One year in review 2018: novelties in the treatment of rheumatoid arthritis

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ABSTRACT

The current approach to treatment of rheumatoid arthritis (RA) includes early and aggressive intervention aiming to reach early and persistent low disease activity and remission. New drugs have improved the therapeutic armamentarium of rheumatologists, providing new options for patients. Beyond these innovations, new evidence has improved the safety of therapies and provided tools for the optimisation of long-term management of RA. This paper reviews the most relevant studies published over the last year in the field of treatment of RA.

Introduction

Rheumatoid arthritis (RA) is a chronic autoimmune disease characterised by synovitis and joint damage, which can produce a loss of function, impair quality of life and enhance morbidity and mortality. The current therapeutic approach of RA includes early and intensive treatment, aiming to reach early and persistent low disease activity and remission. Recently, new drugs increased the therapeutic options for patients, including both novel targeted therapies and biosimilars. New evidence has accumulated on real-world safety and efficacy of various biological disease-modifying anti-rheumatic drugs (bDMARDs). Starting from the last annual review on this topic, this paper reviews the most relevant studies published over the last year on the management of RA (1).

Prevention of rheumatoid arthritis

Despite fascinating, prevention of RA is still one of the forbidden dreams for rheumatologists. A comprehensive review disentangled the potential preventive strategies of RA and future perspectives (2). Most of trials targeted the pre-arthritis phase, typically defined as arthralgia and autoantibody positivity, under the hypothesis that the initiation of a disease-modifying treatment in these patients might prevent disease development. Glucocorticoids (GC), rituximab (RTX), methotrexate (MTX) failed to demonstrate such preventive effect, but several studies are under way testing hydroxychloroquine (HCQ), metilprednisolone and MTX, abatacept (ABA), or atorvastatin. Until positive results are obtained from any of these studies, no evidence is available to support the use of DMARDs in patients without clinical arthritis.

Though preventive strategies in asymptomatic subjects at population level are not feasible, better stratification might allow a timely intervention from the very beginning phases even in absence of overt arthritis. A recent sub-analysis of 22 patients with high risk of RA development enrolled in the PROMPT trial, including patients with suspected RA and comparing 12-months MTX *vs*. placebo on the 5-year risk of RA according to 1987 criteria, demonstrated that only 6 of 11 patients (55%) developed RA, compared to 11 of 11 patients (100%) in the placebo arm (p=0.01) (3).

Glucocorticoids

The use of systemic GC in the management of RA is recommended as initial treatment in the early RA phase, for flares management and in bridge-therapy for established RA according to most of international recommendations and consensus statements, as analysed by a recent systematic literature review (SLR) including articles published between 2011 and 2015 (4). Current recommendations for use of GC are suboptimal and some aspects are partially or completely neglected in "official position" statements. According to the SLR, the recommended dosage

of steroids is defined as "low-dose" or "the lowest possible dose", but controversies still exist about the specific GC "low-dose" definition (less than 7.5/10 mg/day of prednisone equivalents in the majority of papers). Total length of the suggested "short-term" treatment period is debated as well, varying between 3 up to 24 months. Information of tapering schemes are scarce, as it is only advocated to taper "as soon as possible" with a slow tapering strategy (4). The balance between long-term safety and benefit and the role of GC use in the elderly population remain intriguing points to elucidate.

Recently, two studies investigated the initial GC dosage to consider in early RA (5, 6). The COBRA-light extension study evaluated the efficacy and safety of initial COBRA-light (prednisolone 30 mg/day, tapered to 7.5 mg/day in 8 weeks and MTX escalated to 25 mg/week in 8 weeks) *versus* COBRA therapy (prednisolone 60 mg/day, tapered to 7.5 mg/day in 6 weeks, MTX 7.5 mg/week and sulphasalazine (SSZ) 2 g/day) after 4 years of follow-up (5). Between 6 and 12 months patients not achieving minimal disease activity underwent treatment intensification of MTX (in COBRA arm) and addition of etanercept (ETA). 77 patients starting COBRA were compared with 72 patients on COBRA-light strategy. After 4 years, there were no significant differences in terms of prescription of new bDMARDs neither in disease activity score-(DAS) 28, Health Assessment Questionnaire-Disability Index (HAQ-DI), Boolean ACR/EULAR remission and radiographic progression. Despite the study was not powered to explore differences in terms of GC-related comorbidities onset, no significant difference was found between groups, suggesting that moderate dosages of GC can be efficacious and relatively safe in early RA. In the Care in Early RA (CARERA) open-label randomised trial, early RA patients, stratified according to prognostic factors, were assigned to different conventional synthetic DMARDS (csDMARDs) combinations and GC remission induction schemes during the first treatment year (6). High-risk patients were randomised to COBRA Classic strategy, COBRA Slim (prednisolone 30 mg/day, tapered weekly to 5 mg/day, MTX 15 mg/week) or COBRA Avant Garde (prednisolone 30 mg/day, tapered weekly to 5 mg/day, MTX 15 mg/week, leflunomide 10 mg/day) while patients at low-risk were randomised to COBRA Slim or MTX tight step-up (MTX 15 mg/week, no GC allowed). At week 34, GC were stopped in all groups and at 52 weeks comparable remission rates were maintained between different groups, irrespective of csDMARD use and GC dosage. For remission induction, a high GC dose was not more advantageous than a moderate dose, regardless of the csDMARD strategy, suggesting that COBRA Slim could be an effective, safe, low-cost and feasible initial treatment strategy for patients with early RA regardless of their prognostic profile (6).

Regarding long term efficacy and safety outcomes of GC use in combination with MTX, Safy *et al*. performed a follow up analysis of the second Computer-Assisted Management in Early RA (CAMERA-II) trial (7). After 2 years of initial treatment with MTX plus stable (10 mg/day) prednisone or placebo, patients were treated according to standard of care out of the protocol schedules, aiming to GC tapering (79% of patients discontinued prednisone at the end of follow-up). After a median follow-up period of 6.7 years, a significantly lower proportion of patients started a first bDMARD in the MTX plus GC arm (31%) compared to MTX plus placebo (50%); safety outcomes concerning GC-related morbidity were comparable between the two groups. Analysis of the ESPOIR cohort (8), as well, remarked long-term safety of low dose GC use in very early RA management. After a median follow up period of 7 years, patients exposed at least one time to systemic GC during clinical history (386 patients, 64.1%, mean 3.1±2.9 mg/day of prednisone equivalent) had similar safety outcomes (death, cardiovascular diseases, severe infections, fractures) compared to 216 patients never taking GC.

Combination of GC with novel targeted synthetic DMARD (tsDMARDs) use in RA treatment is under investigation. Charles-Schoeman *et al*. reported a post hoc analysis of 6 phase III trials of tofacitinib, in which a stable pre-trial GC dosage (less than 10 mg/day) was allowed (9). 1,767 patients already receiving GC (out of 3,200 tofacitinib-treated) were analysed. GC did not affect the overall efficacy of tofacitinib in all studies, resulting in similar ACR and CDAI (Clinical Disease Activity Index) responses in GC and not-GC paired samples. Regarding safety, Cohen *et al*. demonstrated that GC use was an independent risk factor for serious infections and Varicella-Zoster virus (VZV) infections in randomised clinical trials (RCTs) patients treated with tofacitinib (10).

Conventional synthetic disease-modifying anti-rheumatic drugs

The prompt start of treatment with csDMARDs is essential to control disease burden and prevent radiological progression and MTX remains the "anchor drug" of the initial strategy. In a recent SLR, Bergstra *et al*. investigated the dose-response to MTX in early RA patients considering 6-month effects on DAS28, erythrocyte sedimentation rate (ESR)/C-reactive protein (CRP) and HAQ-DI response in csDMARDs naïve subjects (11). Analysing 31 studies for a total of 5,589 patients, the authors concluded that higher MTX dosages did not meaningfully affect efficacy outcomes when in monotherapy or in association with GC or bDMARDs. Only one study in this SLR, however, considered subcutaneous administration of MTX, possibly resulting in a bias related to the way of administration of the drug and its pharmacokinetic properties. These data were confirmed by a large international observational database, the METEOR database, in which low (less than 10 mg/week) or high (>15mg) dosages of MTX were analysed in monotherapy or in combination with GC or csDMARDs. Different dosages of MTX did not affect efficacy outcomes in all groups, even when adjusting for eventual confounding by indication (baseline and environmental characteristics) (12).

