Editorial

Should We Use Poor Prognosis Factors to Start Early Treatment in Patients With Rheumatoid Arthritis?∗

¿Debemos usar los factores de mal pronóstico para iniciar precozmente un tratamiento biológico en los pacientes con artritis reumatoide?

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Rheumatoid Arthritis: Current Problems

Treatment of rheumatoid arthritis (RA) has undergone a radical change in recent years by optimization not only of classical treatments with disease modifying drugs and the introduction of new biological therapies,1–8 but also of the objectives (treat to target) in the short- and long-terms in monitoring and standardization of patients and procedures.9

It is increasingly evident that there is a window of opportunity period in which, after the diagnosis, the use of more effective therapies and established pretreatment objectives lead to improved long-term prognosis.9,10 In this sense, the proposed new referral and classification11 criteria for RA12 allow this therapeutic approach to be started early. Studies show that in the first two years of treatment any well-considered strategy may induce remission.13,14 What is more controversial is whether long-term strategies based on non-biological agents compared to early introduction of biological drugs, maintain a prolonged remission avoiding further progression of radiologic damage15,16 or disability.17 In this regard, results from trials using biological anti-TNF-alpha drugs in patients with RA cohorts of established RA patients show that active treatment and early introduction of biologic therapies are critical to the achievement of long-term therapeutic objectives.18–21

The reality in our clinical practice is that despite the biological treatment, a proportion of patients with inflammatory activity persist or present radiological progression.22 The question remains whether therapy may be optimized in these patients. Recent publications such as Aletaha et al.23 warn about the importance of the persistence of swollen joints, rather than high values of C-reactive protein (CRP) as a determinant of long-term radiographic progression. It has shown a direct relationship between increases in DAS28, where the number of swollen joints is one of the parameters to take into account (28 Joints Disease Activity Score) and loss of function measured by Health Assessment Questionnaire (HAQ).24

Although referral criteria remain relatively arbitrary, with the introduction of the Clinical Disease Activity Index (CDAI) and Simplified Disease Activity Index (SDAI) indices there is advancement in trying to find a standardized way of assessing clinical remission in our patients25–27, unfortunately they still do not integrate important aspects such as radiological progression, extra-articular manifestations and development of comorbidities of patients. So far the treatment of RA has been “arbitrarily homogeneous,” with strategies that could be called step-up, from “more profitable” drugs and with longer time of use, to more sophisticated therapeutic strategies including non-biological and biological drug combinations,28 knowing that there are significant differences in the clinical prognosis of patients. It is not surprising therefore that absolute remission is achieved and maintained in only 30%, irrespective29 of the therapy employed. This gives us an idea of the heterogeneity of patients with RA and the importance of clinically classifying at least those with an increased risk of progressive damage, as we move forward in understanding the pathogenesis of RA, which allows a more personalized medicine.

Historically we have used rheumatoid factor (RF) in the diagnosis of RA,30 but since the discovery of antibodies to citrullinated proteins and the development of Enzyme Linked Immunosorbent Assay (ELISA) commercial kits for antibodies to citrullinated peptides (anti-CCP), we have seen an increase in the diagnosis of RA and improvements in the prognosis of patients. There is more and more talk of “anti-CCP positive vs. anti-CCP negative patients”.30,31 The sensitivity of anti-CCP and its relationship to radiological progression and extra-articular damage has been demonstrated in several registries.32–35 In RA patients the concentration of anti-CCP antibodies was higher in synovial fluid than in blood, suggesting that they may be produced in the swollen synovial membrane itself.36,37 One might argue whether the production of antibodies against citrullinated proteins is a consequence of chronic synovial inflammation, or one of the factors that trigger it.

It should also be noted that although the presence of the protein tyrosine phosphatase, non-receptor type 22-lymphoid (PTPN22)

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shared epitope and other non-genetic determinants are both related to the evolution of the disease, they do so due to the ability that these patients have to generate antibodies against proteins that are physiologically citrullinated.

Antibodies to Citrullinated Proteins: Etiopathogenic Implications in Rheumatoid Arthritis

The posttranslational citrullination is a phenomenon consisting in transforming the essential amino acid arginine to the non essential amino acid citruline, a process catalyzed by the calcium-dependent enzyme peptidyl-arginine deaminase (PAD). It occurs physiologically in the process of keratinization, chemotaxis, inflammation, trauma, aging, neuronal growth, embryonic development and apoptosis. So far 5 isoforms of PAD (PAD-1, 2, 3, 4, and 6) have been described and there are PAD isoforms-2 and PAD-4 which have been demonstrated in joint structures and have been linked to the pathophysiology of RA. Yet the mechanism by which a physiological process becomes pathological, triggering an immune response against autoantigens formed de novo in the context of RA is unknown. Is it the size or type of immune response against these antigens? Is a specific cellular and humoral microenvironment with a genetic predisposition associated with HLA favoring an abnormal pattern of response?

