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Prevention and Cure: The major Unmet needs in the Management of RA

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Abstract

The outcome of treatment of patients with rheumatoid arthritis (RA) has qualitatively improved in recent years due to better and earlier treatment approaches, and new drugs. It is now generally accepted that the phenotype of RA is the end-point of a disease continuum. Large retrospective studies have identified anti-citrullinated protein antibodies (ACPAs) and rheumatoid factor (RF) in the stored serum of patients, years before the development of clinical RA. Recent data suggest mucosal sites such as the oral mucosa (in particular the periodontium), lung and gut may be the sites where auto-immunity is initiated. The role of bacteria at these sites is reviewed. Much recent work has focussed on the role of high resolution imaging namely ultrasound (US) and magnetic resonance imaging (MRI) in identifying subclinical inflammation in at-risk individuals with early musculoskeletal symptoms (e.g. arthralgia) but without clinical synovitis. Importantly the first musculoskeletal site involved is usually not the Joint (synovium). Sub-clinical disease predicts the onset of clinical arthritis, and its timing, in symptomatic at-risk individuals. These and other predictive markers will be described. The ability to identify patients at-risk of RA, before joint involvement has led to interventions aimed at preventing/delaying disease.

Once arthritis occurs, rapid remission is the target of therapy. The percentage of patients with RA achieving clinical remission has improved markedly compared with a few decades ago. The optimum outcome is to induce remission sufficiently profound so that therapy can be stopped, without flare, that is drug-free remission, which is effectively cure. Limitations of the tools used to measure remission, the outcome of tapering therapy, and new approaches

to achieve successful drug cessation are described. Overall, this article reviews progress towards meeting the unmet needs of prevention/cure.

Introduction

The treatment of patients with rheumatoid arthritis (RA) has been revolutionised by early diagnosis and early treatment of patients using effective targeted therapies. However, despite progress there are ongoing challenges. For most patients, RA remains a life-long, incurable disease associated with the burden of long-term therapy, debilitating disease flares and substantial socioeconomic cost.

Currently, the aim of therapy in a new patient is to achieve clinical remission. However, future ambitions will be to either to prevent RA, or in those who develop arthritis, to treat with intensive remission-induction so that therapy can be stopped, effectively a cure. Thus, prevention/cure represent two of the most significant unmet needs. Achieving them would resolve many of the other unmet needs.

In this article the progress towards these outcomes is reviewed. For prevention, the first and biggest hurdle is seeing at-risk individuals at the right time, next is identifying robust predictors of progressive disease. For cure, validation of the biomarkers which predict the ability to successfully stop therapy is needed; then the appropriate therapy needs to be applied to a population, stratified on the basis of the biomarkers, with the target of normalising such prognostic indicators. This theoretical approach will need to be undertaken as a research programme as therapeutic algorithms are determined more by cost than efficacy. For example, it is widely accepted that the best chance of clinical remission occurs with the first disease modifying anti rheumatic drug (DMARD), therefore as remission is the aim, logic should mean that the drug with the best early remission rate is used first. However, the drugs with the best remission statistics, the biological (b)DMARDs and targeted synthetic (ts)DMARDs, are restricted to patients who have failed conventional synthetic (cs) DMARDs, e.g. methotrexate. Even less logical, in many countries, failure requires not only poor response to **two** csDMARDs, but additionally requires a high level of disease activity, (rather than a failure to reach remission). This means that the majority of patients in routine practice

are exposed to a prolonged period of inflammation, with the well documented adverse consequences this has.

This article will document the current status of movement towards the two biggest unmet needs for patients with RA: prevention and drug-free remission(cure).

The Prevention of RA

The prevention of RA would represent a major advance with the potential to completely transform the clinical approach to this disease. Over the last decade, with better understanding of the pre-clinical phase of RA, preventative approaches are now a realistic ambition.

The pre-clinical phase of RA

Once RA develops, there is no cure and long-term therapy is usually required. With the acceptance of the early arthritis paradigm, rheumatologists have focused on identifying synovitis early and treating it aggressively in order to modify the natural history if the disease, with the aim of reducing joint inflammation in order to prevent structural damage. The inability to achieve cure through this approach may be because when patients develop early clinical RA, they have in fact already reached the end-point of a preclinical disease continuum, and have well-established autoimmunity and joint inflammation (figure 1). Understanding the preclinical disease continuum means we can focus on identifying individuals at-risk of developing disease. Consequently, risk-appropriate preventative strategies are now becoming feasible for RA.