In patients without poor prognosis or

with a longer disease duration, triple therapy seems to be a safe option to consider before starting a biological therapy. Peper *et al*. provided results of the open-label extension of the Rheumatoid Arthritis Comparison of Active Therapies (RACAT) trial, which randomised patients with active disease despite MTX monotherapy to receive either triple therapy (MTX, HCQ, SSZ) or MTX-ETA (13). In the double-blind part of the study, inadequate responders at 24 weeks switched from one arm to the other. After a mean follow-up period of 11 months, patients on triple therapy had similar efficacy outcomes compared to MTX-ETA but a significantly longer persistence on treatment (at 1 year, 78% of patients on triple therapy compared to 63% MTX/ETA, p=0.005).

Conflicting results come from lower level of evidence studies, where persistence is also influenced by several non-medical factors. An analysis of administrative databases exploring real-life retention rate in 4,364 US veterans with RA has shown a 13% (95% confidence interval (CI) 9.2, 17.0 higher persistence on treatment at one year in patients treated with tumour necrosis factor inhibitors (TNF-i) plus MTX compared to triple therapy, even when adjusting for baseline clinical characteristics which could have influenced the choice of the treatment strategy (14).

In patients with poor prognostic factors, instead, after MTX failure, b-DMARD combination with MTX is preferred over combination of different csDMARDs, as confirmed in a recent SLR by Mary *et al*. (15). Triple therapy (MTX, SSZ and HCQ) had similar functional and safety outcomes compared to TNF-i plus MTX, while efficacy parameters and radiographic progressions were better for bDMARD combination.

Regarding infectious risk of cs-DMARDs when in combination with biologicals, Baradat *et al*. performed a SLR of RCTs and no difference was remarked in serious infection risk between MTX plus bDMARD users and bDMARD monotherapies (relative risk (RR) 1.15, 95%CI 0.84, 1.58) (16).

Biologic disease-modifying anti-rheumatic drugs

Efficacy

Currently there are 10 bDMARDs approved for RA, but the optimal treatment strategy in patients with inadequate response to cDMARDs is still matter of debate. There are no indications on which bDMARDs to be used in patients naïve to csDMARDs. The C-Early trial evaluated this aspect analysing efficacy and safety of MTX associated to Certolizumab (CZp) compared to MTX + placebo in patients naïve from csDMARDs, with early active RA (<1 years duration) and negative prognostic factors (rheumatoid factor and anti-citrullinated protein antibodies positivity). Both arms received MTX at the maximum-tolerated dosage. The primary end point of sustained remission from week 40 to 52 was achieved by 28.9% of CZp + MTX patients *versus* 15.0% of placebo + MTX patients (p<0.001), while sustained LDA (low disease activity) was achieved by 43.8% CZp + MTX patients *versus* 28.6% in the placebo + MTX group (p<0.001) (17). Regarding the treatment of RA with CZp, it was also published an updated Cochrane review that included 14 trials (12 phase III and 2 phase II; 7 comparing CZp to placebo and 7 CZp to MTX). 11 studies (5,422 participants) were included in the pooled analysis for benefits, two more than previously, and 13 (5,273 participants) in the pooled analysis for safety. The authors concluded that CZp at both dosage of 200 and 400 mg, comparing to placebo or MTX, reached primary major outcome with a high level of evidence (ACR50 at week 24 or 52 and DAS28<2.6 at week 24 or 52) or with a moderate level or evidence (HAQ-DI and radiological changes expressed as total Sharp score, erosion score and joint space narrowing). Serious adverse events (SEAs) were statistically but non-clinically significantly more frequent in CZp: odds ratio (OR) 1.47 (95%CI 1.13, 1.91) and 1.98 (95%CI 1.36, 2.90) for dosage of 200 mg and 400 mg respectively (high level of evidence). Withdrawals due to adverse events (AEs) was higher in CZp group (all dosages): OR 1.45 (95%CI 1.09, 1.94) for a moderate level of evidence (18).

Observational registries indirectly provided data on the efficacy of b-DMARDs in terms of persistence. The CORRONA registry analysed the persistence on treatment of 1,791 bio-naive patients who started ADA. The percentages of patients who stayed on ADA therapy were 64.1%, 48.0%, 26.7%, and 13.3% at 1, 2, 5, and 10 years, respectively and a small proportion (10%) of patients continued to be treated for up to 12 years (19). Also, data from RABBIT register evaluated the persistence in treatment with TCZ for a prolonged period (up to 3 years) stratifying the patients for the number of biologicals taken before starting TCZ. 885 patients were enrolled: 318 (35.9%) were biologic-naïve (first-line TCZ), 286 (32.3%) had one bDMARD failure (second-line TCZ), 186 (21.0%) two (third-line TCZ), and 95 (10.7%) ≥3 prior failures (fourth-line TCZ). The persistence in treatment at 3 years was significantly lower only in patients belonging to the fourth-line TCZ group, while it was comparable in the other cases. Consistently, the mean value of DAS28 at 3 years was significantly higher in patients previously treated with ≥3 bDMARDs. Nevertheless, even in the fourth-line of the TCZ group, 48% of patients reached a LDA. (20). Choy *et al*. carried out a prospective study to provide a real-world evidence of effectiveness and persistence for patients who initiated TCZ compared with TNF-i in routine clinical practice (ACTiON study). The study included a follow-up of 52 weeks and enrolled 1,216 patients, 423 (35%) initiating TCZ-IV (intravenous) and 793 patients (65%) anti-TNF-i. At baseline the TCZ group had shorter disease duration, higher values of DAS28-ESR and greater use of steroids than the TNF-i group while use of MTX was similar (74.7% TCZ *vs*. 79.7% TNFi-treated patients). Therapy with TCZ was significantly more effective than TNF-i and in terms of DAS28-ESR (mean difference week 24 -0.831, 95%CI, 1.086, - 0575; week 52 -0.910, -1.204, -0.617; both p<0.001); similar results were obtained using CDAI.

Treatment persistence was higher in TCZ than in TNF-i (p<0.001) with a comparable safety profile (21).

Safety

• *Cardiovascular outcomes*

RA is characterised by an increased risk of cardiovascular disease (CVD). DMARDs, especially biological drugs, are good candidates to reduce cardiovascular (CV) risk in RA, controlling systemic inflammation.

Kang *et al*. compared ABA and TNF-i in reducing CV risk in RA, by conducting a cohort study using longitudinal data from 2 large US healthcare claims databases Medicare and MarketScan analysing patients who started a biological (TNF-i or ABA). The risk of the composite CV outcome was lower in ABA initiators *versus* TNF-i in Medicare (hazard ratio (HR) 0.81, 95%CI 0.66, 0.99 but not in MarketScan (HR 0.95, 95%CI 0.74, 1.23), probably because this cohort generally consists of younger and healthier patients than those in Medicare. This trend, even not reaching statistical significance, was more evident in the subpopulation of patients with greater CV risk (age> 65 years and presence of diabetes mellitus) (22).

An SLR and meta-analysis evaluating composition of body mass using dual-energy x-ray absorptiometry in patients affected by RA and spondyloarthritis revealed that TNF-i increased in the short term (over 6 months) the lean mass but also the fat mass, that is associated with CVD risk (23).

On the other hand, a fundamental risk factor for CVD is endothelial dysfunction and clinical and preclinical evidence has suggested a role of TNF in the genesis of accelerated atherosclerosis. Ursini *et al*. performed a SLR and a meta-analysis regarding the medium and long-term effect of TNF-i on endothelial function and concluded that the TNF-i improve endothelial dysfunction assessed by flow mediated dilatation (FMD), laser Doppler iontophoresis, peripheral arterial tonometry and venous occlusion pletismography (24).

