicted FVC per visit compared with the previous one)	Rituximab exposure resulted in a lower risk of functional respiratory impairment compared with non-exposure [HR 0.51 (95%CI 0.31, 0.85)]
Manfredi (89)	Retrospective cohort	28 RA-related ILD	Median follow-up 30 months	Tocilizumab i.v. or s.c.	Variation of 10% of FVC or DLCO compared to baseline Improvement, worsening or stability of HRCT	FVC remained stable in 14 patients (56%), improved in 5 (20%) and worsened in 6 (24%). DLCO remained stable in 14 patients (56%), improved in 5 (20%) and worsened in 6 (24%). HRCT was stable in 25 cases (89%), worsened in 2 (7%) and improved in 1 (4%).
Narvaez (90)	Longitudinal cohort	7 RA-related ILD refractory to rituximab	6 months	Nintedanib	Relative decline of ≥10% %pFVC or ≥15% in the predicted DLCO corrected for haemoglobin, or a relative decline in the %pFVC of 5-10% or <15% in the DLCO corrected for haemoglobin, as well as a worsening of respiratory symptoms and increased fibrosis at HRCT.	Nintedanib as an add-on treatment to immunosuppressive therapy was able to reverse the decline of lung function parameters, achieving stabilisation.

i.v.: intravenous; s.c.: subcutaneous; HRCT: high resolution computer tomography; MMRC: Modified Medical Research Council; FVC: forced vital capacity; DLCO: carbon monoxide diffusing capacity; 6MWT: 6-minute walking test.

on residual pain, but its inflammation-independent component may still need to be targeted in the long term even though early anti-inflammatory approach are implemented.

Chronic pain in arthritis may be multifactorial: inflammation-dependent joint degeneration along with the coexistence of comorbidities, as well as abnormalities in pain processing, may require a comprehensive strategy based on analgesics ahead of anti-inflammatory medications. Since the management of chronic non-malignant pain became more liberal, the first-line use of NSAIDs has been increasingly combined with opioids to treat refractory pain and to reduce the risk of gastrointestinal, CV, and renal side effects related to NSAIDs. The prescription of opioids was increased also in the management of early inflammatory arthritis before diagnosis, as reported using national public registry data on 12,115 adult patients with either seropositive RA, seronegative RA, or undifferentiated arthritis in Finland (2010–2015) (59). Opioids were used at least once by a quarter of patients and the prescription rate increased before the diagnosis, but decreased rapidly after it. Moreover, opioid exposure seems to be increased in RA, especially in case of history of mental health conditions, as reported in a large retrospective cohort of veterans in the United States (60), where 38.3% of patients (n=8,607) had both RA and mental health conditions. A significant association was observed between chronic opioid therapy and history of mental health conditions, benzodiazepines and non-benzodiazepine sedative hypnotics, selective serotonin reuptake inhibitors, and antipsychotics. Notably, chronic use of opioids was associated with both previous non-opioid substance and opioid use disorders. These findings suggest that opioid prescriptions should be carefully planned, particularly if patient's history is positive for mental health conditions and prior substance use.

In summary, the initiation and switching of bDMARDs may be associated with increased usage of psychotropic medications for depression and anxiety, but reduced usage after the start of the new treatment. Anti-inflammatory drugs, including DMARDs, proved to be effective on RA pain, but the residual amount of refractory pain still needs to be targeted by alternative analgesic strategies, and the use of opioids should

be considered carefully in light of comorbid mental health disorder and prior substance abuse.

Surgery outcomes in RA patients

A significant proportion of patients with RA undergo total joint replacement (TJR), mainly due to secondary osteoarthritis (OA). How to manage concomitant drugs during perioperative periods is still matter of debate.

The number of TJRs decreased from the approval of biologics, and relevant changes were observed in the characteristics of RA patients undergoing TJR. Control of inflammation, disease duration and age were independently associated with time from RA onset to TJR (61), suggesting that improvement in the management of RA in the past 20 years has impacted TJR. Surgical site infections after knee and hip replacement are more frequent among patients with RA, possibly related to immunosuppressive drugs. However, surgical site infections are not associated with ongoing medication with DMARDs in patients with inflammatory joint disease (62). Data from 494 primary elective hip and knee arthroplasties (32% TNFis) showed that the rate of surgical site infection was 3.8%, and the rate of periprosthetic joint infection was 1.4%, all of which occurred after knee arthroplasty. Periprosthetic joint infection occurred in only one patient medicating perioperatively with a TNFi. Limitations of this study include the low event rate, and the majority of patients on TNFis as bDMARDs. Whether mechanisms different from TNF inhibition are related to perioperative infection is unclear. Compared with csDMARDs and/or GCs without ABT, adding ABT to the treatment did not appear to increase the incidence rates of post-operative AEs in patients with RA undergoing orthopaedic surgery (63). Patients receiving ABT were matched individually with patients receiving csDMARDs or GCs. No between-group differences were detected in the IRs of each AE or in the IRs of total AE (control *vs*. ABT: 15.5% *vs*. 20.7% in total, 5.2% *vs*. 3.1% for death). In RA patients treated with TCZ from the French registry REGATE, the rate of surgical complications was low, as well (64). Only 8.6% of patients had complications with 10 severe infections, including 5 surgical site infections (33.3%). In multivariate analysis, previous treatment with RTX during the last year tended to be associated with post-operative complications. Concerning post-operative infections, diabetes mellitus tended to be associated with this complication. Finally, the median time between surgery and last infusion was relatively short, according to the half-life of TCZ (approximately 5 weeks), but this did not influence the rate of post-operative complications.

As a way of resuming, currently approved DMARDs seem to be safe in relation to orthopedic surgery, with no red flags emerging for any of the drugs.

Efficacy and safety of traditional Chinese medicine and Western medicine

Over the years, several botanical resources have been proposed by traditional Chinese medicine (TCM), which might have a positive effect on both symptoms and disease progression. Among the most used medicines of botanical origin used for RA, Tripterygium wilfordii Hook. f., Aconitum carmichaelii Debx., Curcuma longa L., Guizhi-Shaoyao-Zhimu Decoction, Xinfeng capsule, and a novel antioxidative and anti-inflammatory formulation prepared from the ethanol extracts of Artemisia asiatica (DA-9601) are enlisted. Xing *et al*. performed a meta-analysis, comparing efficacy and safety of integrated therapy of TCM and Western medicine (WM) for RA (65). Based on the review of 20 included RCTs, it has been observed that patients with integrative TCM-WM treatment have achieved better outcomes compared to patients receiving WM treatment alone, both in terms of disease activity and AEs. Reduction in DAS28 was higher for the TCM-WM compared to the WM treatment group. The meta-analysis shows how the integration of WM and TCM can guarantee not only effectiveness, but also a better therapeutic adherence considering the reduction of side effects related to csDMARDs. However, it is hard to imagine how much these findings could impact on western attitudes in treating RA subjects.