Research over the last two decades has transformed our understanding of the preclinical phase of RA. Seminal evidence for preclinical RA-related autoimmunity came from large retrospective studies which identified anti-citrullinated protein antibodies (ACPAs) and rheumatoid factor (RF) in the stored serum of patients, years before the development of clinical RA (1, 2). The disease is likely to begin with a complex interplay of genetic and environmental risk factors, which come together to initiate the RA-autoimmune response.

Where this disease initiation occurs is a critical question with significant implications for preventative strategies. Recent data suggest mucosal sites such as the oral mucosa (in particular the periodontium), lung and gut may be particularly important. These mucosal surfaces are sites of local inflammation and dysbiosis, which can be readily influenced by environmental factors such as cigarette smoking and diet. It is possible that mucosal inflammation may cause a localised, mucosal autoimmune response, which, rather than being protective, may instead trigger systemic autoimmunity in genetically predisposed individuals. Whether particular mucosal sites are more important than others in this process, or whether mucosal dysbiosis and localised autoimmune responses occur at multiple sites in the same individual is not yet clear.

Once initiated, the systemic RA-related autoimmune response diversifies and matures over time; there is an expansion in the fine specificity of ACPAs due to epitope spreading, which is reflected in rising anti-cyclic citrullinated peptide (CCP) antibody titres as at-risk individuals approach onset of clinical arthritis (3). Interestingly, following the development of arthritis, ACPA fine specificity does not appear to expand any further (4), suggesting maturation of the ACPA repertoire is a pre-clinical phenomenon, potentially suppressed by the initiation of therapy. In addition to ACPA, anti-carbamylated protein antibodies (anti-CarP) are also detectable in the pre-clinical phase of RA and are associated with progression to arthritis (5, 6). Although present only in a minority of ACPA-negative RA patients, there is significant overlap between ACPA and anti-CarP positivity, which may be due to cross-reactivity between the two antibody types (7). Testing anti-CarP alongside ACPA does not appear to significantly improve overall predictive accuracy in at-risk individuals (5), although triple positivity for ACPA, RF and anti-CarP confers very high specificity (98-100%) for RA (8).

In some individuals, pre-clinical systemic autoimmunity may represent a relatively benign state that never causes symptoms and does not progress to clinical disease. However, in others, the maturation of the RA-autoimmune response eventually leads to the development of inflammation, which usually heralds the early symptoms of RA. There are two important questions which must be addressed in this area. Firstly, why the synovial joints and tendons are the main targets of RA-related autoimmunity, and secondly, where exactly the primary site of articular inflammation occurs. These questions are critical to understanding the so called ‘second hit’ of RA pathogenesis and as such are key areas of ongoing research. Much

recent work has focussed on the role of high resolution imaging in identifying subclinical inflammation in at-risk individuals with early musculoskeletal symptoms (e.g. arthralgia) but without clinical synovitis. High resolution ultrasound (US) and magnetic resonance imaging (MRI) have both demonstrated excellent sensitivity for the detection of subclinical joint inflammation, which predicts the onset of clinical arthritis and its timing in symptomatic at-risk individuals (9, 10). Recent imaging studies have also provided important pathogenic insights. MRI studies have identified a high prevalence of extra-capsular inflammation (i.e. inflammation outside the joint capsule) in at-risk individuals without clinical synovitis, suggesting the tendons and peri-articular structures may be important early sites in the development of RA (10-12). Indeed, extra-capsular inflammation appears to be more prevalent and specific than joint inflammation in at-risk individuals (figure 2). It is therefore possible that, at least in some individuals, inflammation centred outside the joint capsule may be primarily responsible for the prodrome of pain and stiffness which often precedes the onset of clinical synovitis. Such observations are intriguing; whether this extra-capsular prodromal phase of the disease represents a 'window of opportunity' to prevent progression to synovitis will be important to explore in further studies including clinical trials.