It is known that central and peripheral tolerance against autoantigens at certain checkpoints (bone marrow and secondary lymphoid organs) is impaired in autoimmune diseases, leading inevitably to self-reactive B cells, which should not circulate in peripheral blood, but which are able to complete their normal development and maturation with the consequent possible production of autoantibodies. Samuels et al. postulated that this alteration could be developed in the early stages of the evolutionary cycle of the B cell, at the time of assembly of the V(D)J fragments of the BCR (B-cell receptor) and it would explain the existence of a long latency period, even over several years (between 1.5 and 9), between the determination of anti-CCP antibodies in patients with undifferentiated arthritis until they meet the criteria for RA of the American College of Rheumatology (ACR).

Anti-CCP antibodies were detected and first described in 1964 as a “perinuclear anti-factor” antibody by Nienhuis and Mandema, and then by Young et al. as an anti keratin antibody using as substrate rat esophagus. Although subsequent studies demonstrated a high specificity of these antibodies in RA patients, standardization for their detection is extremely complex and was not achieved until 1995 when two antibodies against filamentous elements of the same group, both directed against filaggrin, a protein constituent of epithelial cells epiteliales were described.

These antibodies have been detected in other clinical conditions such as psoriasis, juvenile idiopathic arthritis (JIA), multiple sclerosis, RA, Alzheimer’s disease and various cancers, all linked to the presence of PAD enzymes and with a citrullinated substrate sensitivity and specificity different from those reached in RA.

Commercial assays used in routine laboratories detect the presence of immunoglobulin G (IgG) antibodies by ELISA. Specifically in patients with RA, it has been shown that anti-CCP antibodies are produced in response to antigenic stimulation triggered by proteins such as filaggrin, fibrinogen or the residue of vimentin, and are present in both the liquid and synovial tissue which are likely to be citrullinated. In hindsight, other stimulant antigen leads to this objective.

The detection of anti-CCP has demonstrated a high specificity and sensitivity, high predictive value and cost-effectiveness and provided a key tool for the diagnosis and treatment implementation for early-onset RA. Although routine measurements focus on the detection of IgG anti-CCP, IgM and IgA in RA and JIA show interesting results in terms of progression and severity of the disease and, despite a small sample size, the presence of these three isotypes has been associated with a worse prognosis.

Recent studies establish associations between the immune response to citrullinated antigens and genetic predisposition taking account the HLA of patients with RA, the class II HLA shared epitope (HLA-DRB1*0401/*0404) and mutations in the PTPN22 gene. This partnership represents a greater relative risk of RA. However, other studies have not been able to establish an association between the shared epitope and the presence of anti-CCP. Patients with smoking and a genetic predisposition due to HLA-DRB1 present citrullinated proteins in broncho-alveolar cells in the bronchial lavage, which has been related to smoking as a triggering environmental factor to be taken into account in the multifactorial pathophysiology of RA.

Another factor that should be considered is possibly triggering the abnormal formation of anti-CCP is the bacterial pathogen Porphyromonas gingivalis, an etiologic agent of bacterial gingivitis and epidemiologically linked to RA, which is capable of generating citrullinated antigens correlated with the development of RA.

Several theories about the possibility of antigen presentation by immune system components, along with a failures in immunoregulation in genetically susceptible patients are discussed as a cause of developing a multifactorial syndrome such as RA. Contemplating the multifactorial pathogenesis of RA, perhaps we should try to more precisely identify the formation of anti-CCP as an important event, something that can help in the future to define profiles of patients who benefit from specific therapeutic lines.

Anti-CCP as a Factor of Poor Prognosis in Rheumatoid Arthritis

The search for biomarkers associated with response to biological and biological therapies has thus far been frustrating. Although clinical factors have been associated with remission in RA (male gender, older age of onset of illness, no smoking, low degree of initial disability as measured by HAQ, negative acute phase reactants or absence of RF and anti-CCP), none of them assures the success of our therapeutic actions.