Interleukin (IL)-6 is a key cytokine in the induction of atherosclerosis, so it would be reasonable to think that its inhibition and therefore treatment with TCZ, should reduce cardiovascular risk but its effect on the lipidic status raises doubts about its actual effect on CVD development. Generali *et al*. conducted a retrospective study on the data collected by a Health Care database of Northern Italy to investigate the effect of TCZ on the risk of CV events compared ETA. The study concluded that TCZ is not associated to an increased risk of cardiovascular events compared with ETA: general CV events (HR 1.05, 95%CI 0.62, 1.78; p=0.848), myocardial infarction (HR 0.43, 95%CI 0.14, 1.27; p=0.127), stroke (HR 2.53, 95%CI 0.61, 10.52; p=0.202), other CV events (HR 1.18, 95% CI 0.68, 2.03; p=0.564) (25). Bacchiega *et al*. performed a pilot study evaluating the response on endothelial function and change lipid profile patterns after 16 weeks of therapy with TCZ, csDMARDs, or TNF-i. 60 patients were enrolled: 18 started therapy with TCZ at a dose of 8 m/kg IV every 4 weeks. For the control groups, 24 patients were enrolled in treatment with either MTX 15 to 25 mg/week (n=12) or leflunomide 20 mg/day (n=12), while 18 patients started ETA 50 mg/week (n=14) or ADA 40 mg every 2 weeks (n=4) Endothelial function was evaluated by mean increase in FMD, and was significantly improved only in patients treated with TCZ (from 3.43% to 5.96%, p=0.03) while it was not significantly increased for TNF-i (from 4.78% to 6.75%, p=0.09), and in the csDMARD group (from 2.87% to 4.84%, p=0.21) (26).

• *Risk of malignancy*

Due to their effect on the immune system, bDMARDs are still under surveillance for the risk of malignancies and infections. Maneiro *et al*. carried out a SLR and meta-analysis of RCTs and long-term extension studies to verify the risk of all neoplasms and solid, haematological and cutaneous (non-melanoma skin cancer (NMSC) and melanoma) malignancies in patients treated with bDMARDs or tofacitinib compared to the control groups (placebo or csDMARDs). No significant differences in the risk of neoplasm emerged for patients in bDMARDs or tofacitinib. From the meta-analysis of long-term extension trial appeared a reduced incidence ratio per 100 patients per year of solid neoplasms with ABA *vs*. ADA and of ABA *vs*. GOL (golimumab) in haematological malignancies. With regard to NMSC, a numerically lower value was found, although not significant, of incidence ratio for ETA compared to ABA, ADA and tofacitinib at the dosage of 10 mg BID but not at the dosage of 5 mg BID (27). Other studies assessing the risk of malignancies have been conducted from different registries giving consistent results. Mercer *et al*. evaluated the incidence of invasive cutaneous melanomas using data from eleven biologic registers from 9 European countries including 130,315 RA patients. While limited data were available for tofacitinib and ABA-treated patients, no significant differences in the melanoma incidence were observed between biologic-naïve patients and patients exposed to TNF-i, RTX, ABA or tofacitinib (28).

Wadström *et al*. performed a nationwide cohort study including 15,129 new courses of TNF-i as first or second bDMARD, 6,358 of non-TNF-i, and 46,610 csDMARDs users. A general population cohort of 107,491 subjects was identified as comparator. Evaluating the overall risk of cancer, there was no significant signal in patients starting the first or second TNF-i (HR 0.93, 95%CI 0.85, 1.01; HR 0.89, 95%CI 0.76, 1.04) and for those initiating a non TNF-I biologics (TCZ HR 0.89, 95%CI 0.67, 1.18; ABA HR 0.88, 95%CI 0.68, 1.14 and RTX HR 0.86, 95%CI 0.73, 1.03), compared to biological naïve patients (csDMARDs group). The risk of developing invasive squamous cell skin cancer was not significantly increased for the first or second TNF-i (first 1.09, 95%CI 0.84, 1.42, second HR 0.86, 95%CI 0.54, 1.39) whilst an increased risk was found for ABA (HR 2.15, 95%CI 1.31, 3.52). The results of the BSRBR-RA register confirmed a lack of increase of risk of melanoma in RA patients exposed to TNF-i in first or second line (first HR 0.85, 95%CI 0.60, 1.18; second HR 0.92, 95%CI 0.52, 1.61) (28, 29). From the same dataset, lymphoma risk was confirmed as not in-

creased in patients with RA treated with TNF-i compared to those treated with cDMARDs (crude HR 0.61, 95%CI 0.40, 0.92; adjusted HR 1.00, 95%CI 0.56, 1.80) (30).

• *Serious adverse effects*

A network meta-analysis was performed to compare the risk of SAEs including death for the 10 bDMARDs currently approved by the FDA (Food and Drug Administration) and the EMA (European Medicines Agency) and for tofacitinib compared to treatment with cDMARDs. 117 trials were included, for a total of 47,615 patients with RA, treated for approximately 30,971 person-years. The analysis shows that CZp was associated with a greater risk of SAEs compared to controls (rate ratios (RR) 1.45, 95%CI 1.13, 1.87) and compared to other bDMARDs: ABA (1.58, 95%CI 1.18, 2.14), ADA (RR 1.36, 95%CI 1.02, 1.81), ETA (RR 1.60, 95%CI 1.18, 2.17), GOL (RR 1.45, 95%CI 1.00, 2.08), RTX (RR 1.63, 95%CI 1.16, 2.30); but also compared to tofacitinib (RR 1.44, 95%CI 1.03, 2.02). TCZ was associated with more SAEs than ABA (1.30, 95%CI 1.03, 1.65), ETA (1.31, 95%CI 1.04, 1.67) and RTX (1.34, 95%CI 1.01, 1.78). Furthermore, the sensitivity analysis revealed that with co-administered csDMARDs in recommended dose, ABA associates with fewer SAEs than tofacitinib. As monotherapy and in recommended dose, tofacitinib had significantly lower rates of SAEs compared with ADA, TCZ, controls (*i.e.* no csDMARDs use) and tofacitinib plus csDMARDs. ADA monotherapy had a higher rate of SAEs than when used with concomitant csDMARDs (31).

Regarding the risk of tuberculosis, a meta-analysis including 29 studies (14 IFX, 2 GOL, 9 ADA, 1 ETA and 3 CZp) for a total of 11,879 patients (affected by RA but by all other pathologies in indication), showed that treatment with TNF-i was associated with an increased occurrence of tuberculosis with control groups (placebo or standard care) (OR 1.94, 95%CI 1.10, 3.44; p=0.02), without differences between different drugs included in the analyses (IFX 1.82, 95%CI 0.82, 4.06; ADA 2.11, 95%CI 0.73, 6.12; CZp 2.38, 95%CI 0.42,13.42). Evaluating only patients with RA, tuberculosis risk was higher compared to other indications (OR 2.29, 95%CI 1.09, 4.78; p=0.03). Subanalysis was also performed by differentiating the studies conducted in high or low tuberculosis prevalence area (OR 2.39, 95%CI 0.97, 5.90 and 1.64, 95% CI 0.70, 3.88, respectively) (32).

Specific AEs of TCZ (neutropenia and elevation of liver enzymes) were also assessed. Moots *et al*. performed an analysis of long-term safety data from TCZ phases 3 and 4 trials, long-term extensions and pharmacology studies involving 4,098 patients (1,454 received placebo+csDMARDs and 2,644 received TCZ ± csDMARDs). Reduced neutrophil counts (all grades) resulted greater in TCZ-treated patients than in placebo-treated patients. The occurrence of serious infection does not appear to be correlated with neutrophil decrease (33). Genovese *et al*. investigated liver enzyme abnormalities in data from phase 3 or 4 clinical trials, long-term extensions, and a pharmacology study comparing 4,171 patients treated with TCZ-IV and csDMARDs. A total of 2.5% of patients withdrew from TCZ treatment following liver enzymes elevations. A total of 7 hepatic SAEs (0.04 per 100 patient-years, 95%CI 0.02, 0.09) occurred in the TCZ studies (34).

