Editorial

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of

How we can improve the predictive value of prognostic biomarkers in rheumatoid arthritis

"The lack of good response rates ... and biological high-cost treatments highlight the need to create a predictive multifaceted model in a cost-effective and feasible manner."

Keywords: biomarkers • citokynes • radiographic progression • rheumatoid arthritis

Even though the treat-to-target concept is an effective strategy to improve rheumatoid arthritis (RA) outcomes, a portion of patients are still unresponsive to biologics and non-biologic disease-modifying antirheumatic drugs. Given this situation, plus the high cost of the disease treatment and varying accessibility to medication in different countries, it is imperative to find predictive factors for the prognosis and responsiveness to therapy.

According to preliminary definitions, a biomarker is 'an anatomical, physiological, biochemical, molecular or imaging feature that can be used to refine diagnosis, measure the progress of disease or predict and monitor the effects of treatments'. Therefore, a biomarker allows us to accurately define the severity of the disease [1].

In RA patients, bad prognosis factors have been yet determined, such as female gender, poor scholarship, and, in the last years, tobacco exposure. All of these factors work for a first approach, and together with the swollen join count, C-reactive protein (CRP), seropositive condition and early radiographic damage, give us a better prediction of prognosis. In the BeSt study, a predictive model was made on CRP levels, the presence of autoantibodies and X-ray changes, which allowed authors to define a group of patients that have rapid radiographic progression [2]. Although the Sharp-van der Heijde Scoring (SHS) test is helpful, since the score can only be read after 1 year of observation and by trained radiologists, a more timely and accessible test is needed. Studies are being conducted to find new predictive markers, some of them in the genetic area, others among cytokine profiles or structural changes evaluated by MRI.

Regarding genetic biomarkers, Reneses *et al.* worked with the shared epitope (SE), and polymorphisms in the TNF gene promoter, together with the rheumatoid factor (RF), and followed up radiographic progression for 1 year. In multiple linear regression analysis, radiological outcomes after 1 year were highly predicted by SE homozygosis but not by RF status, anticyclic citrullinated peptides (CCP) status or TNF polymorphisms [3]. On the other hand, Criswell *et al.* showed that SE presence in double copy (0101 and 0404) was associated with a better response to adalimumab [4]. Another study showed that the presence of a susceptibility polymorphism in the -308 position of the TNF gene promoter is correlated with a high frequency and aggressive course in RA and it can affect the responsiveness to anti-TNF therapy; however, differences between ethnic backgrounds have produced controversial results [5,6].

Cytokines seem to be an easy assessment to help us to anticipate the disease progression or probability of successful therapy, however the following considerations must be made: the method of detection used, the circadian rhythm, age or gender influence, food intake, and using serum or plasma for cytokine detection [1]. Given the lead role of TNF in RA, several authors have looked for relationships between its plasma values and prognosis or response to biological drugs. Elevation of TNF serum levels during the

Lilian Soto*[1,2], Diego Catalan*[,2], Juan C Aguillon[2] & Miguel Cuchacovich[1]

[1]Department of Medicine, Hospital Clinico de la Universidad de Chile, Chile

[2]Programa Disciplinario de Inmunologia, Instituto de Ciencias Biomedicas, Facultad de Medicina, Universidad de Chile, Chile

*Author for correspondence: lsoto@hcuch.cl

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TNF inhibitors treatment has been associated with better response to these drugs. Actually, only responsive patient showed a statistically significant overall increase in TNF concentration over time [7].

Calprotectin is a heterodimeric complex of two S100 calcium-binding proteins, myeloid-related protein-8 (S100A8) and myeloid-related protein-14 (S100A9), expressed in granulocytes and monocytes, which is released at sites of inflammation. A systematic review of 17 studies concluded that calprotectin levels were high in patients with an active disease and were particularly elevated in RF-positive patients. Furthermore, the calprotectin levels decreased with effective treatment. Also, high baseline calprotectin levels predict future erosive damage [8].

There is interesting research being done in the metalloproteinases (MMPs) field, in order to observe how bones and cartilage remodel. These extracellular enzymes degrade bone and cartilage components (collagen and proteoglycans). They are active in the normal process of degradation, but they are more active in RA. Galil *et al.* investigated the relationship between the serum levels of MMP3 and features in MRI in RA patients. They found a positive correlation between baseline MMP-3 levels and progression in an MRI erosion score and the DAS28 score [9].

