One year in review 2020: novelties in the treatment of rheumatoid arthritis

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Received on March 14, 2020; accepted in revised form on March 16, 2020.

Clin Exp Rheumatol 2020; 38: 181-194.

Key words: rheumatoid arthritis, disease modifying anti-rheumatic drugs, biological agents, JAK kinases, personalised medicine

Competing interests: C.A. Scirè received consultancy fees from Abbvie and BMS. T.W.J. Huizinga/the Department of Rheumatology LUMC has received research support/lecture fees/consultancy fees from Abblynx, Merck, UCB, BMS, Biotest AG, Janssen, Pfizer, Novartis, Roche, Sanofi-Aventis, Abbott, Crescendo Bioscience, Galapagos, Nycomed, Boeringher, Takeda, Zydus, Epirus and Eli Lilly.
The other co-authors have declared no competing interests.

ABSTRACT

Rheumatoid arthritis (RA) management is driven by evidence, and new 2019 EULAR recommendations help in refining the relevant place of different disease-modifying anti-rheumatic drugs (DMARDs) in treatment schedules. At present, new drugs are in phase of development, mainly Janus Kinase inhibitors (JAKis), however, specific treatment strategies seem to count more than individual DMARDs in terms of treatment responses, given the substantial lack of head-to-head comparisons between specific biological (b) and targeted synthetic (ts)DMARDs, and with the general perception of a similar efficacy profile across drugs. In this setting, when reliable biomarkers able to predict treatment responses are lacking, treatment decisions are mainly driven by specific clinical or individual factors, given the recognised role of comorbidities, treatment-specific side effects, patients' preferences, and costs on drug choice. In this narrative review, the authors give their specific point of view on the management of RA, based on a critical revision of the literature published in 2019, focusing on relevant novelties and future research directions.

Introduction

Rheumatoid arthritis (RA) is a systemic autoimmune disease, characterised by chronic synovitis leading to progressive damage and loss of function, while systemic involvement and extra-articular manifestations are responsible for relevant morbidity. Several drugs are now available for the treatment of RA, and treatment approaches are driven by evidence, summarised under international recommendations (1). As new drugs have been recently approved, relevant questions raise, focusing on comparative efficacy among drugs with different mechanisms of action, and safety concerns. Treatment strategy to adopt remains the main weapon for the clinician to slow down disease progression over specific disease-modifying anti-rheumatic drugs (DMARDs), in the absence of fully validated biomarkers able to stratify treatment interventions. In this setting, sharing decisions with patients assumes relevant importance, bearing in mind the role of relevant comorbidities, as well as potential side effects of drugs and their costs.

This review is part of an editorial initiative of *Clinical and Experimental Rheumatology* focusing on relevant novelties on rheumatic diseases published in the last year (2-12). Starting from the last annual paper on this topic (2), the authors give their specific point of view arising from a critical review of articles published in 2019 on the management of RA, and they aim at resuming lessons learned, relevant novelties and future directions.

New drugs for the management of rheumatoid arthritis

Targeted synthetic (ts)DMARDs have demonstrated their rapid efficacy in the treatment of RA. However, safety concerns have emerged with broad-spectrum Janus Kinase (JAK) inhibitors (JAKis), such as baricitinib and tofacitinib, possibly due to their ability in interfering with different types of JAKs. New drugs development programs have focused on selective targeting of specific JAK proteins and, in 2019, the Food and Drug Administration (FDA) and European Medicine Associations (EMA) have approved the first selective JAKi for the treatment of RA. Upadacitinib, a selective

JAK1 inhibitor, has demonstrated, in phase III randomised controlled trials (RCTs), its efficacy and safety in RA, and new JAKis are under development. From a clinical point of view, there is urgent need of understanding how significant this selectivity can be at single patient level, how much relevant might be comparative efficacy among different tsDMARDs and between ts- and biologic (b)DMARDs monotherapies, and how much consistent with expected outcomes should be the safety profile of selective JAK1 inhibitors.

In phase III RCTs, upadacitinib has already demonstrated its efficacy compared to placebo in patients with inadequate response (IR) to either conventional synthetic (cs)DMARDs or TNF inhibitors (TNFis) (SELECT-NEXT, SELECT-BEYOND)(2). New results from phase III SELECT-COMPARE (13,14) and SELECT-MONOTHERAPY (15) RCTs have underlined a superiority for upadacitinib plus methotrexate (MTX) compared to adalimumab (ADA) (plus MTX) in MTX-IR patients, and a statistically significant improvement in clinical outcomes for upadacitinib monotherapy *versus* MTX monotherapy in MTX-IR. In SELECT-COMPARE trial (13, 14), upadacitinib 15 mg once daily (OD) or ADA were administered in combination with stable MTX to MTX-IR patients with established disease (mean disease duration 8 years). While primary outcome was American College of Rheumatology (ACR)20 response at week (w)12 for upadacitinib *versus* placebo, the study was also powered to test non-inferiority/superiority for upadacitinib *versus* ADA. After 12 and 26 weeks, not surprisingly, upadacitinib treatment resulted in better clinical and radiological outcomes compared to placebo, and, strikingly, upadacitinib was superior to ADA at w12 in ACR50 response, reduction in disease activity score 28-C-Reactive Protein (DAS28-CRP), pain and Health Assessment Questionnaire disability index (HAQ-DI). Safety patterns were similar between upadacitinib and ADA, with no specific highlight on cardiovascular (CV) safety, while proportions of patients with herpes zoster, lymphopenia, liver transaminase and creatine phosphokinase elevations were numerically higher in upadacitinib-treated patients. Efficacy and safety results were maintained till w48 (14), and rescue-switchers from one treatment to another were able to recapture disease control, with switchers from ADA to upadacitinib gaining better clinical outcomes across the study compared to upadacitinib-to-ADA switchers. The role of upadacitinib as monotherapy was investigated in SELECT-MONOTHERAPY RCT (15). In MTX-IR patients, upadacitinib 15 mg OD, upadacitinib 30 mg OD, or MTX were administered for 14 weeks. At w14, upadacitinib monotherapy was superior to MTX in reaching primary outcomes (ACR20 and DAS28-CRP low disease activity), with almost one third of upadacitinib-treated patients achieving ACR70. Safety outcomes were comparable to other studies with upadacitinib, suggesting dose-relationship for herpes zoster infection and higher risk of major adverse CV events (MACEs) in patients with known risk factors. Again, even if upadacitinib was demonstrated superior to ADA in combination to MTX in MTX-IR patients, clinicians still wait for comparative studies between b- and tsDMARDs monotherapies.

Another selective JAK1 inhibitor, filgotinib, has demonstrated superiority over placebo in bDMARD-IR patients (16). In FINCH2 phase III RCT, filgotinib 200 mg and 100 mg OD (with stable background csDMARD) reduced disease activity at w12, with a 35% ACR20 response difference for filgotinib 200 mg *versus* placebo (95% confidence interval (95%CI) 23.5–46.3). This difference was even higher in refractory patients – failure of more than 3 biologics – (52.6% filgotinib 200 mg, 41.2% filgotinib 100 mg). Main safety signals with filgotinib were in line with other JAKis, and most of them were mild in their course. Pan-JAK inhibitor peficitinib has been approved for the management of RA in Japan. It has demonstrated its efficacy and safety profiles in phase IIb studies (2), and 2 years extension results (17) with peficitinib 100 mg OD strengthen these results in csDMARD-IR. One of the limitations of this global long-term extension study was that, among 611 patients entering long-term extension, only a half completed the study, mainly due to protocol amendments not permitting increasing dosages in not-responders. Most frequent adverse events (AEs) were upper respiratory tract infections and urinary tract infections, and safety was comparable with other available JAKis. Peficitinib was not further investigated in Western-population, with phase III RCTs (RAJ4, RAJ3)(18,19) confirming its efficacy and safety profile in combination with MTX after cs/bDMARDs failure in Asian patients (12 weeks).