Monotherapy

It is known that, after MTX failure, combining MTX with bDMARDs is more efficacious than bDMARDs monotherapy. Data from the National Register for Biologic Treatment in Finland involving 2,053 patients initiating TNF-i revealed that concomitant treatment with MTX (but not with other csDMARDs) improved clinical response: 6-month DAS28 remission was 51% in the case of combination with MTX, 41% in monotherapy and 39% in patients taking a csDMARD other than MTX (35). Nevertheless, evidence from registry data show that approximately one-third of RA patients are treated with biological agents as monotherapy.

Tarp *et al*. performed a network meta-analysis of RCTs to assess the efficacy and safety of the individual biological agents used in monotherapy. 28 RCTs were selected including 8,602 patients. ACR50 (primary outcome) occurred more frequently with ETA or TCZ monotherapy than with other biological agents (36). Use of TCZ monotherapy can be considered effective, as well as on the control of disease activity, also on radiographic progression. In U-Act-Early strategy trial, Sharp van der Heijde score (SHS) changes from baseline were significantly lower in the TCZ plus MTX arm compared with the MTX alone arm after 52 weeks (p=0.016), but after 104 weeks, less progression in joint damage was noted in both TCZ arms (TCZ plus MTX, p=0.021; and TCZ-alone, p=0.038). Joint space narrowing did not change significantly in the three treatment arms, while for erosion scores at 104 weeks significantly lower erosion progression scores were found in the TCZ plus MTX (p=0.016) and TCZ arm (p=0.023) when compared with the MTX arm. After correcting for DAS28 score over time, it was no longer statistically significant (TCZ plus MTX: mean SHS 0.55, 95%CI 1.22, 0.11; p=0.10 *vs*. MTX; TCZ: mean SHS 0.39, 95%CI 1.05, 0.28; p=0.26 *vs*. MTX) (37). A phase III study (MONARCH trial) evaluated the efficacy and safety of sarilumab (IgG1 monoclonal antibody that binds specifically to both soluble and membrane-bound IL-6RS) *vs*. ADA. Both drugs were administered as monotherapy in RA patients with intolerance or inadequate response to MTX. 369 patients (185 ADA and 184 sarilumab) were included. Sarilumab achieved primary endpoints (change from baseline in DAS28-ESR at week 24 -3.28 *vs*. -2.20, mean difference −1.08, 95%CI −1.36, -0.79; p<0.0001). Odds of achieving DAS28-ESR remission (secondary endpoint) with sarilumab were approximately three times greater at week 12 (OR 2.61, 95%CI 1.31, 5.20; p=0.0051) and approximately five times greater at week 24 (OR 4.88, 95%CI 2.54, 9.39; p<0.0001) compared to ADA (38).

One of the reasons for the different efficacy of bDMARDs as monotherapy may be related to the different immunogenicity of biological drugs and

therefore to the different production of anti-drug antibodies (ADAbs) that can be associated with loss of efficacy and risk hypersensitivity. Strand *et al*. performed a systematic review of studies evaluating the immunogenicity of 10 approved bDMARDs for all the indication including 443 publications (394 studies) (39). As expected, ADA, infliximab (IFX) and IFX biosimilar were associated with the increased production of ADAbs (>50%) compared to other drugs such as GOL, ustekinumab, ETA, secukinumab (<20%) (39). Immunogenicity of TCZ was evaluated in 3,099 patients (616 monotherapy and 2,483 in combination with csDMARDs) from 5 TCZ-SC (subcutaneous) and 8 TCZ-IV phase III clinical trials and 1 TCZ-IV clinical pharmacology safety study. The development of ADAbs was found in 1.5% (47 patients) and 1.2% (69 patients) in TCZ-SC and TCZ-IV, respectively, with a low frequency of significant hypersensitivity reaction (1/47 (2.1%) in TCZ-SC group and 6/69 (8.7%) in TCZ-IV including 5 anaphylaxis). Finally, there was no difference between patients taking TCZ as monotherapy or concomitant csDMARDs in risk of developing ADAbs (40).

Cycling versus switching

To date, there is still much debate as to whether the best strategy after a TNF-i failure could be cycling to another TNF-i or switching to a drug with different mechanism of action (MOA). There has been a growing interest in understanding how to select the subsequent therapy, but data from different studies are sometimes contradictory. Codullo *et al*. evaluated the efficacy of ADA in the first and second treatment lines from data of two Italian registries (GISEA and Lohren). 2,262 ADA patients were analysed, of which 1,780 (78.7%) on the first and 482 (21.3%) on the second line. Although the response in terms of DAS28 and HAQ-DI was significantly better at 1 and 2 years from the beginning of ADA therapy in 1st line patients, a not negligible and incremental response was observed from the first to the second year also in 2nd line patients (DAS28 remission achieved in the first and second year for 20% and 26% of patients respectively and LDA in 30 and 38% respectively) (41).

Recently a real-world analysis was conducted to compare these two different strategies, focusing on disease activity and on treatment persistence; in this longitudinal retrospective study new MOA switchers (ABA, RTX or TCZ) seemed to show better clinical outcomes than TNF-i cyclers, but the difference was not statistically significant after adjusting for baseline disease activity. On the contrary data on the persistence rates supported the choice of changing the MOA, as a discontinuation of the second-line biologic was more frequently observed in TNF-i cyclers (42).

A German study performed a retrospective cohort analysis showing a longer drug survival in RA patients starting a new non-TNF-i therapy after the failure of a first TNF-i. In line with existing literature, an overall considerable percentage of these patients stopped or switched the second bDMARDs within the first year; about 57% of them switched, while resting patients stopped (35.7%) or restarted therapy after a period of discontinuation (7.7%). Anyway in this study the group treated with a second-line non TNFi therapy switched to a third line therapy less frequently than TNF-i cyclers and at 12 months an higher proportion of them were still in therapy (66.3% *vs*. 53.4%) (43).

Other indirect findings on the effectiveness of switching or cycling emerged form a recent SLR based on 18 observational studies and 6 RCTs, which failed to demonstrate consistent and conclusive differences between the two strategies. In the TNF-experienced population with RA, subsequent therapy with another TNF-i, non-TNF biologic or tofacitinib showed not robust and consistent statistically differencest results. For instance, the 6 month ACR 50 response rate in cycling to TNF-i was 0.18 (95%CI 0.12, 0.24) *vs*. non-TNF-i bDMARDs 0.27 (95%CI 0.22, 0.32), while switching to tofacitib showed better ACR50 response in one study (0.37, 95%CI 0.28, 0.95) (44).

Tapering

The opportunity to taper bDMARDs in RA patients on sustained remission has been widely discussed in the last years and different strategies have been compared in many studies, but the best approach to adopt remains unknown. Available recommendations suggest the order to follow for therapies reduction: first GC, then bDMARDs and finally csDMARDs (45). However, there is limited evidence about patient or disease characteristics predicting the best clinical and radiological outcomes after reducing bDMARD therapy.

Lenert *et al*. tried to clarify some of these aspects by a review of all tapering strategies in RA patients. Despite the differences among final outcomes considered in each study, best results were observed in RA patients with a deeper and longer remission (defined by DAS in most cases) and a shorter disease duration before down dosing the bDMARD. Also the presence of a negative musculoskeletal ultrasound examination (both for grey-scale and power Doppler) at the moment of the dose reduction seemed able to predict a successful tapering; three studies have investigated this aspect by using different "target" joints but leading to the same conclusion: higher total grey-scale and power Doppler scores at baseline were associated to more frequent relapses after the de-escalation of therapy. Finally a positively influence on the disease course after tapering was shown for combination therapies with csDMARDs (46).