Preventing the initiation of RA-related autoimmunity

The initiation of RA-related autoimmunity is likely to take place at sites distant to the joints; individuals with serum RA autoantibodies often have no discernible clinical, imaging or histological evidence of joint inflammation (13). Instead, recent evidence suggests inflammation at mucosal sites (e.g. the oral mucosa, lung and gut) plays an important role in triggering the RA autoimmune response. RA has well-recognised epidemiological associations with smoking and periodontal disease, which intuitively suggests the oral cavity and lungs may be involved in pathogenesis. Indeed, smoking in the context of the strongest genetic risk factor for RA (HLA-DR shared epitope) can increase an individual's risk of developing RA by up to 21-fold (14). A role for mucosal sites and the mucosal immune system is also suggested by the prevalence of the different ACPA isotypes in individuals at-risk of developing RA (15). First-degree relatives (FDRs) of RA patients have a higher prevalence of ACPA compared with controls. This is predominantly in the form of IgA ACPA, which are similarly prevalent in FDRs

and RA patients (16, 17). In contrast, IgG ACPA is much more prevalent in RA patients than FDRs. Given IgA antibodies are the hallmark of mucosal immunity, this suggests a mucosal ACPA response may be particularly important in at-risk individuals (i.e. individuals in the pre-clinical phase of disease) and this matures and develops into an IgG-dominant response with disease progression. Such observations have led to significant interest in the investigation of mucosal inflammation, citrullination and localised autoimmunity at the oral mucosa (especially the periodontium), the lung and the gut.

The putative role of the oral mucosa and periodontium in the initiation of RA-related autoimmunity is centred on the association between periodontal inflammation and local citrullination. Periodontitis shares important clinical and epidemiological associations with RA (18); both conditions begin with soft tissue inflammation which progresses to bony structural damage and loss of function (19). Furthermore, cigarette smoking is a well-recognised shared environmental risk factor. The local microbiome is perturbed in periodontitis, with enrichment of periodontopathic bacteria including *Porphyromonas gingivalis*. Periodontitis and periodontal dysbiosis has been demonstrated in patients with early RA (20) and is therefore unlikely to be a consequence of chronic RA-related inflammation but rather an early phenomenon, which may be related to disease initiation. *P. gingivalis* is able to citrullinate local proteins by virtue of its unique peptidylarginine deiminase enzyme (PPAD). Oral *P. gingivalis* exposure also induced periodontitis, anti-CCP antibodies and clinical arthritis in an *in vivo* animal model (21). One study has suggested another periodontopathic bacterium, *Aggregatibacter actinomycetemcomitans* is also capable of inducing periodontal citrullination, by activating local endogenous PAD production in neutrophils (22). If periodontal inflammation were to be capable of triggering RA-related autoimmunity, one may expect clinical periodontitis, and the citrullinating periodontopathic bacteria associated with it, to be increased prior to the onset of RA. Indeed recent data support this; clinical periodontal disease, inflamed periodontal surface area and abundance *of P. gingivalis* were all increased in anti-CCP positive at-risk individuals compared with controls (23). These at-risk individuals had no clinical or subclinical (US-detectable) joint inflammation, suggesting periodontal inflammation and associated dysbiosis precedes joint inflammation in subjects at-risk of RA. Furthermore an increased prevalence of periodontitis was also identified in Swiss and Colombian cohorts of at-risk FDRs (24, 25).

Taken together, these recent studies suggest periodontopathic bacteria, in the presence of local inflammation (i.e. periodontitis), may be capable of triggering RA-related autoimmunity in certain predisposed individuals. Thus far there has been much focus on specific bacteria, in particular *P. gingivalis*, with the potential to directly induce citrullination. However, it is likely that broader, more nuanced perturbations in the microbiome as a whole are important. Indeed, perturbation of the oral microbiome has been demonstrated in patients with early RA (26) and even at healthy periodontal sites in RA patients (27). The role of the oral microbiome will be an important ongoing area for future research.

Treating periodontal disease in individuals at-risk of RA is an attractive concept. Studies have shown that treatment of periodontitis can improve disease activity measures in patients with established RA (28, 29). It is tempting to speculate that treating periodontal inflammation and reducing the burden of periodontopathic bacteria in at-risk individuals may influence the development of RA. One logical target population would be those with genetic predisposition (e.g. FDRs of RA patients) and periodontitis, in whom periodontal treatment may prevent the development of systemic autoimmunity, i.e. primary prevention of RA. It is also possible that periodontal treatment may prevent the propagation of RA-related autoimmunity and the development of joint inflammation in anti-CCP positive at-risk individuals. These questions must now be addressed in clinical trials. Of note, qualitative data suggests individuals at-risk of RA may also prefer relatively conservative interventions such as periodontal treatment, which is beneficial for general health, as compared to immunomodulatory drugs (30).