Novel Coronavirus disease-19: impact on RA treatment

The COVID-19 has impacted dramatically on RA treatment. Since immunemodulating drugs are known to increase the risk of viral and non-viral infections, there has been an urgent need to understand whether the use of RA medications is safe during the COVID-19 pandemic (66-72).

Italy was one of the first countries significantly affected by the COVID-19 pandemic. The Italian Society for Rheumatology promptly launched a retrospective and anonymised data collection to monitor COVID-19 in patients with rheumatic diseases, the CONTROL-19 surveillance database, which is part of the COVID-19 Global Rheumatology Alliance (73). Preliminary data from the first 232 patients (RA patients representing 34.1% of the study population) showed that immunomodulatory treatments were not significantly associated with an increased risk of intensive care unit admission/mechanical ventilation/death. However, the report mainly included the most severe cases occurring before 3rd May 2020. One year later, we have known that the impact of rheumatic diseases on COVID-19 severity could be related to disease severity, treatment, or both (68). In hospitalised patients with rheumatic musculoskeletal diseases (RMDs), having a connective tissue disease (CTD) but not chronic inflammatory arthritis (CIA), nor previous immunosuppressive therapies, was associated with severe COVID-19 (74). In the first published matched-cohort study by Pablos and colleagues, 456 non-rheumatic controls were randomly sampled 1:1 and matched by age, gender and polymerase chain reaction (PCR)-date to hospital PCR+ COVID-19 rheumatic patients with CIA (60%) or CTDs (40%). The primary outcome was severe COVID-19, defined as death, invasive ventilation, intensive care unit admission or serious complications. Most patients (74%) had been hospitalised, and the risk of severe COVID-19 was 31.6% in the rheumatic and 28.1% in the non-rheumatic cohorts. In logistic regression analysis, independent factors associated with severe COVID-19 were increased age,

male sex and having a CTD, but not previous immunosuppressive therapies. The use of immune-modulating medications as a risk factor for COVID-19 severity was assessed by a meta-analysis of observational and case-controlled studies of patients with autoimmune diseases (75). Patients with autoimmune diseases had an increased risk of COVID-19, primarily attributed to GCs use. b/tsDMARDs monotherapy was associated with a lower risk of severe COVID-19, suggesting its safety in the COVID-19 pandemic. Meta-regression analysis showed GCs were significantly related to the risk of COVID-19. Again, GCs, csDMARDs and b/tsDMARDs plus csDMARDs combination therapy increased the rates of hospitalisation and mortality, whereas b/tsDMARDs monotherapy, particularly TNFis, were associated with a lower risk of hospitalisation and death.

Although many immune-modulating therapies do not increase the risk of severe COVID-19, GC use has been associated with hospitalisation and poor outcomes due to COVID-19. Data from a German cohort including 468 patients with rheumatic diseases with SARS-CoV2 infection (48% RA) showed that age and current or prior treatment with GCs in dosages higher than 5 mg/day were significant risk factors for hospitalisation, as well as other comorbidities such as CVD, ILD/COPD, chronic kidney disease (76).

Patients with RMDs were more likely to be admitted with COVID-19 than the general population. Danish patients with RMDs (n = 58,052) had an increased partially adjusted incidence of hospitalisation with COVID-19 compared with the 4.5 million people in the general Danish population, with the strongest associations for patients with RA and vasculitides. There was no increased incidence of COVID-19 hospitalisation associated with TNFis, HCQ, nor GC use. COVID-19 admitted patients with RA also had a slightly higher HR for a severe outcome (77).

Take home messages on COVID-19 impact on RA management

- More research is needed to disentangle the relative contribution of inflammatory burden and disease activity over GC use to affect the outcome of COVID-19 severity in patients on active treatment for RA (73-75). While the unfavourable association between GCs use and COVID-19 outcomes has also been shown by data from the Global Rheumatology Alliance (71, 72), more intense immune-suppression with RTX, but not TNFis, associated with mortality, suggesting that some mechanisms could be more harmful than others.
- Clinicians must take into account that moderate to high rheumatic diseases activity was also an independent risk factor for hospitalisation, underlining the importance of continuing adequate treatment during the pandemic (76).

Telemedicine in RA: myth or reality?

According to the definition of the World Health Organisation, "telemedicine uses information and communication technologies to overcome geographical barriers, and increase access to health-care services". The interest in telemedicine for patients suspected for or diagnosed with RA is not recent and, in 2020, it increased in reason of the spread of COVID-19 pandemic and its effect on health-care access.

Novel publications focusing on telemedicine for the improvement of RA management have been surprisingly sparse, so far. In a Cochrane systematic review updated until July 2019, out of 19 trials with different conditions, only 1 focused on 85 RA patients who were randomised to the intervention (video-consultations between physical therapist and rheumatologist in the presence of the participant) or to usual care (*i.e.* in-person visits at rheumatology clinics) and monitored for 9 months (78). Little or no difference between groups were reported for disease activity and health-related quality of life (Table II). Notably, more than 40% of participants withdrew in the intervention group due to patient's preference for travelling into town for in-person appointment. The certainty of evidence was graded as low and the overall confidence in the effect estimates was judged to be limited. In another RCT on 94 DMARDs-naive RA patients with high-to-moderate disease activity, participants were monitored either by using a smartphone application as the intervention, or by conventional visits as control over 6-months of follow-up (79). The primary endpoint of the reduction of the number of intermediate physical visits in the intervention group was reached (4.4% *vs*. 86.4% in the control group had at least two physical visits), and no differences were detected in the secondary outcomes of disease activity (Table II). Conversely, the number of phone-call visits was significantly higher in the intervention group and the total number of visits (sum of in-person and phone-call visits) was not different between the groups. Finally, in a third RCT, 166 early DMARDs-naive RA were monitored over 12 months by enhancing the follow-up with text messages via short message service (SMS) every other week in the first 6 months against the usual care as control group (80). In most cases, a combination of csDMARDs was started and the rate of disease remission according to Boolean definition was not different between the two groups at 6 and 12 months. Changes in disease activity, quality of life, and patient's confidence to the treatment were not significantly different between the intervention and the control. Conversely, the number of nurse's telephone contacts was higher in the intervention group, whilst no differences between the groups were reported in terms of physician's contacts and unscheduled visits.