Other attempts to predict a successful tapering or discontinuation of bDMARD derived from a sub-analysis of the DRESS study that demonstrated comparable rate of prolonged flare between patients treated with standard doses of subcutaneous TNF-i and patients reducing TNF-i doses after achieving stable LDA. In this setting the predictive value of a multi-biomarker score measuring disease activity (MBDA) was tested. The analyses failed to demonstrate MBDA as valuable predictor of flares in patients tapering TNF-i.(47).

Once a patient is considered eligible for a bDMARD, tapering it remains a question of which kind of de-escalation

to adopt. Kikuchi *et al*. proved the feasibility of "spacing" drugs: they evaluated the outcomes with a six-week extended dosing interval of TCZ-IV and demonstrated a good retention rate and an acceptable control on clinical outcomes and on radiographic progression. In fact, at week 54, 87.5% of patients maintained DAS28-ESR remission and CDAI and Simplified Disease Activity Index were comparable to baseline; in addition only one of the 22 patients enrolled showed a significant increase in structural damage evaluated by the modified total SHS score (48).

The same endpoints were evaluated in the MATADOR pilot trial that enrolled 53 patients in sustained remission or LDA using intravenous ABA; for the maintenance therapy the dosage administrated was reduced in all subjects with one year follow up. Only 5 patients experienced a flare and re-increased the drug dose achieving a new remission status, while other 5 patients did not complete the protocol. In all other cases high rates of remission/LDA were observed suggesting the possibility to continue with a reduced doses for maintenance (49). Both these studies agreed on the feasibility of a reduction of therapy, but they included a limited number of patients and further reports are needed.

Conversely, more data are available regarding the tapering of TNF-i. The OPTTIRA trial compared two tapering regimens in patients treated with ETA and ADA; in this open label trial patients were randomised in three different groups: about half of patients continued biologic at the initial dosage, one group reduced dose by 33% and the last group tapered biologic by 66% for 6 months. After this period control subjects were randomised to taper TNF-i by 33 or 66%, while patients of tapering groups further increased the time between injections until they stopped (exploratory phase). By comparing tapering groups, the authors concluded that a reduced TNF-i dose by one third was not associated with a significant number of flares (DAS28 scores ≥0.6 with a DAS28 >3.2 plus an increase in the swollen joint count), while a further de-escalation showed significantly reduced time to flare (adjusted HR 2.81; p=0.051). In the exploratory trial, after one year, 45% RA patients randomised in tapering groups achieved the complete withdrawal of bDMARD without flaring but the mean DAS28 score switched from 1.51 (95%CI 1.14, 2.65) to 2.27 (95%CI 1.71, 3.98) by 6 months (50).

Similar conclusions were obtained in the extension phase of the DRESS study which examined a population of 172 patients reducing doses of TNF-i (ADA and ETA) based on disease activity indices. In the long-term observation period of 3 years a treat-to-target approach was adopted with dose adjustments to optimise the treatment, but the overall use of TNF-i remained lower in patients randomised to dose reduction respect patients administrating the usual care. Clinical and radiological outcomes were similar in the two groups but also the AE rates were comparable; so these data confirmed the non-inferiority of this therapeutic strategy but to date the only advantage appeared the reduction in TNF-i use (51).

A potential role in the tapering decision could be assigned to the therapeutic drug monitoring with a strategy of modifying the dose or time interval on the base of concentration measurement. This approach has been studied for ADA in a randomised, open-label, non-inferiority trial: patients with serum drug concentrations at baseline above 8 μg/mL were assigned to a prolongation group (40 mg once every 3 weeks) or to a continuation group (standard interval of every other week). With the limitations due to the short period of observation (28 weeks), this study confirmed the effectiveness of this dosing down strategy: the increase of ADA dosing interval from 2 to 3 weeks showed no significant clinical consequences in most of patients, who rather achieved a minimal improvement of mean DAS28 (1.9±0.79 at baseline *vs*. 2.0±0.8 at week 28). A significant increase in disease activity (DAS28 ≥0.6 points) was observed in similar proportion in both groups; as regard ADA concentration, 73% patients remained above 5 μg/mL, the minimum threshold necessary to block TNF according to previous studies (52).

Biosimilars

It is established that biologic treatment has dramatically changed the outcomes of RA and other inflammatory disease patients, however, their high cost may limit the access to these medications. In this view, biosimilars of products no longer protected by patent have been developed and have lower costs than bio-originators. Currently, there are several biosimilars of IFX, ETA, RTX and ADA, but others are under development, also of other bio-originators with different mechanisms of action. We know that biosimilars cannot be considered bioequivalent, while they are a replica of a biopharmaceutical that has met criteria for bio-similarity, according to a defined pathway established to demonstrate equivalent pharmacokinetics, pharmacodynamics and efficacy and comparable safety and immunogenicity, and has been reviewed and approved by a regulatory authority in a highly regulated area. Since the large areas of uncertainty, in the previous years a set of recommendations for the use of biosimilars have been issued (53). While it is recognised that a biosimilar, approved by the EMA or FDA, is neither better or worse than its bio-originator, increasing interest has grown around the possibility of switching between the bio-originator to the biosimilar, and many RCTs and real-life studies have been published while other are currently ongoing to assess the safety and efficacy of switching. The extension period of the PLANETRA study, found similar efficacy and safety results in RA patients treated with CT-P13, an IFX biosimilar, compared to IFX bio-originator both in combination with MTX, for 1 year after the switch (54). Similar results have been obtained with a different IFX biosimilar, SB2, up to 78 weeks, ETA biosimilar, SB4, over 2 years, RTX biosimilar up to 2 years, and ADA biosimilar, SB5 (55–58). Of interest, similar data regarding the immunogenicity have been reported, with ADAbs occurring in the same proportion of patients on the biosimilar or bio-originator and also after switching (54–57). Real-life evidences are also becoming increasingly available. In Denmark, a national guideline

by May 2015 dictated a non-medical switch, that is, all patients treated with IFX, of which 403 were RA, should switch to CT-P13 for economic reasons. Data from the DANBIO registry, which follows prospectively patients treated with biologics, show that to CT-P13 had no negative impact on disease activity, however, adjusted 1-year CT-P13 retention rate was slightly lower than for IFX in a historic cohort (59). Based on the results of a recent multicentre observational study, the discontinuation of CT-P13 after open-label switching from IFX originator could be mainly driven by an increase in the subjective tender joint count and the Patient's Global Assessment of Disease Activity and/or in self-reported adverse events (AEs), rather than by an increase in objective signs and symptoms (60).
The recommendations currently state that a single switch from a bio-originator to one of its biosimilars is safe and effective and there is no scientific rationale to expect that switching among biosimilars of the same bio-originator would result in a different clinical outcome. Conversely, multiple switching between biosimilars and their bio-originators or other biosimilars should be assessed in registries. Finally, no switch to or among biosimilars should be initiated without the prior awareness of the patient and the treating healthcare provider (53).

Targeted synthetic disease-modifying anti-rheumatic drugs

Several JAK (Janus kinase) inhibitors are in clinical development, each having a selectivity for inhibition of one or more of the 4 identified JAKs (JAK-1, JAK-2, JAK-3, Tyk-2). These small-molecule have been recently categorised as tsDMARDs and intensively investigated for the treatment of RA. The current placement of tsDMARDs is as monotherapy or in combination with MTX for the treatment of moderate to severe active RA in adult patients with an inadequate response or intolerance to one or more bDMARDs. In the last few months, various studies implemented data on safety and efficacy introducing some preliminary concepts on tapering strategy summarised below.