Citrullination at the lung mucosa may also be important in the initiation of the RA-related autoimmune response. Cigarette smoking is associated with increased citrullination and PAD2 expression at the lung mucosa (31) and shared citrullinated protein targets have been identified in the lungs and synovial fluid of RA patients (32). More recently, IgA anti-CCP antibodies and neutrophil extracellular traps (NETs) have been identified in the sputum of seronegative at-risk individuals (i.e. FDRs with no detectable serum anti-CCP antibodies), suggesting localised citrullination and mucosal autoimmunity in the lung precedes the onset of systemic autoimmunity (33, 34). Furthermore, increased bronchial inflammation may be identified by high-resolution computed tomography (HRCT) in at-risk individuals who have no evidence of joint inflammation (35).

While there is credible evidence for a link between mucosal citrullination and disease initiation at the oral cavity and lung, the role of the gut mucosa is, at present, less well understood. The gut microbiome appears to be perturbed in RA patients compared with controls (26, 36-38). One study showed an increased abundance of *Prevotella Copri* in untreated early RA patients (37). Interestingly, the same gut organism was also enriched in a separate cohort of individuals at-risk of RA (39). The mechanistic link between *P.Copri* and RA-autoimmunity is unclear and is the subject of ongoing investigation. Indeed, as described for the oral microbiome, the role of the gut microbiome in disease initiation is likely to extend well beyond the influence of a single organism. It is certainly possible that mucosal dysbiosis may occur at multiple sites in individuals at-risk of RA or that different sites may be responsible for triggering autoimmunity in different individuals. The relative influence of different mucosal sites will be best assessed by multi-site sampling in large prospective cohorts of at-risk individuals.

Predicting progression to RA

Prospective cohort studies of individuals at-risk of RA have identified a variety of multi-modal biomarkers that are associated with the development of clinical synovitis. In seropositive at-risk individuals, these include clinical risk factors such as small joint tenderness, early morning stiffness duration and intermittent symptoms (40, 41), which may be easily assessed in the clinic. Many of these symptoms are intuitively recognised by rheumatologists and have been collectively termed 'clinically suspect arthralgia' (42). Anti-CCP antibody titre and the additional presence of serum RF have also been shown to be strongly associated with arthritis development in UK and Dutch cohorts of symptomatic at-risk individuals (40, 41, 43) as well as FDRs (44). More recently, the presence of intra-articular power Doppler (PD) signal on high-resolution US (9) and subclinical inflammation (especially tenosynovitis) on MRI (10, 45) have also been associated with progression to clinical synovitis. Risk prediction may also be achieved using novel immunological assays, including T-cell subset frequencies (46) and serum type 1 interferon signature (47).

By combining clinically accessible biomarkers that are associated with disease progression, pragmatic risk prediction tools have been created (40, 41). These tools enable personalised

risk stratification based on the number and type of risk factors that a particular individual has. In this way, very high risk individuals (>60% risk of developing arthritis at 18 months) may be differentiated from those at more moderate risk (31% risk at 18 months) (41). Importantly, these tools also identify those individuals who are very unlikely to develop arthritis, so they can be appropriately reassured about their prognosis.

Risk stratification in this way represents significant progress and must be an essential pre-requisite for appropriately designed, risk-appropriate prevention trials. However, the published risk prediction tools are currently based on prospective data from large single-centre at-risk cohorts. These must now be validated in comparable cohorts to ensure they are sufficiently robust to inform i) individual patients about their own risk and ii) case selection for clinical trials. A 'core set' of biomarkers may be useful to determine for different at-risk populations e.g. high-resolution imaging may be most valuable in symptomatic at-risk individuals whereas mucosal inflammation and dysbiosis may be more appropriate to assess in those with genetic predisposition or autoimmunity who have not yet developed symptoms. Another important question is whether an individual's risk remains stable or whether it changes and therefore should be re-assessed. If so, how frequently? Prospective data from longitudinal cohorts will be required to address these questions.

Preventing disease progression in at-risk individuals

There is currently no guidance or consensus on how individuals at-risk of RA should be managed. This poses a major problem for rheumatologists, who are routinely referred symptomatic anti-CCP positive individuals without synovitis from primary care practitioners (48). A recent UK survey suggests the clinical management of these patients is strikingly heterogeneous, with different disease-modifying anti-rheumatic drugs (DMARDs) often being used based solely on the clinician's judgement (48). There is clearly urgent need for evidence-based guidance, particularly as these patients may be in a unique 'window of opportunity' for preventative intervention.