We know that the presence of IgA RF detected at the beginning of RA is associated with a worse prognosis and poorer response to biological therapy. The presence of both RF and anti-CCP antibody years before the development of clinical inflammation makes us objectify synovitis in our patients as just the consequence of activation of an wrong innate–adaptive immune response. Therefore, activity in the bone marrow and lymphoid organs secondary to antigen presentation and the development of a humoral response must have a certain importance.

Other factors related to remission are more dependent on medical intervention, as early treatment with non-biological disease modifying drugs leads to good or moderate responses in the first three to six months, and the early introduction of a biological agent leads to this objective.

Even so, obtaining remission in our patients, beyond the concepts outlined above, remains purely random, not exceeding ACR 70 in more than 20% of patients. We do not know if this clinical
remission is always accompanied by extraarticular, radiological, or much less immune remission.

Nevertheless, although RA is a multifactorial disease and we are still far from understanding the pathogenetic cycle of each of our patients, optimizing the prognosis of patients, especially those at risk of progressing, is in our hands.

The presence of elevated anti-CCP and CRP, HAQ or erosive disease at the beginning of the disease, has been identified as a criterion of poor prognosis\textsuperscript{27–29}; existing recommendations are based on not delaying treatment in these patients and not precisely emphasizing drug combinations with biologics.\textsuperscript{80} Recently, radiographic damage in RA in which an array of combinations of different factors, including so-called “poor prognosis” ones have been associated with the development of rapidly progressive radiological damage.\textsuperscript{81,82}

The concept of step-down in patients with poor prognostic factors could be used in clinical practice taking into account the recommendations of the SER clinical guidelines, starting directly with a biological agent to induce early remission,\textsuperscript{67} further reducing doses\textsuperscript{83} or even discontinuating the treatment. The BeSt trial results and study shows that combining therapies with biological drugs and an early induction of remission in RA could lead to drug discontinuation and maintenance of remission in 12% and up to 30% of patients with RA.\textsuperscript{15,20,21}

In this regard, recent studies in cohorts of patients with poor prognostic factors and no previous use of methotrexate (MTX) show that the results based on DAS 28, ACR 50, ACR 70 and HAQ undergoing early biological therapy are superior to those obtained with MTX alone. In this study, patients in an open phase receiving step up biological therapy showed improved results, but never became comparable with those in which biological treatment was as the initial option.\textsuperscript{84}

It might be argued that although the levels of IgG anti-CCP are changed after the use of anti-TNF\textsuperscript{85} therapies,\textsuperscript{86} their concentrations do not relate directly to improvement or clinical relapse in all patients. Although controversial, it was noted that patients treated with monoclonal antibodies against the TNF-\alpha molecule (adalimumab) significantly reduced their titers of IgG anti-CCP and were clinically responsive, reaching at least an ACR 20 response at 24 weeks.\textsuperscript{87}

Highlighting humoral immune activity a priori, something “pathognomonic” in patients with RA, is interesting to evaluate different evidence that indicates that the RF and anti-CCP negativity are factors associated with better clinical outcome and better response to anti-TNF therapies.\textsuperscript{88,89} This is also associated to increased survival of anti-TNF drugs and clinical improvement in patients with “seronegative arthropathies”.\textsuperscript{90}

Furthermore, the role or antibody-forming plasma cells, such as inhibition of the IL-6 receptor (IL-6R)\textsuperscript{91} have also proven highly effective in RA. The impact of other therapeutic targets, beyond the inhibition of TNF-\alpha, has in the humoral response which mediates the production of anti citrullinated protein antibodies in RA is still undetermined. It is interesting to note that, unlike anti-TNF therapies, therapeutic targets related to B cell (anti-CD20, anti-IL-6R or CTL4Ig)\textsuperscript{92,93} have shown no utility in these other “seronegative diseases” so at least in part, their efficacy in RA patients could be attributed to an altered humoral response regulation.

Conclusions

It is possible that future studies demonstrate that induction of remission in early RA can help us step down and even suspend biological therapies to maintain remission and make them more cost effective. While not being completely accurate, biological use in all patients should be employed to manage at least in the early phase, those patients at risk for a worse prognosis.

The reality is that we are still far from offering therapeutic strategies tailored to patient profiles, although therapies are increasingly adapted to their clinical conditions and comorbidities. Even without understanding the pathophysiologic mechanism mediating the ability to generate antibodies against proteins and then develop more aggressive disease, the literature supports this as a determining factor in the poor outcome of our patients. The challenge is to understand how the different therapies that modulate humoral immunity go wrong, which could lead to a better understanding of factors associated with a worse outcome in our patients, improving the use of the therapeutic arsenal available to us today.

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