Tofacitinib

Tofacitinib is an oral JAK inhibitor that preferentially inhibits signalling by receptors associated with JAK1 and JAK3, with functional selectivity over JAK2. In recent years phase 3 and long-term extension studies have proved efficacy and safety of tofacitinib administered as monotherapy or in combination with csDMARDs. In 2017 Fleshiman *et al*. published the first phase 3b/4, double-blind, head-to-head, randomised controlled trial (ORAL strategy trial) to assess the comparative efficacy of tofacitinib monotherapy, tofacitinib plus MTX, and ADA plus MTX for the treatment of RA in patients with a previous inadequate response to MTX (61). The primary outcome was non-inferiority in ACR50 at month 6 and it was attained in 147 (38%) of 384 patients with tofacitinib monotherapy, 173 (46%) of 376 patients with tofacitinib and MTX, and 169 (44%) of 386 patients with ADA and MTX (61). Tofacitinib and MTX demonstrated to be non-inferior to ADA and MTX (difference 2%, 98.34% CI -6, 11), while tofacitinib monotherapy was not shown to be non-inferior to ADA and MTX or tofacitinib and MTX. This trial suggested that patients generally respond better to the addition of tofacitinib or ADA to MTX than switching from MTX directly to tofacitinib monotherapy (61).
The efficacy of tofacitinib has been further studied in a post-hoc analysis on data pooled from two open-label, long-term extension trials that evaluated the potential impact of discontinuing concomitant MTX or GC (62). By year 3, 11.6% of patients (186/1608) discontinued MTX and 22.2% (319/1,434) discontinued GC (62). At year 3, patients receiving tofacitinib generally maintained the same response to treatment achieved at month 3, irrespective of whether they discontinued MTX or not. Similarly, discontinuation of concomitant GC did not negatively impact CDAI response at year 3 (62).
A first prospective cohort study in RA patients with LDA explored the concept of discontinuation of tsDMARDs showing that 52 weeks after discontinuation of tofacitinib 37% of patients (20/54) remained tofacitinib-free without disease flare (63). Park *et al*. analysed the topic of therapy discontinuation rates of tofacitinib and biologics in RA patients with inadequate response to a previous treatment using Bayesian network meta-analysis based on RCTs (64). The discontinuation rates between tofacitinib and biologics were similar in the group with a previous inadequate response to csDMARDs. In the group with a previous inadequate response to biologic, TNF-i and RTX showed significantly lower total discontinuation rate than tofacitinib (64).
Various studies have explored the safety profile of tofacitinib. In the ORAL strategy trial, safety was similar between the treatment group in terms of SAEs except for the incidence of VZV infection that was higher in the tofacitinib plus MTX group (2%, 8/376 patients *vs*. 4/384 (1%) in the tofacitinib monotherapy and 6/386 (2%) in the ADA plus MTX group (61).
The increase in herpes infections with tofacitinib motivated a further analysis aimed to explore whether the risk of VZV was greater in patients receiving tofacitinib and concomitant MTX and GC (65). Data were extracted from an integrated safety summary conducted across the tofacitinib RA development program including 2 phase I, 9 phase II, 6 phase III and two long-term extension studies in adult patients with active RA. VZV was reported in 636 tofacitinib-treated patients, with an incidence rate (IR) per 100 patient-years of 4.0, 95%CI 3.7, 4.4 and classified non-serious, with the involvement of only 1 dermatome in the majority of cases (94%). The IRs were numerically lowest for monotherapy with tofacitinib 5 mg twice daily without GC (IR 0.56, 95%CI 0.07, 2.01) and highest for tofacitinib 10 mg twice daily with csDMARDs and GC (IR 5.44, 95%CI 3.72, 7.68). Enrolment in Asian countries was an independent risk factor for VZV, equal to 8.0 (95%CI 6.6, 9.6) in Japan and 8.4 (95%CI 6.4, 10.9) in Korea (65). Integrated analysis of data from the global clinical tofacitinib provided additional information of long-term – up to 8.5 years – safety profile for events of special interest. Out of a total 19,406 patient-years' exposure, IR

per 100 patient-years for serious AEs was 9.4 (95%CI 9.0, 9.9); IR for serious infections was 2.7 (95%CI 2.5, 3.0) and IRs did not increase with longer treatment exposure (10). IR for opportunistic infections (excluding tuberculosis) was 0.3 (95%CI 0.2, 0.4) and was 0.2 (95%CI 0.1, 0.3) for tuberculosis (10). IR for malignancies (excluding NMSC) was 0.9 (95%CI 0.8, 1.0); IR for NMSC was 0.6 (95%CI 0.5, 0.7) and stable up to 84 months of observation (66). Of the 83 patients with NMSC during the study, 19 (22.9%) had ≥1 further occurrence or a second NMSC event whilst receiving tofacitinib (66).

The Maineiro *et al*. meta-analysis expanded the malignancy data showing that there was no statistical significant increase in the risk of malignancies or any specific type of malignancy in RA patients treated with either bDMARDs or tofacitinib in RCTs compared to placebo or csDMARDs (27).

Finally, given the importance of JAK2 signalling in erythropoiesis and the involvement of JAK1 and JAK3 in lymphoid a study expressly evaluated the haematological safety characterising changes in haematological parameters in patients with RA from phase 3 RCTs and long-term extension studies. Overall, tofacitinib decreased mean lymphocyte counts and slightly increased mean haemoglobin levels in RA patients, with few cases of anaemia (reduction ≥3 g/dl from baseline or haemoglobin ≤7 g/dl) experienced in less than 1.0% of patients (67).

Baricitinib

Baricitinib is an orally-administered, small-molecule, which selectively inhibits the JAK1 and JAK2 subtypes and received its first global approval, in Europe, on 13 February 2017 (68). Between the end of 2016 and the beginning of 2017 four phase III studies established the efficacy of baricitinib as a treatment for RA at different nodes of the treatment pathway: RA-BEGIN in patients naïve to MTX; RA-BUILD in patients with an inadequate response or intolerance to csDMARDs; RA-BEAM in MTX failure patients naïve to bDMARDs and using placebo and ADA as comparator, and RA-BEACON in patients with inadequate response or intolerance to bDMARDs (68). On this background Lee *et al*. clarified the comparative efficacy and safety of baricitinib in various treatment regimens conducting a network meta-analysis aimed to compare the once-daily administration of baricitinib 2mg and 4mg in active RA (69). Regarding efficacy, the network meta-analysis suggested that baricitinib 4mg + csDMARD was the most effective treatment for active RA (OR 3.13, 95% Credible Intervals (CrI) 2.32, 4.33), followed by baricitinib 4mg (OR 3.00, 95%CrI 1.50, 6.24), baricitinib 2mg + csDMARD (OR 2.83, 95%CrI 1.94, 4.34) with a comparable safety between the different baricitinib dosages and placebo, with or without csDMARDs.

Kremer *et al*. conducted a subgroup analysis in RA-BEAM and RA-BUILD studies to explore the influence of baseline patient (such as age <65 or ≥65 years, gender, ethnicity, tobacco use, weight, body mass index) and disease-related clinical characteristics (disease duration, number of csDMARDs used previously, seropositivity, disease activity) on the response to baricitinib (70). This post-hoc analysis performed in over 1,400 patients with RA confirmed the beneficial clinical effect with baricitinib 4 mg treatment irrespective of all listed demographics and baseline disease characteristics (70).

Recently, additional data on safety and efficacy of baricitinib have been reported in patients with inadequate response to csDMARDs, collected both in the double-blind 24-week phase II (71) that in its open-label extension study (72). Treatment with baricitinib determined a dose-dependent increase in serum lipid levels (low-density lipoprotein, high-density lipoprotein, cholesterol, triglycerides) from baseline to week 12. Low-density lipoprotein levels increased by 3.4 mg/dl and 11.8 mg/dl in the 1 mg and 8 mg treatment groups, with a shift in large LDL particles and a reduction of the number of small, dense LDL particles (71). In the open-label extension study, 133 of the 301 initially randomised patients completed 128 weeks of study treatment. The safety and tolerability profile of baricitinib was generally consistent with prior observations gathered during shorter durations of exposure (72).