Take home messages on telemedicine in RA

- Regular monitoring by a healthcare professional is pivotal to adequately manage the evolving disease activity in RA patients and telemedicine could play a role. However, despite the growing interest in response to urgency of the COVID-19 pandemic, telemedicine applied to RA is still largely under-investigated. Data from 3 randomised controlled trials showed no differences between the use of information and

Table II. Experimental studies on the use of telemedicine to support the management of care of patients with RA.

Study	Study type	Trial registry* (I)	Intervention	Comparison (C)	Participants	Setting	Primary endpoint	Effect estimate	Secondary endpoints
Taylor-Gjevre 2018 (91)	RCT	NCT02371915	Video-consultations between physical therapist and rheumatologist	Usual care, *i.e.* in-person visits	85 (I:54 / C:31)	1 urban clinic, 5 rural clinics (Canada)	Reduction of DAS28-CRP (9 months)	MD 0.9 (95% CI, -1.2-3.1), p=0.33	mHAQ (MD 0.2, 95%CI -0.1-0.5, p=0.14) RADAI (MD 0.9, 95%CI -0.5-2.4, p=0.19) EQ5D (MD -0.1, 95%CI -0.4-0.1, p=0.29)
Pers 2020 (79)	RCT	NCT03005925	Connected monitoring interface on a smartphone by "SATIE-PR" application	Usual care, *i.e.* conventional monitoring	94 (I:48 / C:46)	1 Rheumatology clinic (France) (6 months)	Reduction of consultations	I: 0.42 *vs*. C: 1.93, p<0.05	Number of phone-call visits (I: 2.67 *vs*. C: 0.41, p<0.01) DAS28 (MD, I: -1.37 *vs*. C: -1.48, p=0.63) HAQ (mean, I:0.56 *vs*. C: 0.78, p=0.04) RAPID-3 (p=0.25) SF-12 (mean, PCS, I: 40.2 *vs*. C:35.6, p=0.14; MCS, I: 41.8 *vs*. C:39.3, p=0.35)
Kuusalo 2020 (80)	RCT	NCT02424877	Text message (SMS)–enhanced monitoring by "SandRA" software	Usual care, *i.e.* routine follow-up	166 (I: 84 / C: 82)	6 Rheumatology clinics (Finland)	Boolean-based definition of remission (6 months)	I: 51% (95% CI 40-62) *vs*. C: 42% (95% CI 32-53), p=0.34	Remission at 12 months (I: 57% *vs*. C: 43%, p=0.17 DAS28 at 6 months (mean, I: 2.18 *vs*. C: 2.21, p=0.18) DAS28 at 12 months (mean, I: 1.79 *vs*. C: 2.08, p=0.28) SF-36 at 6 months (MD, PCS, in favour of the intervention, p=0.04)

*ClinicalTrials.gov identifier. RA: rheumatoid arthritis; RCT: randomised controlled trial; MD: mean difference; CI: confidence interval; DAS28-CRP: 28-joint disease activity score with C-reactive protein; mHAQ: modified Health Assessment Questionnaire; RADAI: Rheumatoid Arthritis Disease Activity index; EQ5D: EuroQol 5 dimensions questionnaire; RAPID-3: Routine Assessment of Patient Index Data 3; PCS: Physical health composite score; MCS: Mental health composite score; SF-12: Short-Form 12; SF-36: Short-Form 36.

communication technologies and usual care with regards to disease activity and quality of life in RA patients (78-80).

- The real advantage for RA patients still needs to be elucidated in the face of the unclear optimisation of the use of the health-care resources. Nevertheless, the field of telemedicine applied to RA patients seems to be promising and further studies are expected to be performed in the short-to-medium term in response to the new health care needs prompted by the COVID-19 pandemic.

Safety and efficacy of vaccines in RA: still unsolved problems?

Patients with RA are at increased risk for infections resulting in significant morbidity and mortality compared to the general population. Vaccines are effective for prevention of infectious diseases, but their uptake is known to be suboptimal in RA, while their efficacy and safety are still matter of debate due to the concerns about the impaired immunological response and the risk of recrudescence of the disease.

In 2020, two RCTs on influenza vaccines in RA were published, and the high-dose trivalent influenza vaccine (HD-TIV) was compared to the standard-dose quadrivalent influenza vaccine (SD-QIV) to assess immunogenicity and safety (81, 82). In the first large study (81), among 248 RA patients included, those who received HD-TIV were more likely to seroconvert for influenza strains, including A/H1N1, than those who received SD-QIV. The frequency of mild-to-severe AEs following immunisation was similar with both vaccines, and the most frequent were rated as mild–moderate new-onset myalgias, headaches, and tiredness. Compared with the SD-QIV, the HD-QIV was not associated with an increase in disease activity. Notably, MTX in csDMARD-only regimens or in combination with bDMARDs did not reduce the seroconversion rate after the HD-TIV, and patients on bDMARDs (excluding RTX) had a greater seroconversion with the use of HD-TIV rather than with SD-QIV. In the smaller study (82), the findings of a greater proportion of strain-specific seroconversion post-vaccination in RA patients (n=51) who received HD-TIV compared to SD-QIV were confirmed, but the statistical significance was not reached. When compared to 51 age- and gender-matched controls, RA subjects had similar seroconversion rates following administration of influenza vaccines, and the treatment with TNFis was not associated with a reduction in antibody responses to either HD-TIV or SD-QIV. Another common infection in immunocompromised individuals, par-

ticularly JAKis-users, is HZ. In the *post-hoc* analysis of a RCT on RA patients treated with tofacitinib with or without MTX, or ADA with MTX, 216 out of 1,146 patients received live zoster vaccine (LZV) 28 days before the initiation of study treatment (83). A total of 18 HZ infections occurred, mainly mild, with similar incidence rates across treatment groups and between vaccinated and non-vaccinated patients (2/216, 1.4%, and 15/930, 1.6%, respectively). No serious LZV-related AEs or zoster-like lesions were reported in the 42 days following vaccination. Nevertheless, definitive conclusions on vaccine efficacy cannot be derived since this study was not powered for this purpose.