At present, the real significance of selective JAK inhibition in clinical practice – both at single-patient level and in comparison with other JAKis – is far from being understood. A recently published 2019 update of European League Against Rheumatisms (EULAR) recommendations for the management of RA (1) has itemised different JAKis among drugs suitable to be started in patients failing csDMARDs therapy, but no priority was highlighted, even with respect to bDMARDs. Given the lack of direct head-to-head comparisons, network meta-analysis has been exploited to compare efficacy outcomes of multiple interventions, combining evidence across networks of RCTs. Upadacitinib (plus MTX) demonstrated higher efficacy than tofacitinib in reducing disease activity in cs/bDMARD-IR patients, in terms of ranking probability based on the surface under the cumulative ranking curve (0.820, 0.762, 0.623 for upadacitinib 15, upadacitinib 30 and tofacitinib 10 mg OD, respectively) (20), but statistical significance for superiority was not reached, and safety profiles were similar. Thus, while new head-to-head comparisons are expected, a similar efficacy profile across different JAKis is perceived.

Treatment strategies in rheumatoid arthritis

Despite the on-going development of new drugs with new molecular targets, treatment strategies still retain crucial importance in the management of the patient with RA. Analysis of comparative effectiveness, induction and treat-

to-target strategies, and tapering behaviours remain the best characterised, however homogeneous conclusions have not been reached.

*C*omparative efficacy and safety among the different drugs in RA represent one of the most important and prolific research fields. In spite of this, the evidence that accumulates is conflicting, and substantially based on observational studies. The inconsistency of the results relies on the heterogeneity of the populations compared, the residual confounding and the poor validity of many outcome measures.

The ARTIS Register (Sweden) analysed the effectiveness of new courses of bDMARDs from 2010 to 2016, both as first bDMARDs (n=9,333), or after switching from TNFis as first bDMARDs (n=3,941). The non-TNFi bDMARD strategy resulted more effective than TNFis both in the first line and after failure of a first TNFi (21). Patients starting non-TNFis (*vs*. TNFis) as first bDMARD had a higher proportion of remaining on drug and reaching favourable outcomes (1-year EULAR Good Response/HAQ-DI improvement: TNFis 24.9/25.4%, rituximab (RTX) 28.6/37.2%, abatacept (ABT) 31.9/33.7%, tocilizumab (TCZ) 50.9/43.1%). After switching from a first TNFi, RTX and TCZ, but not ABT, were associated with significantly better response compared to TNFis (1-year EULAR Good Response/HAQ-DI improvement: TNFis 11.6/16.1%, RTX 24.8/33.2%, ABT 13.1/17.5%, TCZ 34.1/29.4%). A further study combined 3 non concurrent bDMARDs registries from France including RA patients treated with RTX (1,947 patients), intra-venous ABT (823 patients) and intra-venous TCZ (1,364 patients), both in monotherapy and in combination with csDMARDs (22). Analysing a 24-months follow-up period, RTX and TCZ showed a significantly better drug survival than ABT, even after propensity score matching. The 6-month EULAR response strongly favoured TCZ (72.9%) *vs*. RTX (54.5%) and ABT (48%), with no major differences in serious AEs. No data on function and structural progression were available. Data from the CORRONA registry (U.S.) analysed the 6-month response to TNFis *vs*. ABT in anti-citrullinated proteins antibodies (ACPA)-positive propensity score matched RA patients (23). While the Clinical Disease Activity index (CDAI) mean difference (MD) in the overall cohort (330 patients per strategy) did not significantly differ, and given a tendency towards higher effectiveness of TNFis in bDMARDs-naïve cohort, ABT showed, in TNFis-IR patients, a 3.09 mean difference compared to TNFis in CDAI response (p=0.03). The ANSWER cohort (Japan) retrospectively analysed 4,466 bDMARDs treatment courses and comparatively assessed persistence and reasons of discontinuation during 36 months (24). In this study, the best overall survival was observed for ABT [ABT (72.7%) *vs*. TCZ (69.4%)], due to a combination of good survival for effectiveness and lack of toxicity. Conversely, the analysis of 8,987 courses of non-TNFi bDMARDs from two national cohorts (ARTIS, Sweden, and DANBIO, Denmark) reported a not significant difference of serious infection rates among RTX, ABT, and TCZ, but a tendency towards a higher risk of serious infections in ABT *vs*. TCZ (relative risk (RR) 1.13, 95%CI 0.91–1.42) (25). A pharmaco-economic evaluation, based on real-world data from Finland in the biosimilar era, explored the cost-effectiveness of a cycling strategy *versus* a swapping strategy in TNFis-IR patients (26). This patient-level simulation, based on observational data, showed that TNFis were associated with the lowest costs and highest quality-adjusted life-years (QALYs), whereas RTX had the highest costs and lowest QALYs. ABT and, to a lesser extent, TCZ were superior to RTX.

The absence of robust comparative data, both in terms of efficacy and safety, does not substantially allow formulating recommendations based on solid evidence. Therefore, the best possible strategy remains driven by external factors, including cost-effectiveness.

The idea of carrying out induction therapies for RA has fascinated rheumatologists for many years. However, the evidence accumulated so far, as well as the most recent ones, confirm that the adoption of formally-considered "second-line" bDMARDs since the onset of the disease does not improve long-term outcomes**.**

A systematic literature review compared bDMARDs, combination of cs-DMARDs and single csDMARDs induction strategies for early RA on remission over 12 months (27). The meta-analysis showed a pooled RR of 1.73 (95%CI 1.59–1.88) for bDMARD-based remission induction strategies and 1.20 (95%CI 1.03–1.40) for combination of csDMARDs-based remission induction strategies over single csDMARD-induction strategies. However, when additional glucocorticoid (GC) "bridging therapy" was used in single csDMARD-initiating strategies, the proportion of patients achieving target in remission was no longer statistically significant (pooled RR 1.06, 95%CI 0.83–1.35). A pooled analysis of the U-Act-Early and CAMERA II trials indirectly compared TCZ plus MTX and MTX plus prednisone in early RA as a starting treatment in a treat-to-target strategy (28). The strategy including TCZ plus MTX in the first therapeutic approach compared to MTX plus prednisone showed no major improvements after 24 months in disease activity, and absolutely no difference in terms of function and damage. Ten-year follow-up of the NEORACO RCT, which compared a regimen with 6-month early treatment with infliximab (IFX) *versus* placebo on a background cs-DMARD combination treatment (FIN-RACO scheme) and treat-to-target strategy, did not show significant differences in disease activity, functional and structural outcomes between the two arms (29). The overall remission rate according to DAS28 was >70% in both groups with more than 60% of patients with absence of functional impairment. An observational study compared two cohorts of early RA treated according to different strategies, 155 RA patients receiving intensive strategy aiming at remission with high dose prednisone (60 mg/day) and high dose MTX (25 mg) *versus* 124 patients receiving routine care characterised by initial MTX and aiming at low-disease activity (30). After a median follow-up of 7.8 years, no major differences in terms of drug-

free survival were observed. However, the subgroup of ACPA positive patients showed a tendency to higher rate of drug-free remission in the intensive treatment arm, both in univariate (Hazard ratio (HR) 3.1, 95%CI 0.9–11) and propensity score adjusted analyses (HR 1.3, 95%CI 0.8–2.1).