In the last few months, patient reported outcomes (PROs) data related to 3 out of 4 phase 3 studies mentioned above were published (73–75). In RA-BEACON, RA-BEGIN and RA-BEAM studies, baricitinib treatment produced significantly greater improvements compared with placebo or MTX monotherapy or ADA in most of the prespecified PROs including HAQ-DI, Patient's Global Assessment of Disease Activity, pain, Functional Assessment of Chronic Illness Therapy-Fatigue, Short Form 36 physical component score, EuroQol 5-Dimensions index scores and Work Productivity and Activity Impairment-Rheumatoid Arthritis daily activity. These PROs were improved at weeks 24 and 52, compared to MTX monotherapy in RA-BEGIN (74) study and at week 24 compared to placebo in RA-BEACON study (75). When compared with ADA, the baricitinib-treated patients showed statistically significant improvement in work productivity loss and impairment of regular activity at week 12; these improvements continued through week 52 but were not statistically significantly different (73).

Other JAK-inhibitors

New other JAK inhibitors with varying selectivity profiles are in development for RA.

Filgotinib (GLPG0634, GS-6034) is a highly selective orally available JAK-1 inhibitor currently under study. Vanhoutte *et al*. presented the first results of two 4-week exploratory, double-blind, placebo-controlled phase IIa trials conducted in 127 MTX failure patients with RA assigned to filgotinib oral capsules (over a 30–300 mg dose range) or placebo, added onto a stable regimen of MTX (76). In study 1 at the end of 4 weeks of treatment, 83% of the filgotinib-treated patients achieved an ACR20 response, in study 2 at week 4 of treatment, the majority of patients receiving 300 mg filgotinib (65%) achieved an ACR20 response, but the difference from the placebo group was not statistically significant. Filgotinib showed an encouraging safety profile,

without the early side effects seen with other less selective JAK inhibitors (79). The results from these studies informed the design of a phase II dose-finding study (DARWIN II) (77). In this study filgotinib induced higher ACR20 response rates compared to placebo after 12 weeks (≥65% *vs*. 29%, $p<0.001$), in patients with active RA and previous inadequate response to MTX. Interestingly, a dose-dependent increase in haemoglobin was observed, and the percentage of patients with treatment-emergent adverse events was similar in the placebo and filgotinib groups (~40%), also for SAE being present in 2.9-4.3% of patients in the filgotinib treatment arms up to week 24 (77).

Peficitinib (ASP015K) is an orally administered once-daily JAK inhibitor in development for the treatment of RA in patients with an inadequate response to MTX. Peficitinib inhibits JAK-1, JAK-2, and Tyk-2 enzyme activities with a moderate selectivity for JAK-3 inhibition (78). In a third phase IIb randomised study the peficitinib had a statistically significant difference in the ACR20 response at week 12 compared with placebo (ACR20 response at week 12 achieved by 48.3%, 56.3%, and 29.4% of patients in the peficitinib 100 mg, 150 mg and placebo groups, respectively), resulting well tolerated with limited safety issues (78).

Novel treatment targets

Albeit the increasing available treatment strategies, up to 50% of patients still do not reach low disease activity, while others manifest adverse events or contraindications to currently available therapies, therefore there is the necessity for new strategies to treat RA.

IL-17 inhibition has become of particular interest in psoriasis and spondyloarthritis treatment. Secukinumab, an anti-IL-17A monoclonal antibody, has been evaluated in RA patients who had an inadequate response to or intolerance of TNF-i, and ACR20 response rates at week 24 were 30.7% in patients receiving 150 mg secukinumab ($p=0.03$), 28.3% in those receiving 75 mg secukinumab ($p=0.09$), and 42.8% in those receiving ABA, compared with 18.1% in the placebo group. A significant reduction in the DAS28-CRP was seen in patients treated with 150 mg secukinumab ($p=0.049$), but not in patients treated with 75 mg secukinumab. Improvements in the HAQ-DI and ACR50 response rates were not significant in the 2 secukinumab dose groups compared with the placebo group. The overall safety profile was similar across all treatment groups (79). Another IL-17A inhibitor, CNTO6785, has been evaluated in RA patients with insufficient response to MTX, but the primary endpoint, or ACR20 response at week 16, was not met, furthermore, there were no significant findings in any additional efficacy variables through week 32. CNTO6785 was well tolerated, with infections occurring with similar frequency across all groups, and injection site reactions being mild or moderate without a dose-response relationship (80). Inhibition of other cytokines involved in the IL-17 pathway has been evaluated with ustekinumab, an anti-p40 IL-12/23 monoclonal antibody, and guselkumab, an anti-IL-23 monoclonal antibody, however, similarly to the previous results, at week 28, there were no statistically significant differences in the proportions of patients achieving an ACR20 response between the combined ustekinumab group (53.6%) or the combined guselkumab group (41.3%) compared with placebo (40.0%) ($p=0.101$ and $p=0.877$, respectively) (81). Therefore, based on the current evidences, IL-17 inhibition does not seem to play a major role in RA treatment strategy, except for secukinumab 150 mg, which may be effective in reducing symptoms and signs of RA.

Dual inhibition of TNF and IL-17 is currently under investigation to evoke a greater clinical response than that achieved by targeting either cytokine alone. ABA-122 is a novel dual variable domain immunoglobulin that selectively and simultaneously targets human TNF and IL-17A. Although patients included in a phase I study had essentially inactive RA, exploratory clinical parameters suggested potential anti-inflammatory effects following treatment with ABA-122. Furthermore, no clinically significant findings regarding the safety were observed, with only 1 serious event was observed in patients treated with ABA-122 (82).

Targeting granulocyte-macrophage colony stimulating factor (GM-CSF), a pro-inflammatory multifunctional cytokine, has demonstrated promising results. In particular, Burmester *et al*. reported the results of a phase IIb study on mavrilimumab, a fully human monoclonal antibody targeting GM-CSF receptor-α in moderate-to severe RA. Mavrilimumab subcutaneous treatment significantly reduced DAS28-CRP scores from baseline compared with placebo, and significantly more mavrilimumab-treated patients achieved ACR20 compared with placebo (week 24: 73.4%, 61.2%, 50.6% *vs*. 24.7%, respectively ($p<0.001$)). No particular safety signals emerged from this dose-finding study (83). Mavrilimumab compared to GOL in patients with RA who have had an inadequate response to csDMARDs and/or inadequate response to TNF-i (anti-TNF-IR) at week 24, differences in the ACR20, ACR50, and ACR70 response rates were in all patients -3.5% (90%CI -16.8, 9.8), -8.6% (90 CI -22.0, 4.8), and -9.8% (90%CI -21.1, 1.4), respectively, while in the anti-TNF–IR group, 11.1% (90%CI -7.8, 29.9), -8.7% (90%CI -28.1, 10.7), and-0.7% (90%CI -18.0, 16.7), respectively. Differences in the percentage of patients achieving a DAS28-CRP of <2.6 at week 24 between the mavrilimumab and GOL groups were -11.6% (90%CI -23.2, 0.0) in all patients, and -4.0% (90%CI -20.9, 12.9) in the anti- TNF–IR group. The percentage of patients achieving a >0.22 improvement in the HAQ-DI score at week 24 was similar between the treatment groups. Treatment emergent AEs were reported in 51.4% of mavrilimumab-treated patients and 42.6% of GOL-treated patients (58). A long-term study on mavrilumab 100 mg every other week compared to GOL 50 mg every 4 weeks, plus MTX, has not shown safety issues with the most frequent infections being nasopharyngitis and bronchitis. Interestingly, after 2 years, 6.2% patients showed reduction in forced expiratory volume in 1 second, 3.4% patients showed reduction in forced vital capacity, respectively (>20% reduction from baseline to <80% predicted), however

most pulmonary changes were transient and only infrequently associated with adverse events. Mavrilumab treatment demonstrated sustained efficacy. In total, 117 patients (65.0%) achieved low disease activity of DAS–CRP <3.2 and 73 (40.6%) achieved DAS-CRP <2.6 at Week 122. DAS–CRP <3.2 and <2.6 response rates (17). Namilumab, an immunoglobulin G1 monoclonal antibody that binds with high affinity to the GM-CSF ligand, in a phase 1b study in mild-to-moderately active RA has been demonstrated to produce a greater improvement in DAS28-CRP and swollen and tender joint counts compared with placebo. Regarding safety, AEs were similar across the three groups (namilumab 150 mg: 63%; namilumab 300 mg: 57%; placebo: 56%), with most of them being nasopharyngitis (17%) and exacerbation/worsening of RA (13%). No anti-namilumab antibodies were detected (84).