Clinical trials have shown that immunomodulatory therapy in patients with undifferentiated arthritis (UA), i.e. early clinical synovitis, is effective in delaying or preventing progression to classifiable RA. In the PROMPT study, Methotrexate (MTX) delayed but did not prevent onset

of RA in UA patients (49). Abatacept also altered disease progression from UA to RA but ultimately could not prevent RA development (50). Importantly, the failure to demonstrate a beneficial effect of MTX in PROMPT may have been due to suboptimal risk stratification, as many of the UA patients included were ACPA negative and low-risk (49, 51). In a subsequent re-analysis, the investigators showed a clear preventative effect of MTX in the subgroup of ACPA-positive high-risk UA patients, although patient numbers were small (51). This highlights the critical importance of accurate risk stratification in informing case selection for prevention studies. It also suggests MTX, or other immunomodulators, could be effective in preventing the onset of clinical synovitis in ACPA positive high risk individuals.

Two studies have evaluated the effectiveness of corticosteroids in patients with early clinical arthritis (52, 53). Neither demonstrated a preventative effect but the STIVEA trial reported less DMARD requirement at 6 months compared with the placebo arm, suggesting delayed progression to RA (52).

Several clinical trials assessing the preventative effect of immunomodulation in at-risk individuals without arthritis are now in progress. However, only two studies have been published thus far. In the first, Bos et al randomised 83 patients with ACPA and/or RF positive arthralgia to receive two intramuscular injections of dexamethasone or placebo at baseline and six weeks (54). In this study, patients receiving dexamethasone were equally as likely to develop RA at 26 months follow up as those receiving placebo injections. More recently, the PRAIRI study compared the preventative benefit of a single infusion of rituximab (RTX) with placebo in high risk individuals with imminent clinical arthritis; the 81 subjects included were all ACPA and RF positive with subclinical inflammation as evidenced by a raised C-reactive protein (CRP) level and/or US and/or MRI inflammation. After median follow up of up to 29 months, 40% of patients in the placebo arm developed arthritis compared to 34% of patients who received RTX. Although not a significant preventative effect, RTX appeared to delay the onset of arthritis by a median of 12 months (55).

Several trials in progress are seeking to assess the preventative benefit of a variety of drugs, including MTX, hydroxychloroquine, abatacept and simvastatin in a range of different at-risk populations. As such, it will be important to optimise future efforts by ensuring at-risk populations for trials are clearly defined and the biomarkers and end-points to be used are

standardised. At present it is unclear if specific preventative approaches have disproportionate benefit in different at-risk populations; e.g. immunomodulation may be more effective in symptomatic at-risk individuals with or without subclinical inflammation, while conservative lifestyle interventions (dietary modulation, periodontal therapy, smoking cessation) may be more efficacious in individuals with early autoimmunity. Although such assumptions are logical from a pathogenic perspective, they are not currently supported by any clear evidence. Patient perspectives are also critical, as lower risk individuals without symptoms may favour lifestyle modification over taking a drug for RA prevention (30).

Cure of RA: The first step is Remission

As mentioned above, due to the significant improvement in both the diagnostic and therapeutic armamentarium for RA, the prognosis of patients has changed drastically in the last 30 years (56). Early diagnosis has been facilitated by an increased awareness and knowledge of the disease, but also by the use of very sensitive imaging tools, such as musculoskeletal US and MRI (57, 58). Early and aggressive therapy, the advent of b-DMARDs, and the application of the “treat-to-target” (T2T) strategy, with tight follow-up of the patients aiming at obtaining clinical remission of the disease, have achieved results which were unimaginable a few decades ago (59, 60).

RA used to be a disease leading inexorably to joint destruction and loss of function, with potential life-threatening complications related to the disease itself and to the prolonged use of medications (i.e., steroids), whereas it is now a condition in which remission, or even cure, represent feasible targets (61). Here we discuss the impediments to achieve these desirable targets.

Observations on remission

The percentage of patients with RA achieving clinical remission has improved markedly compared with a few decades ago. The results of a Swedish Rheumatology registry show that the rate of remission in patients with RA has increased from 16% in 1999 to 45% in 2009 (62). In a Norwegian-registry ("NOR-DMARD"), a 2-fold increase in 6-months remission rates, as well as improvement in other disease activity measures, were observed in the period between 2000 and 2010 in a large cohort of patients with RA. In this study, the authors observed that the baseline disease activity decreased over the same period both in RA patients starting methotrexate MTX or MTX plus a TNF-alfa inhibitor (TNFi) (63), probably due to earlier diagnosis.

However, despite the improved outcome for patients with RA, the majority of patients (up to 75%) do not achieve clinical remission (64). The percentage of patients achieving clinical remission is even lower when "sustained" remission (lasting at least six months) is taken into account (65-67). For these patients, who experience an inadequate response to MTX monotherapy or in combination with b-DMARDs, there is a clear need for further treatment and management options (68). As noted in the introduction, simple changes in the disease management could improve this state of affairs.