Despite the data on efficacy and safety of vaccines, vaccination rates in RA patients are suboptimal. In a small survey performed on 98 RA patients (April 2018-January 2020) in Canada (84), a high number of patients reported to have received influenza vaccine (72.4%) in the past year, but the rates were lower with respect to HZ (18.4%) and pneumococcus (36.7%). This lack of immunisation was mainly attributed to unawareness by the patient and misinformation due to conflicting opinions on whether they should receive the vaccines. An active strategy aiming at facilitating access to vaccination may be considered to improve the uptake among RA patients. In a survey performed on 116 RA patients in 2018 (85), the increase of the uptake of influenza vaccination was 14.1% compared to the uptake in 2015, and patients' age, treatment with bDMARDs, and physician's recommendation were associated with vaccination. Notably, refusal was the most common reason for non-vaccination, and this should prompt to consider the implementation of education campaign along with the recommendation from the attending rheumatologist.

No studies on safety and efficacy outcomes of vaccination for COVID-19 disease have been published in 2020, and the main trials on these vaccines were designed to exclude subjects with immune-modifying drugs or diagnosed with an immunocompromising condition. Thus, novel data about the impact of anti-COVID-19 vaccines on RA patients are awaited (69).

Take home messages on vaccines

- High-dose trivalent and standard-dose quadrivalent influenza vaccines appear to be safe, providing immunogenicity in RA patients treated with MTX and/or bDMARDs (excluding RTX) in 2 RCTs (81, 82).
- Barriers to vaccination need to be targeted to fill in the gap of the suboptimal uptake of vaccines in RA patients (84, 85).
- More data are expected regarding efficacy and safety of anti-SARS-CoV-2 vaccines in rheumatic patients (69).

Conclusions

RA is a variegated disease, and the evolving process guiding treatment decisions is more complex than a mere choice across a yearly updating list of drugs. The most innovative part of this chapter refers to strategies to adopt in specific clinical contexts, bearing in mind the influence of patients' preferences, biological features, comorbidities, as well as the evolving sceneries of socio-economical and sanitary status.

Abbreviations

(*in order of appearanc*e)

RA: rheumatoid arthritis
DMARDs: disease-modifying anti-rheumatic drugs
COVID-19: novel Coronavirus disease-19
T2T: treat-to-target
AHDs: administrative healthcare databases
GC: glucocorticoid
LDA: low-disease activity
bDMARDs: biological DMARDs
MTX: methotrexate
JAK: Janus kinase
JAKis: JAK inhibitors
tsDMARDs: targeted synthetic DMARDs
RCTS: randomised controlled trials
ACR: American College of Rheumatology
OD: once daily
PROs: patient-reported outcomes
DAS28-CRP: Disease Activity Score at 28 joints - C-reactive protein
AEs: adverse events
IRs, insufficient responders
LTE: long-term extension
SDAI: Simple Disease Activity Index
CDAI: Clinical Disease Activity Index
HAQ-DI: Health Assessment Questionnaire Disability Index
csDMARDs: conventional synthetic DMARDs
HR: hazard ratio
RF: rheumatoid factor
ACPAs: anti–citrullinated protein antibodies
IR: incidence rate
PYs: person years
HZ: herpes zoster
HS: herpes simplex
BMI: body mass index
TEAEs: treatment-emergent AEs
95%CI: 95% Confidence Interval
NMSC: non-melanoma skin cancer
VTE: venous thromboembolism
MACEs: major adverse cardiovascular events
MI: myocardial infarction
CV: cardiovascular
SAEs: serious adverse events
SLR: systematic literature review
EULAR: European Alliance of Associations for Rheumatology
TNFis: tumour necrosis factor alpha inhibitors
CTZ: certolizumab pegol
ABT: abatacept
TCZ: tocilizumab
U.S.: United States of America
GOL: golimumab
ETA: etanercept
SIs: serious infections
SIR: standardised incidence rate
TIAs: transient ischaemic attacks
NSAIDs: non-steroidal anti-inflammatory drugs
ADA: adalimumab
IFX: infliximab
MRI: magnetic resonance imaging
SEMIRA: Steroid EliMination In Rheumatoid Arthritis
RTX: rituximab
IHC: immunohistochemistry
PBMCs: peripheral blood mononuclear cells
MBDA: multi-biomarker disease activity
COPD: chronic obstructive pulmonary disease
ILD: interstitial lung disease
SSZ: sulfasalazine
HCQ: hydroxychloroquine
TJR: total joint replacement
OA: osteoarthritis
TCM: traditional Chinese medicine
WM: Western medicine
RMDs: rheumatic musculoskeletal diseases
CTDs: connective tissue disease
CIA: chronic inflammatory arthritis
PCR: polymerase chain reaction
SMS: short message service
HD-TIV: high-dose trivalent influenza vaccine
SD-QIV: standard-dose quadrivalent influenza vaccine
LZV: live zoster vaccine

i.v.: intravenous
s.c.: subcutaneous
HRCT: high resolution computer tomography
MMRC: Modified Medical Research Council
FVC: forced vital capacity
DLCO: Carbon Monoxide Diffusing Capacity
6MWT: 6-minutes walking test
MD: mean difference
CI, confidence interval
mHAQ: modified Health Assessment Questionnaire
RADAI: Rheumatoid Arthritis Disease Activity Index
EQ5D: EuroQol 5 Dimensions Questionnaire
RAPID-3: Routine Assessment of Patient Index Data 3
PCS: Physical health composite score
MCS: Mental health composite score
SF-12: Short-Form 12
SF-36: Short-Form 36

