Editorial

Predicting and managing the progression of structural damage in rheumatoid arthritis: where do we stand?

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Received on December 30, 2011; accepted in revised form on March 16, 2012.

Clin Exp Rheumatol 2012; 30: 459-463.

Key words: rheumatoid arthritis, disease progression, treatment outcome

Competing interests:
M. Govoni has received grants and research support from Abbott, Roche, Pfizer, Schering-Plough, Bristol-Myers Squibb, UCB, and Mundipharma;
R. Caporali has served as a speaker for Abbott, Bristol-Myers Squibb, Merck Sharp & Dohme, Pfizer, and Roche.

In the past decade, the management of rheumatoid arthritis (RA) has undergone a revolutionary shift towards a new paradigm based on early diagnosis, accurate prognosis, early treatment – aimed to reach remission or low disease activity ("treat to target") – and close clinical monitoring of the course of the disease ("tight control"). The introduction of biological agents has facilitated better control of disease activity in affected patients, improved their quality of life and slowed the progression of radiographic damage.

Along with clinical remission, containment of damage has become an essential target that should be included within the modern standard of care for patients with RA. Of note, the new American College of Rheumatology (ACR)/European League Against Rheumatism (EULAR) criteria for remission provided definitions based on their ability to predict non-progression of disease in terms of both patient function and radiographic progression in the context of clinical trials (1).

It is well known that disease activity is largely reversible, mainly in the early phases of the disease, whilst damage, once it has occurred, is usually permanent. Therefore, the identification of predictive factors informing the clinician about the risk of radiographic progression is of utmost importance in prognostic assessment, since their presence or absence can influence therapeutic choices.

RA is a heterogeneous disease, hence a different pattern of disease progression is expected in different patients. It is widely accepted that the most aggressive forms of RA are in patients with rapid progression of radiographic damage ("rapid progressors"). These patients must be promptly recognised and treated according to modern therapeutic regimens, which warrant minimisation of the inflammatory process and to arrest, or to heavily reduce, accumulation of damage. Consequently, in these cases, omitting an appropriate therapy should be regarded as a true iatrogenic side effect.

Risk factors for damage progression

Evidence accumulated in the last 10 years from large observational studies and registries has shown a number of risk factors, such as seropositivity for anti-citrullinated peptide antibodies (ACPA), rheumatoid factor (RF), shared epitope, and a high number of swollen and tender joints and erosions at baseline, to be predictors of severe RA and radiographic progression. In a recent study from the Leiden Early Arthritis Clinic, older age, male gender, longer symptom duration at first visit, involvement of lower extremities and high acute phase reactants were also identified as risk factors (2). If we look at the data from some of the more familiar published randomised controlled trials (RCTs), four further major factors have emerged as highly relevant for determining radiographic outcome: the lag time in initiating therapy, the modality of disease monitoring (tight control), the amount of disease activity or persistent synovitis, and the pharmacological treatment.

Treatment initiation lag time

One historical study has clearly demonstrated that early introduction of conventional disease-modifying antirheumatic drugs (DMARDs) (*i.e.* chloroquine or sulphasalazine) was associated with better disease outcome (3). A 4-month delay in initiation of DMARDs was statistically significantly associated with worse radiographic outcome after 2 years. These data were replicated in

a longer-term follow-up study by van Aken *et al*., which demonstrated that the beneficial effect of early DMARD treatment on radiographic progression was still present at 4 years (4). A recent study based on 250 patients with early RA demonstrated that such beneficial effect is visible for at least 2 years of treatment (5).

Close monitoring of disease activity

Compared with routine care, a more strict monitoring strategy (tight control) has been demonstrated to improve disease outcomes (6). The results of three well known studies (7-9) have been summarised in a recent meta-analysis (10). Greater rates of clinical remission, ranging from 31%–65%, along with a better radiographic outcome were observed with two out of three "intensive care" regimens.

Another important piece of information comes from the BeSt study in which 508 patients with recent-onset active RA were randomised to 4 treatment groups and followed up accordingly to a Disease Activity Score (DAS)-driven strategy: (i) sequential monotherapy or (ii) step-up to combination therapy (both starting with methotrexate [MTX]), (iii) initial combination therapy with MTX, sulphasalazine, and prednisone, or (iv) initial combination therapy with MTX and infliximab (11). At 2 years of follow-up, a similar proportion of patients (about 40%) reached clinical remission (DAS <1.6) regardless of treatment arm. Furthermore, after 3 years of treatment, progression of radiographic damage remained low in all groups but was significantly lower in the initial combination therapy than in the initial monotherapy groups.