Achieving clinical remission

Data from randomized controlled trials, registry-based and observational studies, suggest that a better state of remission, or low disease activity (LDA), could be successfully achieved in RA patients with short disease duration, which are treated early and intensively, and managed according to the T2T strategy following the ACR/EULAR recommendations (69-71).

In a randomized, double-blind, placebo-controlled trial, the authors showed that treating RA patients with less of 12 months of symptoms very early with infliximab (IFX) in combination

with MTX resulted in better clinical, imaging and functional outcomes than treatment with MTX alone (72). In the Dutch Behandel Strategieen (BEST) study, 508 patients with early RA were randomized to 4 different treatment arms: 1) sequential DMARD monotherapy starting with MTX, up to the dose of 30 mg/week; 2) step-up combination with DMARDs, starting with MTX; 3) combination with MTX, sulfasalazine and high dose prednisolone (60 mg/day); 4) combination with MTX and IFX. All the patients were closely followed-up (every 3 months) and switched between the different arms in case of treatment inefficacy. About 50% of the total population achieved remission, with 64% of patients treated with MTX and IFX reaching persistent clinical remission (at least 6 months). In patients with early RA, initial combination therapy (either with prednisolone or IFX) led to improvement in functional outcomes and less radiographic damage in comparison with sequential monotherapy or step-up combination therapy strategies (73).

Regarding RA patients with established disease, some positive observations come from studies showing that achieving clinical remission may be possible in these patients as well. More intensive treatment strategies have been associated with sustained remission, regardless of disease durations (74). Data from the British Society for Rheumatology Biologics Register (BSRBR) for RA, including a cohort of 14436 patients in the period between 2001 and 2013, suggest that adalimumab (ADA) use, baseline MTX, greater physician global assessment and ex-smoker status (vs current smoker) may increase the likelihood of achieving sustained remission. On the other hand, female gender, older age at starting TFNi, IFX use (vs etanercept (ETN)), increased body mass index and higher ESR at baseline were associated with a negative likelihood of reaching the same outcome (75). These results are of course subject to bias both through channelling and a cohort effect. In another study, the authors found that the number of prior DMARDs, more than disease duration, could influence negatively the response to TNFi in RA patients (76).

Defining remission

An important issue is the lack of a uniform definition for remission. Disease activity score (DAS)-erythrocyte sedimentation rate (ESR) score of <2.6 has been adopted as the standard measure for remission in most trials and it is commonly used in clinical practice. DAS28, as well as other disease activity indices, such as the Simplified Disease Activity Index (SDAI) or

Minimal Disease Activity index scores, rely on surrogate markers of inflammation, such as tender or swollen joints count, with the consequent risk of under or overestimating disease activity status (77, 78).

Subclinical inflammation in clinical remission: does it matter?

Several imaging studies, including US and/or MRI, have demonstrated the presence of subclinical inflammation in a considerable proportion of patients with RA in remission according to clinical instruments. Scirè et al., demonstrated the presence of power Doppler (PD) signal in 18 out of 43 (41%) patients with RA in "sustained" clinical remission (DAS <1.6) (79). Similarly, Saleem et al. found PD signal in 21% of 128 RA patients in "sustained" clinical remission. In the latter study, 32 patients were also in "deep" remission (DAS28 <1.17), 25% of whom had significant PD activity (>grade 1) (80). Even when more stringent criteria for remission were used, such as the American College of Rheumatology (ACR)/European League Against Rheumatism (EULAR) Boolean Remission criteria, PD signal was detected in a considerable number of patients (60%), with high PD scores observed in around 1/3 of patients (81). Figure 3 shows the presence of "active" synovitis in the 2nd metacarpophalangeal joint in a patient with RA in clinical remission according to DAS28.

The value of the disease activity indices in the evaluation of remission has also been questioned by the observation that some patients in clinical remission do not achieve a good outcome of the disease, especially as regards progression of structural damage and functional deterioration (82, 83). It has been argued that this might be explained by the presence of subclinical inflammation, which is frequently missed by clinical instruments.

The presence of subclinical inflammation, suggesting ongoing disease activity, was documented by US and MRI in 81% and 96% respectively of 107 RA patients in clinical remission receiving DMARDs (84). In a longitudinal study evaluating the same cohort, deterioration in radiographic joint damage was seen in 19% of patients during the study period, with synovial hypertrophy, PD signal and MRI synovitis scores being significantly associated radiographic damage, also in asymptomatic joints (85). Similarly, Yoshimi et al., found that radiographic progression was significantly associated with the presence of PD

signal at baseline in a small cohort of patients with RA in sustained clinical remission (2 years) (86).