In the BARFOT (Better Anti-Rheumatic Pharmaco Therapy) study, 349 early RA patients were observed for 5 years in order to measure the relation between radiographic progression and blood levels of cartilage oligomeric matrix protein (COMP; thrombospondin 5). COMP is a 435-kDa homopentameric, extracellular protein identified in cartilage, normal ligament, meniscus, tendon, synovium and osteoblasts. In RA COMP, reflected damage in the cartilage and its serum levels were found to be higher in RA patients with a rapidly progressive disease up to 5 years of follow-up [10].

Pyridinoline is a major crosslink of collagen in cartilage, bone and synovium. Pyridinoline levels were determined in 437 patients with early RA recruited at the Leiden Early Arthritis Clinic, where X-rays of hands and feet were followed yearly up to 7 years using SHS. The SHS showed a high correlation with greater levels of pyridoline, and baseline levels were correlated with the severity of the radiographic destruction through the following of the patients. The mean SHS over 7 years was 6% higher for each higher pyridinoline nmol/l at baseline. Also, the progression in SHS in the upcoming year was 17% higher for each higher nmol/l of pyridinoline. The authors concluded that increased pyridinoline serum levels, both at baseline and during the disease course, are associated with more severe joint destruction during the coming year(s) [11].

RA has poor prognosis when BMI is high. This observation could be explained because of the presence of soluble mediators secreted by the adipose tissue (adipokines). Although adipokines originally were thought to be exclusively secreted by adipose tissue, they were later discovered to be secreted by other cell types, including cells present in an inflamed joint. TNF, IL-6, leptin, resistin and visfatin can be considered proinflammatory adipokines. Instead, adiponectin could act as an anti-inflammatory or proinflammatory mediator, depending on its molecular form. Klein-Wieringa *et al.* analyzed 253 patients from an early RA clinic, looking for an association between the levels of these adipokines and radiographic progression. Although some cytokines, as IL-6, TNF-α and some adipokines as visfatin and adiponectin, were associated with structural damage over the follow-up, only adiponectin keeps the statistical correction by anti-CCP antibodies presence. IL-6, TNF-α, visfatin and adiponectin were positively associated with radiographic progression over 4 years, and this association was independent of BMI. When the model was corrected for the presence of anti-CCP antibodies, only adiponectin levels remained significantly associated with radiographic progression [12].

Today, MRI helps in early synovitis detection and to predict progression, because we are able to detect the bone edema and erosion in RA patients. Even though the tomographic assessment of bone erosion is slightly superior to MRI images (because of its accurate view of cortical bone), the bone edema presence and the cartilage damage assessed by an MRI can be more related to disease progression as was demonstrated in the GO-Forward subanalysis data for 1-year follow-up, where x-ray progression was associated with greater baseline values for synovitis and osteitis in MRI [13].

Since no singular biomarker has been proved to be useful on its own, it has been proposed to use a combined model that could improve the prediction capacity of multiple biomarkers. Balsa *et al.* proposed an interesting model to predict disability and sustained remission based on a combination of autoantibodies, erythrocyte sedimentation rate and CRP levels, HLA-DRB1 genotyping, and the results of low-density DNA microarray based on allele-specific probes. The microarray allowed simultaneous analysis of 69 SNPs in 49 genes that were selected because of their potential impact on RA. One SNP (rs2070874), located in the IL-4 gene and controlling the expression of IL-4, remained in the model to predict disability. For the remission model, one SNP mapped to the PTPN22 gene (rs2476601) was significantly associated with remission, and the model improved upon adding anti-CCP antibody levels [14].

An interesting data analysis aimed at clarifying whether matrix risk models designed to predict rapid radiographic progression, defined as a change higher than five units in SHS in 1 year, developed in controlled clinical trials are enforceable to patients treated according to clinical practice, was performed in an observational trial, the Brigham Rheumatoid Arthritis Sequential Study (BRASS). They found a suboptimal ability of models developed in clinical trials to predict the RRP in the BRASS cohort. They suggest that these differences in the results could be explained by the different disease duration, because clinical trials included early RA while BRASS included patients with any disease duration. Furthermore, patients coming from clinical trials had a more severe disease activity and they were treated with different therapeutic approaches (biologics vs synthetic disease-modifying antirheumatic drugs) [15].