References

1. SILVAGNI E, GIOLLO A, SAKELLARIOU G *et al*.: One year in review 2020: novelties in the treatment of rheumatoid arthritis. *Clin Exp Rheumatol* 2020; 38: 181-94.
2. BARBER CEH, MARSHALL DA, SZEFER E *et al*.: A population-based approach to reporting system-level performance measures for rheumatoid arthritis care. *Arthritis Care Res* (Hoboken) 2021; 73: 640-8.
3. ZANETTI A, SCIRÈ CA, ARGNANI L, CARRARA G, ZAMBON A: Can the adherence to quality of care indicators for early rheumatoid arthritis in clinical practice reduce risk of hospitalisation? Retrospective cohort study based on the Record Linkage of Rheumatic Disease study of the Italian Society for Rheumatology. *BMJ Open* 2020; 10: e038295.
4. SEPRIANO A, RAMIRO S, FITZGERALD O *et al*.: Adherence to treat-to-target management in rheumatoid arthritis and associated factors: Data from the international RA BIODAM cohort. *J Rheumatol* 2020; 47: 809-19.
5. OWENSBY JK, CHEN L, O'BEIRNE R *et al*.: Patient and rheumatologist perspectives regarding challenges to achieving optimal disease control in rheumatoid arthritis. *Arthritis Care Res* (Hoboken) 2020; 72: 933-41.
6. BENHAM H, CHIU H, TESIRAM J *et al*.: A patient-centered knowledge translation tool for treat-to-target strategy in rheumatoid arthritis: Patient and rheumatologist perspectives. *Int J Rheum Dis* 2021; 24: 355-63.
7. VOSHAAR MJH, VRIEZEKOLK JE, VAN DULMEN AM, VAN DEN BEMT BJF, VAN DE LAAR MAFJ: Ranking facilitators and barriers of medication adherence by patients with inflammatory arthritis: a maximum difference scaling exercise. *BMC Musculoskelet Disord* 2021; 22: 21.
8. BYWALL KS, KIHLBOM U, HANSSON M *et al*.: Patient preferences on rheumatoid arthritis second-line treatment: a discrete choice experiment of Swedish patients. *Arthritis Res Ther* 2020; 22: 288.
9. DE TORO J, GONZÁLEZ CM, CEA-CALVO L *et al*.: Patients' perceptions on shared decision making during prescription of subcutaneous biological drug treatments for inflammatory arthritis: The RHEU-LIFE survey. *Musculoskeletal Care* 2020; 18: 568-74.
10. HAZLEWOOD GS, MARSHALL DA, BARBER CEH *et al*.: Using a discrete-choice experiment in a decision aid to nudge patients towards value-concordant treatment choices in rheumatoid arthritis: A proof-of-concept study. *Patient Preference Adherence* 2020; 14: 829-38.
11. WESTHOVENS R, RIGBY WFC, VAN DER HEIJDE D *et al*.: Filgotinib in combination with methotrexate or as monotherapy versus methotrexate monotherapy in patients with active rheumatoid arthritis and limited or no prior exposure to methotrexate: the phase 3, randomised controlled FINCH 3 trial. *Ann Rheum Dis* 2021; 80: 727-38.
12. VAN VOLLENHOVEN R, TAKEUCHI T, PANGAN AL *et al*.: Efficacy and safety of upadacitinib monotherapy in methotrexate-naive patients with moderately-to-severely active rheumatoid arthritis (SELECT-EARLY): a multicenter, multi-country, randomized, double-blind, active comparator-controlled trial. *Arthritis Rheum* 2020; 72: 1607-20.
13. SMOLEN JS, XIE L, JIA B *et al*.: Efficacy of baricitinib in patients with moderate-to-severe rheumatoid arthritis with 3 years of treatment: results from a long-term study. *Rheumatology* (Oxford) 2021; 60: 2256-66.
14. FLEISCHMANN R, TAKEUCHI T, SCHIFF M *et al*.: Efficacy and safety of long-term baricitinib with and without methotrexate for the treatment of rheumatoid arthritis: experience with baricitinib monotherapy continuation or after switching from methotrexate monotherapy or baricitinib plus methotrexate. *Arthritis Care Res* 2020; 72: 1112-21.
15. GUIDELLI GM, VIAPIANA O, LUCIANO N *et al*.: Efficacy and safety of baricitinib in 446 patients with rheumatoid arthritis: a real-life multicentre study. *Clin Exp Rheumatol* 2020 Dec 18; PMID: 33338001 [Online ahead of print].
16. WINTHROP KL, HARIGAI M, GENOVESE MC *et al*.: Infections in baricitinib clinical trials for patients with active rheumatoid arthritis. *Ann Rheum Dis* 2020; 79: 1290-7.
17. COHEN SB, TANAKA Y, MARIETTE X *et al*.: Long-term safety of tofacitinib up to 9.5 years: A comprehensive integrated analysis of the rheumatoid arthritis clinical development programme. *RMD Open* 2020; 6: e001395.
18. KERSCHBAUMER A, SEPRIANO A, SMOLEN JS *et al*.: Efficacy of pharmacological treatment in rheumatoid arthritis: A systematic literature research informing the 2019 update of the EULAR recommendations for management of rheumatoid arthritis. *Ann Rheum Dis* 2020; 79: 744-59.
19. SMOLEN JS, LANDEWÉ RBM, BIJLSMA JWJ *et al*.: EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs: 2019 update. *Ann Rheum Dis* 2020; 79: 744-59.
20. BENAGLIO F, FORNARO M, MONTECUCCO C *et al*.: Methotrexate in Italian patients wiTh Rheumatoid Arthritis (MITRA study): an observational study about the use of methotrexate in early RA patients and the adherence to the EULAR 2013 recommendations. A project of the Italian Society for Rheumatology. *Clin Exp Rheumatol* 2020 Dec 18; PMID: 33338006 [Online ahead of print].
21. KARPES MATUSEVICH AR, SUAREZ-ALMAZOR ME, CANTOR SB, LAL LS, SWINT JM, LOPEZ-OLIVO MA: Systematic review of economic evaluations of cycling versus swapping medications in patients with rheumatoid arthritis after failure to respond to tumor necrosis factor inhibitors. *Arthritis Care Res* 2020; 72: 343-52.
22. HETLAND ML, HAAVARDSHOLM EA, RUDIN A *et al*.: Active conventional treatment and three different biological treatments in early rheumatoid arthritis: Phase IV investigator initiated, randomised, observer blinded clinical trial. *BMJ* 2020; 371: m4328.
23. PAPPAS DA, ST JOHN G, ETZEL CJ *et al*.: Comparative effectiveness of first-line tumour necrosis factor inhibitor versus non-Tumour necrosis factor inhibitor biologics and targeted synthetic agents in patients with rheumatoid arthritis: Results from a large US registry study. *Ann Rheum Dis* 2021; 80: 96-102.
24. LAUPER K, MONGIN D, IANNONE F *et al*.: Comparative effectiveness of TNF inhibitors and tocilizumab with and without conventional synthetic disease-modifying antirheumatic drugs in a pan-European European observational cohort of bio-naïve patients with rheumatoid arthritis. *Semin Arthritis Rheum* 2020; 50: 17-24.
25. EBINA K, HIRANO T, MAEDA Y *et al*.: Drug retention of 7 biologics and tofacitinib in biologics-naïve and biologics-switched patients with rheumatoid arthritis: The ANSWER cohort study. *Arthritis Res Ther* 2020; 22: 142.
26. SEPRIANO A, KERSCHBAUMER A, SMOLEN JS *et al*.: Safety of synthetic and biological DMARDs: A systematic literature review informing the 2019 update of the EULAR recommendations for the management of rheumatoid arthritis. *Ann Rheum Dis* 2020; 79: S760-70.
27. SINGH S, FUMERY M, SINGH AG *et al*.: Comparative risk of cardiovascular events with biologic and synthetic disease-modifying antirheumatic drugs in patients with rheumatoid arthritis: a systematic review and meta-analysis. *Arthritis Care Res* 2020; 72: 561-76.
28. EMERY P, BURMESTER GR, NAREDO E *et al*.: Adalimumab dose tapering in patients with rheumatoid arthritis who are in long-standing clinical remission: Results of the phase IV PREDICTRA study. *Ann Rheum Dis* 2020; 79: 1023-30.
29. DIERCKX S, SOKOLOVA T, LAUWERYS BR *et al*.: Tapering of biological antirheumatic drugs in rheumatoid arthritis patients is achievable and cost-effective in daily clinical practice: Data from the Brussels UCLouvain RA Cohort. *Arthritis Res Ther* 2020; 22: 96.
30. VAN MULLIGEN E, WEEL AE, HAZES JM, VAN DER HELM-VAN MIL A, DE JONG PHP: Tapering towards DMARD-free remission in established rheumatoid arthritis: 2-year results of the TARA trial. *Ann Rheum Dis* 2020; 79: 1174-81.
31. POPE J, RAMPAKAKIS E, VAILLANCOURT J