These findings have raised the need for a more comprehensive definition of remission, the so-called "multi-dimensional remission". This definition is not exclusively based on clinical disease activity indices, such as DAS28 or SDAI, but it also includes imaging, serological and immunological parameters as well (i.e., negative autoantibodies or normal T-cells). In a recent study, Gul et al., found a significant association between the "multi-dimensional remission" (Boolean, ultrasound and T-cell remissions) and the patient's perspective of the disease status (patients reported outcomes) (87).

Despite several imaging studies showing subclinical inflammation in RA patients in clinical remission, more longitudinal evaluations are needed to confirm the possible link between such subclinical inflammation and subsequent radiographic or functional deterioration. This is needed before US or MRI can be routinely used as tool for guiding treatment management, including DMARDs discontinuation, in patients with RA (88). Interestingly, in a very recent study, stringent immunological remission, defined on this occasion as disappearance of ACPA and RF, was infrequently observed in patients with RA, and in similar frequencies regardless of achieving sustained DMARD-free remission (89).

Tapering DMARDs in RA patients in clinical remission

As noted, the ideal outcome of therapy is to achieve a remission so profound that therapy can be stopped. Since the number of RA patients achieving clinical remission has grown exponentially in the recent years, whether to taper or suspend the treatment in these patients has become a question of paramount importance. Reducing the therapy could limit costs related to the treatments, especially for b-DMARDS, and might allow avoiding potential over-treatment of these patients, with consequent obvious decreasing of the safety issues.

Therefore, upon achievement of stable and long-standing remission, the following (open) questions arise:

- Should we consider DMARDs tapering or discontinuation in patients with RA in clinical remission?
- How should treatment de-escalation, or discontinuation, be achieved?

- Are all RA patients appropriate for tapering or discontinuing DMARDs?
- Do we have biomarkers that might predict reliably a positive/negative outcome in the patients who are suitable for tapering DMARDs?

At the same time, it is important to keep in mind that a considerable number of patients with RA flare when DMARDs therapy is de-escalated or discontinued, with significant impact on the quality of life and also possible radiographic progression (90, 91).

Moreover, it is important to underline the fact that the great majority of studies investigated tapering or discontinuing TNFi whereas data are lacking regarding biologics with alternative mechanism of action, such as anti-CD20 or Jak-inhibitors.

With regard to this topic, both EULAR and ACR have recommended tapering b-DMARDs in RA patients in sustained clinical remission. In the last EULAR recommendations, the authors suggest considering tapering b-DMARDs, after suspension of steroids, especially if treatment is combined with a c-DMARD (92). As well as EULAR, ACR include the opportunity of tapering DMARDs in the new treatment recommendations. Tapering should be conducted "slowly" and "carefully", after having informed the patients of the risk of flares (93). Overall, specific indication and guidelines on how to taper or discontinue DMARDs in patients with RA in clinical remission are lacking. Moreover, steroids, which are part of DMARD therapy in a considerable number of patients with RA, should be taken into account in the tapering regime.

Whilst the ideal patient for tapering or suspension of b-DMARD therapy is far from being delineated, several prognostic factors for successful de-escalation have been identified. An indispensable pre-requisite is that the patient is in clinical remission which possibly has to be "deep" (DAS28 <2.0 or even <1.8) and "sustained". LDA is a no longer accepted as an appropriate disease state for tapering (94, 95).

Tapering DMARDs and disease duration

Disease duration and early use of biologic agents are other important aspects that might influence positively the outcome of tapering. In the above-mentioned study conducted by Quinn et al. including 20 patients with early RA (<12 months of duration), an induction regime with IFX and MTX for 12 months was significantly superior at achieving clinical and imaging

remission (documented by MRI), than MTX alone. At 1-year follow-up, 70% of patients who stopped IFX remained in clinical remission, showing better function and quality of life outcomes in comparison with the MTX-group (72). Interestingly, 8 years after, the patients who had received INF plus MTX had significantly lower disease activity scores and almost half of them were in remission 10% off therapy (96).