Beyond the initial strategy intensity and drug choice, the treating to target principle, with the more stringent target the better outcome, seems to be the 'anchor' strategy today. However, implementation, sustainability and safety may limit its full translation into practice.

An analysis of the RISE registry, including 27,274 RA patient, pointed out a lower than expected frequency of treatment changes during follow-up, even for patients in moderate/high disease activity by Routine Assessment of Patient Index Data 3 (RAPID3) or CDAI, ranging from 61.7%, in patients on csDMARDs monotherapy, to 34.5% in patients on csDMARDs combination (31). Older patients (age ≥75) and those already receiving combination therapy with csDMARDs or b/csDMARDs combination were less likely to change RA treatment, even after multivariable adjustment. A non-randomised, interrupted time-series trial assessed a learning collaborative intervention focused on treat-to-target *versus* no intervention on a score of adherence to the treat-to-target principle in RA, which included the following dimensions: disease activity score measurement, disease activity score use in the medication change decision, presence of treatment target, and shared decision-making (32). The treat-to-target implementation scores among intervention rheumatologists were 12.4% higher than the control group, with improvement in all the subdimensions. Medication changes were more likely in the intervention *versus* control group (odds ratio (OR) 0.46, 95%CI 0.27–0.79). A RCT on treat-to-target strategies tested the hypothesis that an imaging (Magnetic Resonance Imaging, MRI)-guided treat-to-target strategy aiming for imaging remission (bone marrow oedema) could lead to an increased rate of disease activity remission and less radiographic progression, compared to a conventional treat-to-target strategy after 24 months (33). This RCT included 200 patients with RA with DAS28-CRP in low disease activity, and, despite MRI improvement was statistically significant both in terms of inflammation (particularly tenosynovitis) and osteitis (bone marrow oedema) in the MRI-guided strategy, no significant differences in DAS28-CRP remission rates (85% *vs*. 88%) and in radiographic progression (66% *vs*. 62%) were found. Despite the expected association between clinically-driven treat-to-target strategies and remission measured by clinical outcome measures, imaging-driven strategies still fails to demonstrate better association with structural damage halt in the short/medium term.

Remission without treatment is not an achievable goal to date, at least not for all patients. Tapering of TNFis, and other b/tsDMARDs, seems to be feasible over discontinuation in RA in low disease activity, particularly in patients with deeper remission (clinical, sustained, biological, imaging) and better prognostic factors. Being able to identify these patients could change the perspectives in the future.

An update of a Cochrane systematic literature review and meta-analysis summarised the efficacy and safety of down-titration and discontinuation strategies of TNFis for RA in low disease activity (34). Based on the existing evidence, TNFis dose reduction leads to little or no difference in DAS28 after 26 to 52 weeks (MD 0.06, 95%CI -0.11–0.24) compared with continuation. Conversely, TNFis discontinuation increases the mean DAS28 after 28 to 52 weeks (MD 0.96, 95%CI 0.67–1.25), increases the proportion of participants with minimal radiographic progression after 52 weeks (RR 1.69, 95%CI 1.10–2.59) and may lead to a slight deterioration in function. A single arm intervention study of bDMARDs discontinuation analysed 141 patients with sustained DAS28-CRP <2.6 and no radiographic progression during the previous year (35). bDMARDs were reduced to two-thirds of standard dose at baseline, half after 16 weeks, and discontinued after 32 weeks. At 2 years, 87 patients (62%) had successfully tapered bDMARDs, with 26 (18%) receiving two-thirds of standard dose, 39 (28%) half dose and 22 (16%) having discontinued. The patient profile of successful tapering included male gender, first-line bDMARD, low baseline MRI combined inflammation score or combined damage score, and successful discontinuation included also negative Rheumatoid Factor (RF) IgM status.

bDMARDs tapering strategy should be applied first over csDMARDs tapering in patients on sustained steroid-free remission. The TARA study tested the hypothesis of superiority of gradual tapering of csDMARDs or TNFis in patients with RA with controlled disease (DAS28 ≤2.4 and swollen joints count ≤1) treated with a combination of csDMARDs and a TNFi (36). The cumulative flare rates in the csDMARDs and TNFis tapering group were 33% *vs*. 43% (p=0.17), and also mean DAS28, HAQ-DI and EuroQol EQ-5D did not differ between tapering groups after 1 year and over-time, demonstrating no difference, with potential bDMARDs-related AEs and costs saving.

Treatment strategies are currently one of the best tools for managing RA throughout the history of the disease. However, their effectiveness refers to the average of RA patients. Being able to identify the subgroups of patients to whom the different strategies (as well as the different drugs) can apply could contribute to the further progress of the management of patients with RA.

Precision medicine

Precision medicine remains one of the major unmet needs in the management of RA, still occupying a relevant position in research agenda (1). Genetic biomarkers of response to cs/bDMARDs and serum biomarkers have been widely investigated to guide treatment decisions, but results remain heterogeneous. On the other hand, synovial biomarkers are thought to be intimately closer to inflammatory burden in RA, and their evaluation has helped researchers in understanding how complex and heterogeneous rheumatoid synovitis is. Histological and mRNA expression analysis of synovial samples from early treatment–naïve RA patients have been

linked to first-line DMARDs treatment failure, thus supporting the possibility to be faster in treatment escalation, while higher inflammatory burden in synovial membrane might be related to treatment refractoriness. The use of machine learning, as well as integration of results from multicentre consortia, might help in decoding such a huge amount of information, linking synovial, genetic and peripheral blood biomarkers with different b/tsDMARDs clinical response.