et al.: An open-label randomized controlled trial of DMARD withdrawal in RA patients achieving therapeutic response with certolizumab pegol combined with DMARDs. *Rheumatology* 2020; 59: 1522-8.
32. BURMESTER GR, BUTTGEREIT F, BERNASCONI C *et al*.: Continuing versus tapering glucocorticoids after achievement of low disease activity or remission in rheumatoid arthritis (SEMIRA): a double-blind, multicentre, randomised controlled trial. *Lancet* 2020; 396: 267-76.
33. VAN MULLIGEN E, WEEL AE, KUIJPER TM *et al*.: Two-year cost effectiveness between two gradual tapering strategies in rheumatoid arthritis: Cost-utility analysis of the TARA trial. *Ann Rheum Dis* 2020; 79: 1550-6.
34. HUMBY F, DUREZ P, BUCH MH *et al*.: Rituximab versus tocilizumab in anti-TNF inadequate responder patients with rheumatoid arthritis (R4RA): 16-week outcomes of a stratified, biopsy-driven, multicentre, open-label, phase 4 randomised controlled trial. *Lancet* 2021; 397: 305-17.
35. RODRÍGUEZ-MARTÍN E, NIETO-GAÑÁN I, HERNÁNDEZ-BREIJO B *et al*.: Blood lymphocyte subsets for early identification of non-remission to TNF inhibitors in rheumatoid arthritis. *Front Immunol* 2020; 11: 1913.
36. TAO W, CONCEPCION AN, VIANEN M *et al*.: Multiomics and machine learning accurately predict clinical response to adalimumab and etanercept therapy in patients with rheumatoid arthritis. *Arthritis Rheumatol* 2021; 73: 212-22.
37. LEE EJ, LILJA S, LI X, SCHÄFER S, ZHANG H, BENSON M: Bulk and single cell transcriptomic data indicate that a dichotomy between inflammatory pathways in peripheral blood and arthritic joints complicates biomarker discovery. *Cytokine* 2020; 127: 154960.
38. ROODENRIJS NMT, VAN DER GOES MC, WELSING PMJ *et al*.: Is prediction of clinical response to methotrexate in individual rheumatoid arthritis patients possible? A systematic literature review. *Joint Bone Spine* 2020; 87: 13-23.
39. GOSSELT HR, VERHOEVEN MMA, DE ROTTE MCFJ *et al*.: Validation of a prognostic multivariable prediction model for insufficient clinical response to methotrexate in early rheumatoid arthritis and its clinical application in evidencio. *Rheumatol Ther* 2020; 7: 837-50.
40. GOSSELT HR, VERHOEVEN MMA, BULATOVIĆ-ĆALASAN M *et al*.: Complex machine-learning algorithms and multivariable logistic regression on par in the prediction of insufficient clinical response to methotrexate in rheumatoid arthritis. *J Pers Med* 2021; 11: 44.
41. JURGENS MS, SAFY-KHAN M, DE HAIR MJH *et al*.: The multi-biomarker disease activity test for assessing response to treatment strategies using methotrexate with or without prednisone in the CAMERA-II trial. *Arthritis Res Ther* 2020; 22: 205.
42. LUEDDERS BA, JOHNSON TM, SAYLES H *et al*.: Predictive ability, validity, and responsiveness of the multi-biomarker disease activity score in patients with rheumatoid arthritis initiating methotrexate. *Semin Arthritis Rheum* 2020; 50: 1058–63.
43. ULIJN E, DEN BROEDER N, WIENTJES M *et al*.: Therapeutic drug monitoring of adalimumab in RA: No predictive value of adalimumab serum levels and anti-adalimumab antibodies for prediction of response to the next bDMARD. *Ann Rheum Dis* 2020; 79: 867-73.
44. BOYAPATI A, SCHWARTZMAN S, MSIHID J *et al*.: Association of high serum interleukin-6 levels with severe progression of rheumatoid arthritis and increased treatment response differentiating sarilumab from adalimumab or methotrexate in a post hoc analysis. *Arthritis Rheum* 2020; 72: 1456-66.
45. BURMESTER G-R, ÁLVARO-GRACIA JM, BETTERIDGE N *et al*.: Evolving the comprehensive management of rheumatoid arthritis: identification of unmet needs and development of practical and educational tools. *Clin Exp Rheumatol* 2020; 38: 1056-67.
46. D'AMICO ME, SILVAGNI E, CARRARA G *et al*.: Role of comorbidities on therapeutic persistence of biological agents in rheumatoid arthritis: results from the RECord-linkage On Rheumatic Disease study on administrative healthcare databases. *Scand J Rheumatol* 2021 Mar 4 [Online ahead of print].
47. BECHMAN K, OKE A, YATES M *et al*.: Is background methotrexate advantageous in extending TNF inhibitor drug survival in elderly patients with rheumatoid arthritis? An analysis of the British Society for Rheumatology Biologics Register. *Rheumatology* 2020; 59: 2563-71.