The results of this study yielded important information: first, to achieve clinical remission (*i.e*., no disease activity), a DAS-driven treatment adjustment is probably more important than the choice of therapeutic strategy itself; second, a lower rate of radiographic disease progression appears to be more directly associated with the initial treatment choice, reinforcing the concept that a "window of opportunity" in early phases of the disease does really exist.

Disease activity and synovitis

Clinical remission is generally considered as synonymous with the absence of synovitis. It is now well known that overt or subclinical joint inflammation (*i.e*. synovitis) is the primary process which fuels and maintains radiographic damage. A recent analysis of the Trial of Etanercept and Methotrexate with radiographic Patient Outcomes (TEMPO) showed a significant association between occurrence of the repair process after 1-year of treatment only in joints characterised by an evident amelioration or absence of any inflammatory process (12). Other recent studies have demonstrated that the link between disease activity (*i.e*. clinically detectable inflammation) and radiographic damage is not characterised by a first order linear relationship; this gap is known as "clinical-radiological dissociation". The decoupling between clinical and radiological symptoms has been further highlighted by the use of biological drugs and widespread use of more sensitive imaging techniques. The reason why this clinical-radiological dissociation takes place is complex and still not fully understood (13).

There is no doubt that the choice of the clinimetric instrument to define clinical remission is critical. It is well known that the DAS28 and the ACR criteria "cut off" values for clinical remission allow for residual tender and swollen joints and exclude evaluation of the feet (14-16). The more restrictive clinical disease activity index (CDAI) and the simplified disease activity index (SDAI) have been shown to better represent the actual degree of disease activity in RA (17).

When using composite clinimetric scoring instruments to assess disease activity, another critical point arises when the so called "patient reported outcomes (PROs)" (such as pain and patient global score) are predominant (a typical case is the patient with concomitant fibromyalgia). In these cases, a patient may not show radiographic damage despite still appearing "active" as a result of the contribution of parameters that are poorly related with progression of damage.

Finally, Brown *et al*. have clearly documented that even in patients judged as in prolonged clinical remission, residual synovitis, demonstrated by ultrasound and/or magnetic resonance imaging (MRI), may still be present and is the major contributor in maintaining progression of radiographic damage (18). Therefore, even persistent clinical remission does not appear to be completely protective against progressive radiographic damage.

The availability of power Doppler coupled with morphological ultrasound examination has facilitated the attainment of new relevant information. Recent studies have demonstrated a correlation between DAS28, C-reactive protein and power Doppler scores allowing the use of power Doppler to predict the progression of radiographic damage associated with RA (19), to monitor the therapeutic response (20, 21), and to predict the risk of disease flares (22). MRI is another sensitive technique to detect both subclinical synovitis and early erosions. But, more importantly, it is the only method able to detect bone marrow oedema, which may signal an early stage of an impending erosion, thus representing a sensitive parameter for the prediction of future damage (23).

Taking into account the above mentioned considerations, any therapeutic decision based exclusively on clinical data may be misleading, missing the opportunity to recognise subclinical synovitis or an impending erosion (*i.e*., bone oedema) that may subtly sustain the progression of joint damage, even if the patient looks as if they are in remission or in a low disease activity status. For this reason a more complete definition of remission should also include, in the near future, the concept of radiographic non-progression.

Treatment strategy: the additional benefit of biologic agents

It is now widely accepted that early treatment, tight control, clinical remission and absence of synovitis are major determinants in slowing radiographic progression; however, we must not forget that pharmacological treatment is also just as relevant.

RCTs of biological agents, including especially the anti-tumour necrosis factor (TNF) alpha agents, but also abatacept, rituximab and tocilizumab, have demonstrated superiority in achieving both ACR clinical response and control of radiographic joint damage in combination with, or compared with, MTX monotherapy among subjects with established and early RA (24-33).