Other treatment strategies are under investigation, fosdagrocorat, a potential dissociated agonist of the GC receptor, has been shown to have potential results in improving DAS28-CRP in RA patients, compared to placebo and prednisone 5 mg/day (85).

Special conditions

Pregnancy

Despite already available evidence, concern still exists on the use of biologics during pregnancy and breast-feeding. Novel reassuring evidence comes from a SLR and meta-analysis of observational studies comparing pregnancy outcomes in women with RA (and other chronic inflammatory disease) exposed to TNF-i at conception or during pregnancy *versus* RA controls and general population(86). Due to the low size of RA studies no sufficient power was reached to draw conclusions, but analysing all the exposed populations, TNF-i users show a non-significant trend towards reduced rate of live birth (OR 0.38, 95%CI 0.13, 1.13) and were an increased risk of preterm birth (OR 2.62, 95%CI 2.12, 3.23), spontaneous abortion (OR 4.08, 95%CI 1.12,14.89) and low birth weight (OR 5.95, 95%CI 1.17, 30.38) compared to the general population. Risk of anomalies was not elevated (OR1.46, 95% CI 0.84, 2.56). Among the studies that compared the outcome between TNF-i users and non-users, there were no significant differences in the rates of live birth and pregnancy related complications, suggesting that disease-related factors are the main determinants of adverse pregnancy outcomes. Among TNF-i, novel evidence reinforces the safety of CZp in pregnancy and breastfeeding. The CRIB pharmacokinetic study enrolled 17 pregnant women ≥30 weeks pregnant receiving CZp, analysing maternal, umbilical cord and infant plasma drug concentration, showing therapeutic plasma levels in mother samples, quantifiable drug levels in 3/15 umbilical cord samples, and in 1/15 infants at birth and 0/16 at 4 and 8 weeks (87). The CRADLE pharmacokinetic evaluated CZp concentrations in human breast milk from 17 women, showing that 77/137 (56%) breast milk samples had no measurable CZp, with relative infant dose of 0.15%, and no registered safety issues (88).

Cardiovascular risk

CV morbidity is one of most important new frontiers of stratification and intervention in RA and inflammatory arthritis. In view of substantial new evidence, the EULAR released an update of recommendations for CVD risk management in patients with RA and other forms of inflammatory joint disorders (89). Overall recommendations reinforce the role of rheumatologist as responsible for CV risk management, including life-style risk factor modification and CV risk stratification with the assessment of lipid profile in stable disease, and strengthen the need of optimal control of disease activity with the lowest as possible exposure to non-steroidal anti-inflammatory drugs and corticosteroids. Though active CV screening and appropriate treatment arises as one of the most important strategies to implement to improve patient outcome of RA patients, CV risk factor management is still suboptimal, particularly in high risk populations (90). The cost-effectiveness of different screening scenarios, with different periods and using different CV stratification tools, has been explored in a 10-year simulation study based on Dutch patient data, supporting effectiveness with a mean QALY gain of 0.09 and mean cost saving around 1000 € (91). Targeting disease activity is one of the most important strategy to control the excess of morbidity and mortality due to accelerated atherosclerosis. Analysing arterial stiffness and intima media thickness over a mean of 3 years of follow up of 139 RA patients in persisting low-disease activity or remission compared with matched controls, no significant differences were found (92).

Comorbidities

With population aging and increase of health expectations, data on efficacy and safety of treatment in the elderly and comorbid population are essential for daily management of patients. In a retrospective observational study including RA patients, aged ≥65 years at the bDMARD start, enrolled between 2000 and 2012, determinants of discontinuation were evaluated. In the multivariate analysis the following age- and comorbidity related factors were significantly associated with discontinuation, mainly due to infection: age (years) at first bDMARD (HR 1.07, 95%CI 1.01,1.14), liver disease (HR 4.3, 95%CI 1.6,11.3) and CV disease (HR 2.3, 95%CI 1.12, 4.9) (93). A recent SLR and meta-analysis analysed the probability of remission in RA patients treated with any DMARD according to obesity status. Overall obesity showed a strong decrease of the probability of achieving remission (OR 0.49, 95%CI 0.32, 0.74), with particular influence on tender joints acute phase reactants and tender joints, while no influence on swollen joints (94).

Cancer

Few data describe the safety of b-DMARDs in patients with a history of a previous cancer for which the use of RTX (also for its use in patients with lymphoma) is often preferred compared to TNF-i. The risk of secondary malignant neoplasms in patients treated with TNF-i or other bDMARDs was assessed by a cohort study from DANBIO Registry of patients with a history

of primary cancer treated or not with bDMARDs. 70 patients never treated *versus* 38 patients treated with bDMARDs developed secondary malignant neoplasms. There was no greater risk of occurrence in patients treated with bDMARDs regardless of timing of exposure (before and/or after primary cancer) than patients who had ever been treated (HR 1.25, 95%CI 0.99, 1.57). The HR of secondary malignant neoplasms was 1.25 (95%CI 0.71, 2.18) among patients initiating bDMARDs more than 5 years after the first cancer diagnosis while the HR was 0.92 (95% CI 0.40, 2.10) among patients initiating bDMARDs less than 5 years after the first cancer diagnosis; regarding the type of biologics the HR was 1.21 (95%CI 0.73, 2.03) for TNF-i and 1.05 (95%CI 0.47, 2.34) for RTX (95).

Infection

Novel evidence has accumulated on the management of latent or opportunistic infections in RA patients on immunosuppressive treatment, particularly with bDMARDs and tsDMARDs. An international panel of infectious disease specialists and rheumatologist elaborated recommendations for infectious disease screening in migrants before starting biologic agents (96). These recommendations provide a country-specific baseline risk of latent infections (Hansen's disease, non-tuberculous mycobacteria, multidrug resistant tuberculosis, brucellosis, salmonellosis, leishmaniasis, babesiosis, strongyloidiasis, cysticercosis, Chagas disease, HEV, HTLV-1, histoplasmosis, coccidioidomycosis, paraccoccidioidomycosis), and indicate specific screening based on the a priori risk and indication of screening tests if available and/or surveillance. Another set of recommendations examined the management of major pulmonary fungal infections (*pneumocystis jirovecii* pneumonia, pulmonary cryptococcosis pulmonary coccidioidomycosis, pulmonary histoplasmosis and invasive pulmonary aspergillosis) in RA patients treated with cs- and bDMARDs, in terms of diagnosis, prophylaxis, infection treatment and DMARD re-challenge after recovery (97). Hepatitis B virus (HBV) infection management has been reviewed in national clinical practice guidelines by an inter-disciplinary panel of experts from Italy (98). Screening is recommended for all RA patients since the disease onset, and inactive HBV carriers to be treated with immunosuppressive therapies should receive prophylaxis with lamivudine that should be continued for 12 months after their discontinuation (up to 24 months in the case of RTX treated patients); active carriers and acute HBV infections should follow the same approach as non-RA patients. Among latent infections, interest has been renewed about VZV, due to the safety signal observed with JAK-inhibitors in a phase II, 14-week, placebo-controlled trial, 112 RA patients on MTX treatment received live Zoster vaccine and were randomised to receive placebo or tofacitinib. Serological response was not different between groups (geometric mean fold rise ratio tofacitinib/placebo at 14 weeks of 1.05 (95%CI 0.88, 1.27). One patient, who lacked pre-existing VZV immunity, developed cutaneous vaccine dissemination 2 days after starting tofacitinib (16 days post-vaccination) (99).

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