48. KOH JH, LEE S-K, KIM J, KIM H-A, SHIN K, MIN J-K: Effectiveness and safety of biologic and targeted synthetic disease-modifying anti-rheumatic drugs in elderly patients with rheumatoid arthritis: real-world data from the KOBIO Registry. *Clin Exp Rheumatol* 2021; 39: 269-78.
49. LOPEZ-OLIVO MA, COLMEGNA I, KARPES MATUSEVICH AR *et al*.: Systematic review of recommendations on the use of disease-modifying antirheumatic drugs in patients with rheumatoid arthritis and cancer. *Arthritis Care Res* 2020; 72: 309-18.
50. DE GERMAY S, BAGHERI H, DESPAS F, ROUSSEAU V, MONTASTRUC F: Abatacept in rheumatoid arthritis and the risk of cancer: A world observational post-marketing study. *Rheumatology* 2020; 59: 2360-7.
51. HUDSON M, DELL'ANIELLO S, SHEN S, SIMON TA, ERNST P, SUISSA S: Comparative safety of biologic versus conventional synthetic DMARDs in rheumatoid arthritis with COPD: A real-world population study. *Rheumatology* 2020; 59: 820-7.
52. KANG EH, JIN Y, DESAI RJ, LIU J, SPARKS JA, KIM SC: Risk of exacerbation of pulmonary comorbidities in patients with rheumatoid arthritis after initiation of abatacept versus TNF inhibitors: A cohort study. *Semin Arthritis Rheum* 2020; 50: 401-8.
53. IBFELT EH, JACOBSEN RK, KOPP TI *et al*.: Methotrexate and risk of interstitial lung disease and respiratory failure in rheumatoid arthritis: a nationwide population-based study. *Rheumatology* (Oxford) 2021; 60: 346-52.
54. NAGY G, ROODENRIJS NMT, WELSING PMJ *et al*.: EULAR definition of difficult-To-Treat rheumatoid arthritis. *Ann Rheum Dis* 2021; 80: 31-5.
55. MICHAUD K, POPE J, VAN DE LAAR M *et al*.: A systematic literature review of residual symptoms and unmet need in patients with rheumatoid arthritis. *Arthritis Care Res* (Hoboken) 2020 Jul 3 [Online ahead of print].
56. BOURNIA V-K, TEKTONIDOU MG, VASSILOPOULOS D *et al*.: Introduction and switching of biologic agents are associated with antidepressant and anxiolytic medication use: data on 42 815 real-world patients with inflammatory rheumatic disease. *RMD Open* 2020; 6: e001303
57. BRENNER P, CITARELLA A, WINGÅRD L, SUNDSTRÖM A: Use of antidepressants and benzodiazepine-related hypnotics before and after initiation of TNF-α inhibitors or non-biological systemic treatment in patients with rheumatoid arthritis, psoriatic arthritis or ankylosing spondylitis. *BMC Rheumatol* 2020; 4: 9.
58. OLOFSSON T, WALLMAN JK, JÖUD A *et al*.: Pain over 2 years after start of biological versus conventional combination treatment in early rheumatoid arthritis: results from the randomised controlled SWEFOT trial. *Arthritis Care Res* (Hoboken) 2020 May 20 [Online ahead of print].
59. MUILU P, RANTALAIHO V, KAUTIAINEN H, VIRTA LJ, PUOLAKKA K: Opioid use among patients with early inflammatory arthritides compared to the general population. *J Rheumatol* 2020; 47: 1285-92.
60. LIBERMAN JS, D'AGOSTINO MCGOWAN L, GREEVY RA *et al*.: Mental health conditions and the risk of chronic opioid therapy among patients with rheumatoid arthritis: a retrospective veterans affairs cohort study. *Clin Rheumatol* 2020; 39: 1793-802.
61. ASAI S, TAKAHASHI N, ASAI N *et al*.: Characteristics of patients with rheumatoid arthritis undergoing primary total joint replacement: A 14-year trend analysis (2004-2017). *Mod Rheumatol* 2020; 30: 657-63.
62. BORGAS Y, GÜLFE A, KINDT M, STEFÁNSDÓTTIR A: Anti-rheumatic treatment and prosthetic joint infection: An observational study in 494 elective hip and knee arthroplasties. *BMC Musculoskelet Disord* 2020; 21: 410.
63. ITO H, TSUJI S, NAKAYAMA M *et al*.: Does abatacept increase postoperative adverse events in rheumatoid arthritis compared with conventional synthetic disease-modifying drugs? *J Rheumatol* 2020; 47: 502-9.
64. MOREL J, LOCCI M, BANAL F *et al*.: Safety of surgery in patients with rheumatoid arthritis treated with tocilizumab: Data from the French (REGistry - RoAcTEmra) Regate registry. *Clin Exp Rheumatol* 2020; 38: 405-10.
65. XING Q, FU L, YU Z, ZHOU X: Efficacy and Safety of Integrated Traditional Chinese medicine and Western medicine on the treatment of rheumatoid arthritis: a meta-analysis. *Evid-Based Complement Altern Med* 2020; 2020: 4348709.
66. FERRO F, ELEFANTE E, BALDINI C *et al*.: COVID-19: the new challenge for rheumatologists. *Clin Exp Rheumatol* 2020: 38: 175-80.
67. FERRO F, ELEFANTE E, PUXEDDU I *et al*.: Editorial COVID-19: the new challenge for rheumatologists. First update. *Clin Exp Rheumatol* 2020: 38: 373-82.