Genetic biomarkers have been extensively studied, and, despite contributing in understanding the relevant pathogenic features of the disease, none of them demonstrated full replicability in antedating therapeutic responses. In a work by Guan and co-workers (37), the adoption of machine learning was helpful to integrate baseline demographic, clinical, and genetic biomarkers with clinical response to TNFis at 24 months, using a Gaussian process regression model. The authors demonstrated that clinical factors were more important than genetics in predicting TNFis response, but combination of both in integrated response models resulted in better prediction of treatment refractoriness. More deeply, when synovium transcriptomic analysis and genetics are combined, it might be possible to depict specific genetic features of TNFis responders. Starting from gene co-expression modules analysis in RA synovium, Aterido *et al*. (38) identified specific gene signatures associated with systemic response to ADA, suggesting these genes are involved in nucleotide metabolism and epigenetic marks of T regulatory cells (Tregs) and myeloid precursors. In line with genetics, serum biomarkers have failed in being integrated across personalised treatment algorithms, even if a prognostic role for acute phase reactants levels, RF and ACPA is well known (1). During the last year, a systematic literature review has demonstrated a slight (but significant) role for ACPA positivity in predicting ABT response, both in RCTs and observational studies, while this behaviour was not captured with TNFis (39). Considering multi-biomarker disease activity (MBDA) score, baseline assessment was not able to stratify 6-month response to MTX- and ADA in an early RA RCT (OR 1.01, 95%CI 0.99–1.03), while its variation between baseline and the 3-month time-point was (OR per unit increase 0.98, 95%CI 0.96–1.00) (40). Another option under the lens of researchers is *in vitro* manipulation of peripheral blood mononuclear cells (PBMCs) with available drugs (41,42). At present, results remain contrasting. Following incubation of PBMCs with bDMARDs and stimulation with heat-killed Candida Albicans or a Toll-like receptor 2 (TLR2) agonist (Pam3Cys), Tweehuysen *et al*. (41) were not able to demonstrate a significant additive value for cytokines inhibition *in vitro* in predicting treatment response. Only 4 out of 64 tests showed some predictive value, and main predictors of refractoriness remained clinical factors, such as disease activity. Contrariwise, another group of researchers (42) evaluated reversibility of PTPN22 gene expression, a non-receptor tyrosine phosphatase with anti-inflammatory functions, demonstrating that *in vitro* treatment of PBMCs with biologics (after stimulation with anti-CD3) was able to revert transcript levels of PTPN22, separating clinical responders from non-responders. These results await validation in large datasets. Additionally, RNA expression and serum biomarkers analysis have been investigated for predicting drug-free remission and RA disease-onset. In an exploratory study in patients on clinical and ultrasound (US) remission (43), interruption of csDMARDs was undertaken in order to evaluate predictors of flare at 6 months. An integrated score comprising 5 baseline variables (3 transcripts, one cytokine IL-27, one clinical - Boolean remission) demonstrated a sensitivity of 91% (95%CI 78–100) and specificity of 95% (95%CI 84–100) in differentiating patients experiencing flares from drug-free remission. On the opposite side of the disease, the Fab-glycosylation of ACPA seems to be a useful biomarker for RA development (44). It was demonstrated, in Indigenous North Americans, that glycosylation of the antibody variable (V) domain of ACPA IgG associated with development of clinically overt RA in first-degree relatives (HR 6.07, 95%CI 1.46–25.2). This process is thought to be linked with activation of T cells-dependent autoimmunity in predisposed subjects, underlining a population that needs to be strictly followed for clinical transition.

As synovial membrane is the primary target of inflammation in RA, synovial biomarkers are under investigation in search for precision medicine. Exploiting the large 'Pathobiology of Early Arthritis Cohort' (PEAC) (45,46), the most intimate features of early treatment-naïve rheumatoid synovitis were depicted, with 3 distinct pathotypes based on cellular and RNA expression analysis: lympho-myeloid (rich in B and myeloid cells), diffuse-myeloid (poor in B cells/plasma cells) and pauci-immune patterns (prevalent stromal cells) (45). The latter associated with lower response to DMARDs, while baseline molecular signatures related to lymphoid and myeloid patterns associated both with higher disease activity and improved treatment response (mainly MTX, 6 months). Moreover, when combining baseline molecular signatures with treatment features at 12 months, a higher proportion of patients with lympho-myeloid pathotype required biological therapy (46). After integrating histological and molecular signatures into a prediction model, sensitivity and specificity for predicting requirement of biological therapy increased, highlighting a population in which it might be possible to be faster in treatment escalation. These data are intimately connected with the hypothesis that higher synovial inflammatory burden is related to worse treatment response, and other authors have evaluated CD68-positive cells at immunohistochemistry (IHC) analysis in US-guided synovial biopsies from seronegative treatment-naïve RA patients before undergoing MTX treatment (47). Higher sublining CD68 score predicted lower treatment response. Given the heterogeneity of chronic synovitis, being more enhanced when multiple treatment failures occur, the possibility to integrate synovial gene expression analysis with clinical response exploiting machine learning is fascinating. Kim

and colleagues (48) have evaluated differentially expressed genes from RA synovium (11 datasets), describing different clusters of gene expression. Machine learning implementation enabled the identification of specific genes associated with clinical response to IFX, suggesting data integration from multicentre studies and new technologies implementation might help in selecting the right drug for the right patient, thus approaching precision medicine in RA.

Treatment decisions sharing

Understanding patients' perspectives is advocated in a process of shared treatment decision-making, to improve adherence and foster positive effects on disease outcomes. Patient-physician communication in close cooperation with other health professionals should be part of the comprehensive RA management, where comorbidity screening and prevention are strategically addressed, as well.

Shared decision-making is pivotal in patient-centred health care. In this process, physicians and patients cooperate to make decisions and plan the individual care by combining the evidence consistently with patients' values. The importance of shared decision-making is confirmed as the preferred approach to achieve evidence-informed decisions in the overarching principles of the 2019 update of the EULAR recommendations for the management of RA (1). Thus, understanding patients' perspectives should be preparatory to health decisions, to better reflect patients' goals and increase patients and physicians' satisfaction. Adherence to treatment is key to the successful management of RA and it may be variably affected by patients' beliefs. In a systematic literature review focusing on patients' preferences for DMARDs (49), when treatment attributes were compared, the benefits were generally more important than risks, but this was not always the case. Patients preferred to place a high value on treatment benefits over side effects, costs or route of administration. Serious but rare AEs, such as the hypothetical risk of cancer, had more weight than common but less serious ones, while drug regimens and the schedule of monitoring visits were less important than the expected benefits. Disease severity or previous treatments were less frequently associated with preferences than sociodemographic features like age, ethnicity, and income, and the educational status was positively associated with tolerance to risks and preference for intense treatments. Thus, the variability of patients' preferences should be captured to best individualise treatment choices in RA. Moreover, patient's education, addressing fears of potential side effects from treatments, is as important as the perception of their benefits. In a multicentre cohort study of 606 incident MTX users with RA, patients' beliefs and multi-morbidity strongly linked with non-adherence (50). Over the first 6 months following MTX initiation, 158 (26%) patients were ever non-adherent (71% intentional, 19% non-intentional, 10% unexplained). High medication concerns (despite perceived need) and ≥2 comorbidities (compared to absence of comorbidities) were observed among predictors of ever non-adherence, and they may be potential targets for interventions to improve patients' adhesion. Adherence to treatment assessment may be a "tricky business" in some cases. Rheumatologists-reported anti-rheumatic medications use during visits may be reliable for monitoring patients' adherence, as reported in a prospective study of 2,818 RA patients (51). The overall agreement between patients and rheumatologists' reports collected during a visit was good (kappa: 0.78; 95%CI 0.72–0.83), and higher (0.89) for bDMARDs than csDMARDs (0.76). However, reporting stop dates was higher (19%) for patients-reported data compared with rheumatologists-reported data (13%), which may indicate that patients are discontinuing their use of RA medications before consulting their rheumatologist.

The inclusion of patient-reported outcomes (PROs) in clinical workflows may support medical decisions making to individualise RA treatment changes, taking into account satisfaction and confidence of patients. The integration of PROs in the visits of 196 RA patients by using a multidimensional score (PROMIS™) focusing on pain interference, fatigue, social roles, sleep, anxiety, and depression (among others), has demonstrated to be feasible and well-accepted both by patients and rheumatologists (52). Moreover, patients agreed about their improved awareness of treatment choices, and they felt able to make informed choices. However, the overall impact of PROs on RA management still needs to be fully elucidated. For example, the influence of patient's global assessment (PtGA) in composite and Boolean-based definitions of disease remission appeared to be relevant to patients in terms of risk of overtreatment, according to a large study on 27,768 RA patients from the international longitudinal METEOR database (53). Excluding PtGA from the Boolean-based definition increased the remission rate from 6% to 16%. While PtGA was moderately related to joint inflammation overall, this relationship became weak in low levels of disease activity. Thus, a considerable proportion of patients, otherwise in remission, still perceived high PtGA, putting them at risk of excessive immunosuppressive therapy. Therefore, a little caution is necessary when interpreting the significance of PROs.