In a 24-month, multicentre, randomised, double-blind study (U-Act-Early), 317 patients with very early (symptoms duration: 26 days) and DMARDs-naïve RA were randomized to receive tocilizumab (TCZ) plus MTX, TCZ monotherapy or MTX monotherapy. In patients achieving sustained remission, MTX first and then TCZ, were tapered and then stopped. The rate of remission was 86% of in the TCZ plus MTX arm, 84% in the TCZ monotherapy arm, and 44% in the MTX monotherapy arm. Moreover, the proportion of patient maintaining clinical remission after treatment discontinuation was significantly higher in both the TCZ arms (35% in the combination therapy arm, 27% in the TCZ monotherapy arm) than in the MTX group (11%) (97).

In the above-mentioned BEST study, 64.1% of patients on combination therapy with IFX plus MTX achieved sustained clinical remission and suspended the therapy with IFX. After 2 years, 87% of these patients maintained a state of LDA despite IFX discontinuation. Interestingly, 27% of patients in the combination therapy with IFX plus MTX achieved a status of complete drug-free remission, showing minimal radiographic progression.

On the other hand, treatment-free sustained remission could be a difficult goal for patients with established disease and non-responders to previous DMARDs. In a study carried out by Brocq et al, the authors included 20 patients with long-lasting RA, showing that 75% of them experienced a flare of the disease after TNFi withdrawal (98). Similar (discouraging) results come from the CERTAIN study. In this double-blind, randomised, placebo-controlled trial, certolizumab was discontinued in a cohort of long-standing, refractory RA patients following achievement of clinical remission, according to CDAI, at weeks 20 and 24. After discontinuation, clinical remission was maintained only in 3 out of 17 patients (99).

In these patients with severe, long-lasting, treatment refractory disease, dose reduction rather than discontinuation of TNFi might represent a more realistic target. In the Dose REduction Strategy of Subcutaneous TNF inhibitors (DRESS) study, 180 RA patients (mean

disease duration 10 years) receiving ADA or ETN were randomized to continue the standard dose of b-DMARDs (59 patients) or to gradually decrease the dose of b-DMARDs until disease flare (121 patients). The outcome of patients reducing the dose of ADA or ETN was not inferior to the outcome of patients continuing the standard dose of b-DMARDs, with similar proportion of flares at 18 months, and no significant changes in the radiographic progression between the two groups (100). In the prospective randomized RETRO study, the authors evaluated the risk of flare in patients with RA in sustained remission after treatment tapering or discontinuation. A total of 146 patients with RA (mean disease duration 7.1 years) was included. After a follow-up period of 12 months, about 2/3 of patients remained in remission whereas 1/3 experienced a disease flare. The rate of flares was low in the continuation arm (16%) and significantly higher in the tapering (38.9%) and stopping arms (52%) (101).

Predictors for disease relapse after DMARDs tapering

In the decision-making process of tapering or discontinuing DMARDs in patients with RA, it is critical to define clinical, imaging, or serological biomarkers which might possibly predict the positive or negative outcome of such decision.

The presence of subclinical inflammation on US, especially PD, has been associated with disease flare or failed tapering in several studies (102-104). With respect to serum biomarkers, the best-studied predictor of relapse is ACPA positivity. In the BEST study, as well as in the RETRO and HIT-HARD studies, ACPA positivity was associated with higher relapse risk and failure of b-DMARDs discontinuation (73, 101, 105). In a very recent study, serum calprotectin resulted as an independent predictor of relapse in a cohort of patients with RA and psoriatic arthritis (106). T-cell dysregulation has also been associated with disease relapse in patients with RA in clinical remission (107). A very recent systematic review highlighted other possible predictors of successful b-DMARDs tapering, including better physical function, low or absent RF, low levels of CRP and ESR (108).

Remission: summary

There is a need for a more comprehensive definition of remission, which at present is predominantly defined by clinical instruments with the risk of overlooking residual inflammatory activity. Moreover, further management options are required for the

considerable number of RA patients who do not reach sustained remission despite multiple b-DMARDs. Further longitudinal evaluations are needed to validate the possible predictive value for successful remission and relapse risk for imaging, such as US and MRI, and serological biomarkers. Open questions the best tapering-strategy, which should include also steroids in the tapering regime, and the successful rate of discontinuing non TNFi b-DMARDS, such as anti-CD20 and JAK-inhibitors. However, as U-Act-Early showed what is needed most is early deep remission allowing successful drug cessation.

Conclusion

Future ambitions for the treatment of RA will be prevention of the disease where possible, and when arthritis occurs, to treat temporarily before reaching drug free remission; effectively a cure. This review outlines the current status of progress towards achieving the two greatest unmet needs for patients with RA. These ambitions are reflecting the foremost desire of patients: to have a normal quality of life without medication.

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