68. PUXEDDU I, FERRO F, BARTOLONI E *et al*.: Review COVID-19: the new challenge for rheumatologists. One year later. *Clin Exp Rheumatol* 2021: 39; 203-13.
69. BENUCCI M, INFANTINO M, MAROTTO D, ARDIZZONE S, MANFREDI M, SARZI-PUTTINI P: Vaccination against SARS-CoV-2 in patients with rheumatic diseases: doubts and perspectives. *Clin Exp Rheumatol* 2021; 39: 196-202.
70. LOHSE A, BOSSERT M, BOZGAN A-M *et al*.: Frequency and severity of COVID-19 in patients treated with biological disease-modifying anti-rheumatic drugs for inflammatory rheumatic disease: a cross-sectional study. *Clin Exp Rheumatol* 2020; 38: 1273.
71. GIANFRANCESCO M, HYRICH KL, AL-ADELY S *et al*.: Characteristics associated with hospitalisation for COVID-19 in people with rheumatic disease: data from the COVID-19 Global Rheumatology Alliance physician-reported registry. *Ann Rheum Dis* 2020; 79: 859-66.
72. STRANGFELD A, SCHÄFER M, GIANFRANCESCO MA *et al*.: Factors associated with COVID-19-related death in people with rheumatic diseases: results from the COVID-19 Global Rheumatology Alliance physician-reported registry. *Ann Rheum Dis* 2021 Jan 27 [Online ahead of print].
73. SCIRÈ CA, CARRARA G, ZANETTI A *et al*.: COVID-19 in rheumatic diseases in Italy: First results from the Italian registry of the Italian Society for Rheumatology (CONTROL-19). *Clin Exp Rheumatol* 2020; 38: 748-53.
74. PABLOS JL, GALINDO M, CARMONA L *et al*.: Clinical outcomes of hospitalised patients with COVID-19 and chronic inflammatory and autoimmune rheumatic diseases: A multicentric matched cohort study. *Ann Rheum Dis* 2020; 79: 1544-9.
75. AKIYAMA S, HAMDEH S, MICIC D, SAKURABA A: Prevalence and clinical outcomes of COVID-19 in patients with autoimmune diseases: a systematic review and meta-analysis. *Ann Rheum Dis* 2020 Oct 13 [Online ahead of print].
76. HASSELI R, MUELLER-LADNER U, HOYER BF *et al*.: Older age, comorbidity, glucocorticoid use and disease activity are risk factors for COVID-19 hospitalisation in patients with inflammatory rheumatic and musculoskeletal diseases. *RMD Open* 2021; 7: e001464.
77. CORDTZ R, LINDHARDSEN J, SOUSSI BG *et al*.: Incidence and severeness of COVID-19 hospitalisation in patients with inflammatory rheumatic disease: a nationwide cohort study from Denmark. *Rheumatology* (Oxford) 2020 Dec 28 [Online ahead of print].
78. GONÇALVES-BRADLEY DC, J MARIA AR, RICCI-CABELLO I *et al*.: Mobile technologies to support healthcare provider to healthcare provider communication and management of care. *Cochrane Database Syst Rev* 2020; 8: CD012927.
79. PERS Y-M, VALSECCHI V, MURA T *et al*.: A randomized prospective open-label controlled trial comparing the performance of a connected monitoring interface versus physical routine monitoring in patients with rheumatoid arthritis. *Rheumatology* (Oxford) 2021; 60: 1659-68.
80. KUUSALO L, SOKKA-ISLER T, KAUTIAINEN H *et al*.: Automated text message–enhanced monitoring versus routine monitoring in early rheumatoid arthritis: a randomized trial. *Arthritis Care Res* 2020; 72: 319-25.
81. COLMEGNA I, USECHE ML, RODRIGUEZ K *et al*.: Immunogenicity and safety of high-dose versus standard-dose inactivated influenza vaccine in rheumatoid arthritis patients: a randomised, double-blind, active-comparator trial. *Lancet Rheumatol* 2020; 2: e14-23.
82. STAPLETON JT, WAGNER N, TUETKEN R *et al*.: High dose trivalent influenza vaccine compared to standard dose vaccine in patients with rheumatoid arthritis receiving TNF-alpha inhibitor therapy and healthy controls: Results of the DMID 10-0076 randomized clinical trial. *Vaccine* 2020; 38: 3934-41.
83. CALABRESE LH, ABUD-MENDOZA C, LINDSEY SM *et al*.: Live zoster vaccine in patients with rheumatoid arthritis treated with tofacitinib with or without methotrexate, or adalimumab with methotrexate: a post hoc analysis of data from a Phase IIIb/IV randomized study. *Arthritis Care Res* 2020; 72: 353-9.
84. ABERUMAND B, DYCK BA, TOWHEED T: Identifying perceptions and barriers regarding vaccination in patients with rheumatoid arthritis: A Canadian perspective. *Int J Rheum Dis* 2020;23:1526–33.
85. VALERIO V, BAZAN MC, WANG M *et al*.: A multimodal intervention increases influenza vaccine uptake in rheumatoid arthritis. *Clin Rheumatol* 2021; 40: 575-9.
86. FERNÁNDEZ-DÍAZ C, CASTAÑEDA S, MELERO-GONZÁLEZ RB *et al*.: Abatacept in interstitial lung disease associated with rheumatoid arthritis: national multicenter study of 263 patients. *Rheumatology* (Oxford) 2020; 59: 3906-16.
87. NARVÁEZ J, ROBLES-PÉREZ A, MOLINA-MOLINA M *et al*.: Real-world clinical effectiveness of rituximab rescue therapy in patients with progressive rheumatoid arthritis-related interstitial lung disease. *Semin Arthritis Rheum* 2020; 50: 902-10.
88. VADILLO C, NIETO MA, ROMERO-BUENO F *et al*.: Efficacy of rituximab in slowing down progression of rheumatoid arthritis-related interstitial lung disease: data from the NEREA Registry. *Rheumatology* (Oxford) 2020; 59: 2099-108.
89. MANFREDI A, CASSONE G, FURINI F *et al*.: Tocilizumab therapy in rheumatoid arthritis with interstitial lung disease: a multicentre retrospective study. *Intern Med J* 2020; 50: 1085-90.
90. NARVÁEZ J, VICENS-ZYGMUNT V, ALEGRE J-J, HERRERA-LARA S, NOLLA J-M, MOLINA-MOLINA M: Nintedanib for the treatment of refractory progressive rheumatoid arthritis-related interstitial lung disease: a real-life case series. *Rheumatology* (Oxford) 2020; 59: 3983-6.
91. TAYLOR-GJEVRE R, NAIR B, BATH B *et al*.: Addressing rural and remote access disparities for patients with inflammatory arthritis through video-conferencing and innovative inter-professional care models. *Musculoskeletal Care* 2018; 16: 90-5.