A comprehensive shared decision-making process should rely on rheumatologists, as well as on specialised health professionals. In the 2018 update of the EULAR recommendations for the role of the nurse in the management of chronic inflammatory arthritis, rheumatology nursing was stated to be based on shared decision-making with the patient, as part of a complete healthcare team to provide evidence-based care (54). High levels of agreement were reported on the involvement of specialised nurses in patient needs-based education to improve knowledge of disease and its (self-) management, enhance satisfaction with care, control disease activity, improve patients-preferred outcomes. The contribution of specialised health professionals is expected to be substantial to improve RA management, particularly with regards to comorbidities. In the 3-year longitudinal extension of the Comorbidities and Education in Rheumatoid Arthritis RCT, during the

follow-up of 769 stable RA patients, a 0–100 score was developed to quantify comorbidities screening and management (55). The baseline score application was suboptimal, but it improved by 33% (particularly for CV risk screening, vaccination status and bone mineral density evaluation) after a nurse-led programme aiming at checking systematically for comorbidities screening and patient's advice giving.

Therefore, since shared decision-making is so important, rheumatologists, and their allied health professionals, should focus on communication skills, fostering close cooperation to achieve the best management of RA, beyond the ordinary treatment of the disease.

Cancer and RA treatment

The body of evidence on safety of biological therapies in RA patients with a previous history of cancer is still limited, but the reports from the last large observational studies supported that biological drugs may be considered safe, in terms of recurrences or new primary cancers development. New insights in the interplay among cancer, immunotherapies and inflammatory arthritis have been emerging from the growing experience on the use of the immune checkpoint inhibitors and the treatment of their immune-related AEs, including flares of pre-existing RA and new-onset persistent seronegative polyarthritis.

Physicians' concerns about the hypothetical cancer risk in RA treated with biological drugs, mainly TNFis, limited the experience on patients with a previous history of cancer, due to avoidance or delay in prescriptions. The possibility to treat neoplastic patients with biologics, however, is not completely remote. As reported from the analysis based on the CORRONA Registry involving 880 patients (56), 42% was treated with b/tsDMARDs within 12 months preceding malignancies (non-melanoma skin cancer (NMSC) not included). Among these patients, one third was taking such agents at first post-diagnosis visit, and 10.2% initiated biologic therapy within 3 years, with the majority of DMARD initiations during follow-up being a TNFi (54%). In a meta-analysis based on 13,598 adult RA patients with an history of a spectrum of prior malignancies and subsequently exposed to TNFis or RTX (12 studies) (57), these biologics were not associated with the risk of new and recurrent cancers compared to csDMARDs (TNFis: relative risk (RR) 0.95, 95%CI 0.83–1.09; RTX: 0.89, 95%CI 0.52–1.53). Stratification by type of cancer, timespan between bDMARD start and prior cancer diagnosis, and duration of biologic exposure did not significantly modify the effect sizes. These results are also consistent with a nation-wide study in Denmark on 4,762 miscellaneous patients (18,752 person-years of follow-up), including 2,551 (54%) RA with a previous cancer exposed to TNFis (58). No differences in risk of any cancer development were observed between the overall TNFis-exposed group and the 4,328 unexposed patients (crude HR 0.86, 95%CI 0.66–1.12; adjusted HR 0.82, 95%CI 0.61–1.11). Stratification by recurrent and new primary cancers, non-melanomas and other subtypes as initial primary cancer did not show significant differences. These results about the safety of TNFis and RTX among people who had a prior malignancy are promising, yet further studies are needed to help guiding clinicians in decisions making in the setting of active RA.

The use of the class of medications based on the inhibition of immune checkpoints for a variety of cancers unravelled a number of immune-related AEs, including inflammatory arthritis, whose features, potentially resembling RA, are still being defined. The most recent experiences from two cohorts of 1,293 (59) and 112 (60) patients who received any immune checkpoint inhibitor showed that the prevalence of rheumatic immune-related AEs, particularly polyarticular inflammatory arthritis, was variable (3% (59) to 71% (60)). Other manifestations, such as myositis, sicca syndrome, vasculitis, systemic sclerosis and lupus-like syndromes were not frequent and all immune-related AEs were either new-onset symptoms or flares of pre-existing diseases, including RA. A non-significant association was observed between development of autoantibodies like ACPAs, RF, antinuclear antibodies, and antibodies to extractable nuclear antigens and any immune-related AEs in a cohort of 99 patients, when tested pre- and post-treatment with immune checkpoint inhibitors (61).

A large proportion of patients with immune-related AEs (42% to 76%) may need treatment (mainly GCs), and only a minority may receive DMARDs, included biologics (59,60). In a prospective observational study of 60 patients referred to rheumatologists for inflammatory arthritis due to immune checkpoint inhibitors (62), half of patients persisted with active arthritis symptoms from 1 to 24 months after immunotherapy cessation. In 75% of these patients, immunosuppressive treatment (80% systemic and/or intraarticular GCs, 32% csDMARDs, 18% bDMARDs) was required, and the frequency of progression of their cancer did not differ from patients not receiving DMARDs (OR 0.65, 95%CI 0.17–2.47).

To sum up, the growing use of immune checkpoint inhibitors may increase the number of inflammatory arthritis as immune-related AEs for which a rheumatologist is called upon to treat. Persistence of polyarthritis after immune checkpoint inhibitors cessation may require immunosuppressive treatment, which is expected to be efficacious, with no apparent effects on tumour progression at follow-up.

Cardiovascular risk

RA is associated with increased CV disease (CVD) risk, due to a combination of inflammation, impaired physical activity and alterations in lipids metabolism. A global reduction of inflammation can improve CV outcomes, but it is still unclear whether modulating TNF or other targets of immunity in RA can lead to additive beneficial effects on the CV system (63). On the other hand, specific CV treatment-emergent AEs have been linked with tsDMARDs treatment, despite meta-analysis data are reassuring. Again, CV risk prevention is still suboptimal world-wide, but statins need to be considered for CV risk reduction, and treat-to-target strategies for CV risk factors should be implemented in RA population.