What has been less frequently investigated is whether combination therapy with MTX plus a biological agent is better for inducing a state of clinical and/or radiographic remission if used as initial therapy in newly diagnosed patients. In a recent systematic review, Kuriya *et al*. focused on this interesting point and analysed individual RCTs comparing the impact on clinical remission and radiographic non-progression of initial MTX monotherapy versus the combination of a biological agent plus MTX in early RA (34). The results of this meta-analysis suggest that the impact of initial combination therapy is more beneficial for clinical remission than for radiographic outcome. Clinical remission appeared to be 74% and radiographic non-progression 30% more likely at 1 year when a biological agent was used in combination with MTX, compared with MTX monotherapy. In other words, the efficacy of combination therapy with a biological agent is superior to MTX monotherapy for clinical remission, but has a lesser initial effect on radiographic non-progression. These results are in contrast to results from individual RCTs where the superiority of combination treatment over monotherapy appears more evident. These findings seem to suggest that in the true early phases of the disease or in patients naïve to previous DMARD therapy, different treatment options may be less relevant with respect to the radiographic outcome and confirm what has been mentioned above that, at disease onset, early intervention is of outstanding importance. However, it must be underscored that these results are not generalisable to populations with established disease, those with an inadequate response to MTX, or patients previously treated with DMARDs/biological therapy.

Given these data, a question arises as to what would be the main incremental benefit of biological agents over MTX alone in early disease. In this regard, a recent analysis of the PREMIER study has provided important information (35). In this study, three groups of patients were randomised to treatment with either a combination of adalimumab (ADA) plus MTX, ADA alone, or MTX alone. After 2 years, combination therapy had shown greater efficacy in slowing radiographic damage than the monotherapies. Interestingly, in the ACR20 non-responders, a better efficacy of the ADA monotherapy over the MTX monotherapy was observed. A higher correlation between radiographic progression and the degree of disease activity was observed for the patients treated with MTX monotherapy compared with the other two groups (ADA or ADA+MTX). In contrast, similar efficacy was observed with MTX monotherapy or ADA+MTX in patients without clinically detectable synovitis.

As a result of this study it can be inferred that MTX monotherapy may affect radiographic damage primarily by reducing synovitis, whilst the anti-TNF agent (ADA) is active despite the persistence of a residual synovitis. Also, it can be argued that anti-TNF drugs are able to control the progression of radiographic damage through a different mechanism of action (*i.e*. by inhibiting osteoclastic activity) even in the absence of a clearcut clinical response. MTX alone doesn't induce the same result and requires stricter control of synovitis.

Another point to consider in evaluating the additional contribution of biological agents in controlling radiographic progression regards "the rate of progression" being a shared belief amongst clinicians that some unlucky patients may be classified as "rapid progressors"; thus, a major benefit of biological agents may actually lie in their ability to inhibit progression better and faster among those patients who will be rapid radiographic progressors.

Finally, in patients where any further improvement does not seem reasonably achievable or clinical response does not appear fully satisfactory (*i.e*. poor responders), a therapeutic approach including biological agents could allow the possibility to minimise, also in these difficult cases, the progression of radiographic damage through their ability to affect osteoclastic activation, despite the persistence of a clinically detectable amount of disease activity. More studies in these two conditions are needed.

Conclusive remarks

Although an impressive advance has been gained in the prognostication of radiographic damage, a "grey zone" of uncertainty still remains.

The data discussed above introduce new uncertainties with respect to the right therapeutic approach that must be taken in patients that feel well, since although they look as if they are in remission, they may still be at risk of progression, given the persistence of sub-clinical synovitis or because of incomplete control of osteoclast activation.

Experience from the Leiden Early Arthritis Clinic teaches us that current known risk factors account for only one third of the total variance in joint destruction. All the predictive parameters become less reliable in predicting the progression of radiographic damage in RA when they are applied in the individual patient. The new scenario in the management of RA should consider the use of individual and easy to use risk cards, similar to what is already widely available for cardiovascular risk assessment, where relevant variables influencing radiographic progression should be taken into account. Using a subanalysis of data from the Anti-TNF-α Trial in Rheumatoid Arthritis with Concomitant Therapy (ATTRACT) and Active-controlled Study of Patients receiving Infliximab for the treatment of Rheumatoid arthritis of Early onset (ASPIRE) studies, a model for predicting the rapid progression of radiographic damage has already been developed (36). In addition, increased use of aggressive combination therapy over monotherapy in early RA is supported with data from studies such as the 2-year PREMIER study, showing the superiority of MTX+ADA over MTX monotherapy (37). Finally, combination therapy with anti-TNF alpha

inhibitors over conventional DMARDs is also preferred in patients showing a "rapid progression profile". Given this background, it does not seem out of place to say that also for rheumatologists, a new era in better prognostication and more adequate assessment of damage progression has started, opening new perspectives for a better disease control.

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