CV safety of different DMARDs may drive clinicians' choice of a drug over another in RA patients at higher CV risk (64). In this regard, CV safety of non-TNFis was assessed during the last year. A systematic literature review with meta-analysis (65) of 14 observational studies in adults with RA would suggest that, as compared to TNFis, TCZ may be associated with a 41% reduced risk of MACEs (OR 0.59, 95%CI 0.34–1.00), whereas csDMARDs may be associated with increased risk of MACEs (OR 1.45 [1.09–1.93]) and stroke (OR 1.17, 95%CI 1.01-1.36). There was no difference in risk of MACEs between ABT and TNFis or between TCZ and ABT, or in risk of stroke between different biologics. The CV safety of TCZ was assessed also in a randomised, open-label, parallel-group trial that enrolled patients with active seropositive RA (n=3,080), with inadequate response to csDMARDs, and with at least one CV risk factor (66). Patients were randomly assigned 1:1 to open-label TCZ or etanercept (ETA) and followed up for an average of 3.2 years. Despite increase of serum low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), and triglyceride (TGL) levels, the estimated hazard of MACEs for TCZ was similar to ETA (HR 1.05, 95%CI 0.77–1.43). Another report by Xie *et al*. (67) provided evidence that, despite unfavourable changes in lipid profiles, the global CVD risk with TCZ is comparable to other biologics. The authors conducted a cohort study of 88,463 patients with RA in whom treatment with bDMARDs was initiated. Compared to TCZ, the corresponding adjusted HRs for a composite endpoint of myocardial infarction, stroke, and fatal CVD were 1.01 (95%CI 0.79–1.28) for ABT, 1.16 (0.89–1.53) for RTX, 1.10 (0.80–1.51) for ETA, 1.33 (0.99–1.80) for ADA, and 1.61 (1.22–2.12) for IFX, after adjustment for RA disease activity.

There is uncertainty regarding CV safety of JAKis, due to the reported increased risk of venous thromboembolism events for both tofacitinib and baricitinib at higher dosage, and given EMA recommendations for tofacitinib treatment in patients at high risk of blood clots (68). However, the effect of JAKis (tofacitinib, baricitinib, upadacitinib, peficitinib, decernotinib) on CV risk was assessed via meta-analysis of 26 RCTs randomising 11,799 adults RA patients (69). No significant difference was observed regarding all CV AEs risk following JAKis usage in general or for single drugs. Likewise, there was no significant difference for JAKis treatment overall regarding occurrence of MACEs (OR 0.80, 95%CI 0.36-1.75) or venous thromboembolism events (OR 1.16, 95%CI 0.48-2.81). Dose-dependent impact of JAKis on the risks of all CV AEs, MACEs and venous thromboembolism events was not observed with tofacitinib (5 mg *vs*. 10 mg) and upadacitinib (15 mg *vs*. 30 mg), whereas baricitinib at 2 mg was found to be safer than 4 mg in all CV AEs incidence (OR 0.19, 95%CI 0.04-0.88). Post-marketing data integration is needed to corroborate the safety profile of JAKis.

Although CVDs significantly contribute to mortality excess in RA, CV prevention has been largely insufficient. This year, the Cardiovascular Pharmacotherapy Working Group of European Society of Cardiology published opinion-based recommendations on CV stratification and LDL-C targets, strategies for monitoring of lipid parameters and treatment of dyslipidaemia in RA (including lifestyle, lipid-modifying therapies, and DMARDs) (70). Moreover, the research group introduced a new algorithm for estimation of CV risk and lipid management in RA that stratifies patients according to RA-related factors impacting CV risk (such as RA activity, severity and medications). The specific effect of statins on primary prevention of CVDs in RA patients was addressed in the Trial of Atorvastatin for the Primary Prevention of Cardiovascular Events in Patients with Rheumatoid Arthritis (TRACE RA), a randomised, double-blind, placebo-controlled trial of 3,002 patients with RA, aged >50 years or with a disease duration of >10 years, who did not have clinical atherosclerosis, diabetes, or myopathy (71). Atorvastatin 40 mg daily was safe and resulted in significantly greater reduction of LDL-C levels than placebo in patients with RA, and a 34% risk reduction of a composite of CV death, myocardial infarction, stroke, transient ischemic attack, or any arterial revascularisation, which is consistent with statin effects in other populations. However, the study was terminated early (median 2.51 years) due to lower than expected events rate and the HR for the primary end-point was not significant. Finally, as debate on the efficacy of controlling traditional CVD risk factors in RA is ongoing, for the first time treat-to-target approach of traditional CVD risk factors for primary prevention in patients with well-treated RA proved to be beneficial for reduction of atherosclerosis progression and fatal and non-fatal CV events (72). In the Franciscus Rheumatoid Arthritis and Cardiovascular Intervention Study (FRANCIS), an open-label, RCT of 320 patients with RA aged <70 years without prior CVD or diabetes mellitus, participants were randomised 1:1 to either treat-to-target approach or usual care of traditional CVD risk factors. The mean carotid intima media thickness progression was significantly reduced over 5 years in the treat-to-target group compared with usual care and CV events occurred in 2 (1.3%) of the patients in the treat-to-target group *versus* 7 (4.7%) in those receiving usual care. These evidences reinforce the need for better CV risk monitoring in patients with RA, independently from disease activity reduction and specific b/tsDMARDs CV safety.

Biosimilars, applicability and acceptability in clinical practice

Biosimilars have the potential for appreciable cost savings compared to their reference biologics, even if their safety and cost-effectiveness in diverse clinical settings are still matter of debate. From a practical point of view, costs reduction is maintained in case of dosage escalation, and following switch from biological reference products (BRPs) to biosimilars. Moreover, several trials have demonstrated that switching from IFX, ETA or RTX bio-originator to biosimilar is safe and efficacious.

Despite frequent dose escalation with IFX in clinical practice, savings from the current price of its biosimilar substantially offsets the costs of an alternative infused TNFi biologic for which no biosimilar is available. Curtis et al. analysed Medicare enrolees with RA initiating IFX (n=5,174) or golimumab (GOL) (n=2,843) (73). Dose escalation was rare for golimumab (5%) but common for IFX (49%), and was even more common (72%) for IFX among patients who persisted on treatment. Regardless of dose escalation, the adjusted mean dollar amounts were appreciably higher for GOL ($28,146) than for IFX ($21,216), and greater among persistent patients (cost difference $9,269, favouring IFX). Furthermore, switching from ETA originator to biosimilar did not lead to increased healthcare utilisation and costs in 1,620 adult RA patients from the Danish nationwide DANBIO registry (74). Costs before and after switching were mainly driven by outpatient visits (67%/72% of all costs), while monthly fluctuations of costs were similar before/after switch. After switching, use (8%) and costs (7%) of outpatient services increased, whereas costs of admissions (55%) and medication (5%) decreased. The only factors associated with an increase in use and costs of healthcare resources were longer treatment duration and ageing.

More trials are now demonstrating that switching from the BRP to biosimilar is, at the same time, safe, effective and well tolerated. The NOR-SWITCH extension trial (75) aimed to assess efficacy, safety and immunogenicity in patients on IFX biosimilar CT-P13 throughout the 78-week study period (maintenance group) *versus* patients switched to CT-P13 at week 52 (switch group). This trial extension has shown no difference in safety and efficacy outcomes between patients who maintained CT-P13 and patients who switched from originator IFX to CT-P13. EQUIRA was a phase III, double-blind study conducted in moderate-to-severe cs/bDMARDs-IR RA patients (76). Eligible patients were randomised 1:1 to receive biosimilar ETA (GP2015) or originator-ETA for 24 weeks, along with concomitant MTX at stable dose (10-25 mg/week). At week 24, patients with at least moderate EULAR response in the biosimilar-ETA group continued treatment, and those in the BRP-ETA group were switched to receive biosimilar-ETA for up to 48 weeks. The 48-week results from the EQUIRA study confirmed that switch from ETA BRP to ETA biosimilar does not impact the efficacy, safety, or immunogenicity of ETA. Again, the efficacy and safety of CT-P10, a RTX biosimilar, was confirmed in the extension period of a randomised, double-blind, phase III trial involving patients with RA (77). Patients received 48 weeks' treatment with CT-P10 or reference RTX, and those entering the extension period remained on CT-P10 or originator, or switched to CT-P10 from originator for an additional course. Long-term use of CT-P10 up-to 72 weeks was effective and well tolerated. Furthermore, switching from reference RTX to CT-P10 was well tolerated and did not result in any clinically meaningful difference in terms of efficacy, pharmacodynamics, immunogenicity and safety. Thus, these results corroborate the efficacy and safety profile of TNFis and RTX biosimilars, even after switching from BRPs.

Non-pharmacological management in rheumatoid arthritis

The main innovations in the field of non-pharmacological treatments are related to studies addressing known risk factors for RA. Moreover, some studies have applied non-pharmacological measures to treat fatigue. Despite an increasing interest in targeting established risk factors for the development of RA, strong evidence showing a significant impact on disease activity in patients with a confirmed diagnosis is lacking.

Analysing specific risk factors for RA, the treatment of periodontal disease has not proven to drive significant changes on disease activity in RCTs, despite some positive results in previous and recent observational studies (78-82). In a case-control study, 44 RA and 20 spondyloarthritis patients were compared to 26 healthy controls. Periodontitis was measured by Approximal Plaque Index (API), bleeding on probing index, probing depth and number of teeth. Swabs to detect P.gingivalis were also undertaken. Subjects with periodontitis received periodontal treatment and training in oral hygiene, and they were seen 4–6 weeks later. Periodontitis was detected in 75% of RA patients and gingivitis in 20%, while P.gingivalis in 41%. While CRP and erythrocyte sedimentation rate (ESR) did not significantly decreased after treatment, a statistically significant difference in DAS28 was detected (from 4.32 to 3.84 in DAS28-ESR), although still within the range of moderate disease activity and not exceeding the minimal important difference of the measure (78). Kaushal *et al*. (79) enrolled 22 patients with active RA, and divided them into an arm with periodontal treatment, and controls, without randomisation or blinding. The impact on disease activity was assessed after 8 weeks. Periodontal treatment resulted in no differences in terms of ACPA and RF titres, while there was a statistically significant reduction in disease activity, assessed by Simplified Disease Activity Index (SDAI)(from 30.52 to 19.02, $p<0.0001$).

Besides several observational studies, which showed encouraging results, in 2019 two RCTs on periodontal treatment in RA have been published. A nested RCT (80) was performed in the context of the ESPOIR cohort. Patients were randomised to receive recommendations of good oral hygiene and twice a year scaling, *versus* no intervention. Of the 472 patients randomised, 81 accepted dentist's evaluation, and 52% of them had signs of periodontal disease. Patients were assessed after 2 years, the mean decrease in DAS28-ESR was -0.017 and -0.09 in treatment and control arm respectively (not significant). The negative result was confirmed also in analysis stratified for ACPA status. Monsarrat and colleagues performed an open-label RCT (ESPERA trial) on 22 RA patients with moderate disease activity (81). Patients were randomised to receive or not recommendations on oral hygiene, scaling and systemic antibiotics, and assessed 3 months later. Sample size calculation implied 16 patients per arm, however, recruitment was interrupted before reaching the target

for futility. No differences in term of disease activity, and quality of life impact were found between the two arms, neither ACR20, 50 nor 70 responses achieved. Therefore, despite previous promising results in observational settings, two RCTs failed to demonstrate an effect of periodontal treatment on disease activity in RA. Studies on subsets of patients with more active disease and non-responders might provide further insights on this topic.

The evidence of the impact of smoking cessation in patients with RA is still scarce, despite its known evidence in RA development risk assessment. A Cochrane systematic literature review identified two RCTs (57 subjects with RA) on the efficacy of interventions for smoking cessation (83). The studies assessed a tailored smoking cessation program and cognitive-behavioral approaches in small groups, compared to brief advice and information. Both studies showed no differences in terms of smoking cessations at 6-month follow-up time-point. The overall quality of the evidence was defined very low, due to indirectness, imprecision and high risk of detection bias. The authors concluded that no evidence on the impact of smoking cessation on disease activity can be derived, and, moreover, interventions to stop smoking, known to be effective in the general population, do not seem to work in people with RA (83).

Non-pharmacological interventions might be of value in targeting fatigue, which remains an uncovered need in RA. Cognitive-behavioural approaches delivered by rheumatology teams have proven to reduce fatigue in a 2-year RCT. Hewlett *et al*. (84) performed a randomised trial in 7 centers in the UK, comparing cognitive behavioural treatment delivered by a rheumatology team, plus usual care and usual care alone. An existing course targeted against fatigue in RA, using cognitive behavioral treatment, was delivered by pairs of nurses/occupation therapists, while controls received an information booklet. The primary outcome of the study was fatigue, measured by the Bristol RA fatigue numerical rating scale (BRAF-NRS), collected through a telephone interview at 26 weeks. Secondary outcomes included pain, disability and disease activity. All outcomes were measured through week 104. Treatment and control arms enrolled 175 and 158 patients, respectively. At 26 weeks, there was a significant reduction in BRAF-NRFS in both arms; regression analysis showed a difference in reduction of BRAF-NRS of -0.59 favoring intervention (p=0.03). This difference was maintained at 104 weeks. The only secondary endpoints being significantly different between the two arms were those measuring fatigue. Being female and higher baseline disease activity were predictors of worse outcome.

Moderate-to-high intensity exercise also impacted on fatigue in older patients, despite not being effective on disability (84-86). Lange *et al*. (86) performed a RCT on elderly patients (>65 years old) with RA, comparing moderate-to-high intensity, aerobic and resistance training 3-time a week with home-based light intensity exercises for 20 weeks. The primary outcome was disability, assessed through the HAQ-DI, while physical fitness was a secondary outcome. Intervention was delivered to 36 patients, while 38 were allocated to the control group; 76% of patients were in remission or in low disease activity. No differences in terms of disability were shown between groups, despite a significant in-group decrease of HAQ-DI only in the intervention group at 20 weeks, and in the 52-week extension follow-up. A sub-analysis (85) from the same trial focused, instead, on a multidimensional evaluation of exercise on fatigue, measured through the multidimensional fatigue inventory, which was the primary outcome. Subjective perception of fatigue assessed by visual analogic scale (VAS), anxiety and depression were among the assessed outcomes. After 20 weeks, mental and physical components of fatigue were significantly reduced in the intervention group compared to controls. Moreover, a significant reduction of symptoms of depression was seen at the end of follow-up. At 52 weeks, withdrawal of the supervision during exercise resulted in loss of the achieved benefits.

Miscellaneous in rheumatoid arthritis treatment

Peripheral neuropathies and DMARDs

The risk of peripheral neuropathy is increased in patients using TNFis, compared to those treated with other DMARDs (87). A nested case-control study, based on the US administrative healthcare database Pharmetric Plus, included 61,570 patients with RA (64.7% of the total population), psoriatic arthritis and ankylosing spondylitis treated with biologics. There were 1,358 cases of peripheral neuropathy, with an increased risk for past users of TNFis (RR 2.77, 95%CI 1.67–4.58), compared to subjects receiving MTX and a second DMARD. The risk in recent users was not significantly increased, instead (87).

Glucocorticoids

An intensive initial treatment regimen, including medium-dose GCs, results in a long-term mortality comparable to that of the general population. This evidence supports the concept of the greater impact of a rapid suppression of disease activity over the detrimental effects of GCs on mortality (88). Poppelaars *et al*. (88) presented the data on the long-term follow-up of 155 patients taking part to the COBRA trial in terms of survival. Mortality at 23 years did not differ between intensive treatment (receiving a starting dose of 60 mg/day of prednisone) and control groups. Moreover, it was similar to that of a reference sample of the general population.

Interstitial lung disease

Lung diseases are emerging as one of the main issues in RA. A large retrospective study demonstrated a prevalence of 7.7%, with interstitial lung disease (ILD) as main manifestation (89). RTX is often proposed as therapeutic option, however efficacy is supported only by observational studies. Duarte *et al*. (89), in a retrospective study, reviewed patients with RA undergoing CT scan, and assessed patients with ILD treated with RTX until week 36. In this population, the prevalence of ILD was 7.7%, diagnosed after a median of 9 years of disease duration. ILD was the commonest type of lung involve-

ment. RTX was used in 57.8% of patients with ILD, while mortality related to ILD occurred after a median of 5.3 years after its diagnosis.

Vaccines and RA treatments

In RA patients, vaccine administration is recommended, especially in those receiving b/tsDMARDs, but immune responses can be influenced by the agent in use. In a cohort study (90), when influenza seasonal vaccination was administered in presence of bDMARDs, final seropositivity status was less common during RTX exposure than with TNFis. Besides, better responses were achieved when the interval between the influenza vaccination and RTX administration was longer than 12 weeks. Although vaccine efficacy prior or during treatment with bDMARDs has been largely investigated, little is known about their potential use with tsDMARDs. Some studies have proven that JAKis do not interfere with vaccine immunogenity. For instance, baricitinib did not affect antibody titres at week 5 and week 12 after pneumococcal vaccine administration (both 13-serotype pneumococcal conjugate vaccine and 23-serotype pneumococcal polysaccharide vaccine), regardless of drug dosage (4 mg *vs*. 2 mg OD) or concomitant use of GCs and MTX (91)**.** It is notified that tofacitinib could reduce the absolute lymphocyte count (ALC) and patients with a confirmed ALC nadir of <500 cells/mm3 could be at increased risk of serious infections, especially from varicella zoster (VZV), which shows a trend towards an increased risk with lower ALC values (92). In this view, a post-hoc analysis of the ORAL-STRATEGY trial has demonstrated that administration of live VZV vaccine in RA patients before starting tofacitinib (plus MTX or in monotherapy) associated with similar risk of developing VZV infection compared to non-vaccinated population. The trial was not powered to assess differences between vaccinated and non-vaccinated patients. Regarding safety, no vaccinated patient had zoster-like lesions in the 42 days following vaccination, even in presence of steroids and csDMARDs as concomitant therapy, which independently contributed to increased infection risk in combination with tsDMARDs (93). Interesting data might be obtained investigating the new adjuvanted VZV subunit vaccine, which is not a live vaccine, not formally contraindicated in immunosuppressed patients.

RA therapy with b/tsDMARDs in elderly patients

Therapy with bDMARDs in elderly RA patients could be challenging, due to their potential higher complexity in comparison with younger subjects. A systematic literature review with meta-analysis (94) offered an insight of efficacy and safety in 60-65 year-old patients, treated with TNFis, ABT, TCZ, RTX and tofacitinib: heterogeneous results arose from studies considering TNFis, while a single study on TCZ and another on RTX showed lower efficacy responses in older patients, as compared to younger ones. On the other hand, ABT seemed to have comparable efficacy outcomes between the two groups. Regarding drug safety, the risk of serious infections with TCZ was higher in older population, as well as with tofacitinib, especially VZV infection. This could be associated to the intrinsic age-related immunosuppression, but even to specific DMARDs effects on CRP levels and ALC: in the first case, lower CRP levels could misrepresent initial infections, while in the second case a reduction in lymphocytes count could predispose to them. Given the limited number of studies and heterogeneity in reporting outcomes, meta-analyses of any other outcome for others drugs were not possible. In a study of open-label periods of three phase IV RCTs of ETA for RA (95), efficacy outcomes were similar between subjects aged < and >65 years old. In particular, there was no statistically significant difference between the groups in modified total Sharp score radiological changes from baseline. Further studies involving age-stratified patients are needed to drive shared conclusions.

RA therapy and pregnancy outcomes

Therapeutic strategies with DMARDs in female RA patients are definitely affected during particular phases of their lives, as becoming or being pregnant. The main cause lies in the potential teratogenic effect of many drugs or in the lack of trials involving pregnant patients for others, especially bDMARDs. Nevertheless, interesting data from one study (96) demonstrated how drugs accepted as compatible with pregnancy had the highest discontinuation rates in the first trimester of pregnancy, in particular antimalarials (57.3%), azathioprine (59.1%), sulphasalazine (69.5%) and biologics (50.8%). Variables explaining this aspect included maternal characteristics, patient compliance and healthcare factors, even if the study design, based on administrative data, limited to ensure specific reasons for therapy discontinuation. Studies concerning primarily bDMARDs have shown that TNFis utilisation decrease sharply in the second and third trimesters compared to the first one, but ETA consistently remained the most frequently used drug during any period of pregnancy, if matched with IFX (97). Primary explanation is offered by their different molecule structure and placentar passage rates, notably reduced with ETA. Surprisingly, certolizumab (CTZ), which is the only TNFi with a certified indication for usage during the whole pregnancy period, and GOL had the lowest prevalence in both pregnant and non-pregnant cohorts with a diagnosis of RA, according to an electronic healthcare data analysis (97). In addition, the same study underlined that a higher use of any TNFi in pregnancy correlated with older maternal age, compared with the matched non-pregnant group, mostly due to the intrinsic increase of pregnancy complications given by age, and potentially worsened by other treatments, such as GCs.

Regarding early discontinuation of TNFis in case of pregnancy planning, a retrospective study by Shimada and co-workers (98) compared two groups of RA patients in which discontinuation of TNFis treatment (CTZ or ETA) occurred at the time of conception *versus* after pre-conceptional counselling. Only in the first group these strategies were able to shorten time to pregnancy. Conversely, no relevant differences were observed in possible adverse

pregnancy outcomes, specifically spontaneous abortion, preterm birth, light-for-date and premature rupture of the membranes.

Conclusions

We have reviewed the main novelties in the treatment of RA, following relevant publications across the last year. Since no specific biomarker is currently able to stratify *a priori* treatment responses to specific b/tsDMARDs, and given an apparent similar efficacy profile for drugs with different mechanisms of action, we believe, in line with 2019 EULAR Recommendations (1), that specific treatment strategies have to be carefully evaluated at single-patient level, bearing in mind the role of relevant comorbidities, potential side effects and costs of drugs, as well as patients' point of view. New data from international studies are reassuring regarding the safety profile of biologics (*e.g.* in case of cancers), while new insights are expected for CV risk assessment in JAKis-treated patients. Since the armamentarium of new drugs in the treatment of RA is going to increase, deep knowledge of specific mechanisms of action remains of relevant importance, in search for predictive biomarkers of response, which might be able to unveil the real significance of RA heterogeneity and its links with therapeutic responses.

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