After all these efforts to find better prognostic markers for RA and the failure to design good prediction models, this issue turns to be a pending task. The lack of good response rates, even while using the latest medication, and biological high-cost treatments highlight the need to create a predictive multifaceted model in a cost-effective and feasible manner, in order to achieve better therapy choice with the best probability of success in the worst-prognosis RA patients.

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References

1 Burska A, Boissinot M, Ponchel F. Cytokines as biomarkers in rheumatoid arthritis. *Mediators Inflamm.*d oi:10.1155/2014/545493 (2014) (Epub ahead of print).

2 Visser K, Goekoop-Ruiterman YP, De Vries-Bouwstra JK *et al.* A matrix risk model for the prediction of rapid radiographic progression in patients with rheumatoid arthritis receiving different dynamic treatment strategies: post hoc analyses from the best study. *Ann. Rheum. Dis.* 69(7), 1333–1337 (2010).

3 Reneses S, Gonzalez-Escribano MF, Fernandez-Suarez A *et al.* The value of HLA-DRB1 shared epitope, -308 tumor necrosis factor-alpha gene promoter polymorphism, rheumatoid factor, anti-citrullinated peptide antibodies, and early erosions for predicting radiological outcome in recent-onset rheumatoid arthritis. *J. Rheumatol.* 36(6), 1143–1149 (2009).

4 Criswell LA, Lum RF, Turner KN *et al.* The influence of genetic variation in the HLA-DRB1 and LTA-TNF regions on the response to treatment of early rheumatoid arthritis with methotrexate or etanercept. *Arthritis Rheum.* 50(9), 2750–2756 (2004).

5 Cuchacovich M, Bueno D, Carvajal R *et al.* Clinical parameters and biomarkers for anti-TNF treatment prognosis in rheumatoid arthritis patients. *Clin. Rheumatol.* 33(12), 1707–1714 (2014).

6 Song GG, Bae SC, Kim JH, Lee YH. Association between TNF-alpha promoter -308 a/g polymorphism and rheumatoid arthritis: a meta-analysis. *Rheumatol. Int.* 34(4), 465–471 (2014).

7 Cuchacovich M, Soto L, Edwardes M *et al.* Tumour necrosis factor (TNF)alpha -308 g/g promoter polymorphism and TNF-alpha levels correlate with a better response to adalimumab in patients with rheumatoid arthritis. *Scand. J. Rheumatol.* 35(6), 435–440 (2006).

8 Abildtrup M, Kingsley GH, Scott DL. Calprotectin as a biomarker for rheumatoid arthritis: a systematic review. *J. Rheumatol.* 42(5), 760–770 (2015).

9 Galil SM, El-Shafey AM, Hagrass HA, Fawzy F, Sammak AE. Baseline serum level of matrix metalloproteinase-3 as a biomarker of progressive joint damage in rheumatoid arthritis patients. *Int. J. Rheum. Dis.* doi: 10.1111/1756-185X.12434. (2014) (Epub ahead of print).

10 Andersson ML, Svensson B, Petersson IF *et al.* Early increase in serum-COMP is associated with joint damage progression over the first five years in patients with rheumatoid arthritis. *BMC Musculoskelet. Disord.* 14, 229 (2013).

11 Krabben A, Knevel R, Huizinga TW, Cavet G, Van Der Helm-Van Mil AH. Serum pyridinoline levels and prediction of severity of joint destruction in rheumatoid arthritis. *J. Rheumatol.* 40(8), 1303–1306 (2013).

12 Klein-Wieringa IR, Van Der Linden MP, Knevel R *et al.* Baseline serum adipokine levels predict radiographic progression in early rheumatoid arthritis. *Arthritis Rheum.* 63(9), 2567–2574 (2011).

13 Conaghan PG, Emery P, Ostergaard M *et al.* Assessment by MRI of inflammation and damage in rheumatoid arthritis patients with methotrexate inadequate response receiving golimumab: results of the GO-FORWARD trial. *Ann. Rheum. Dis.* 70(11), 1968–1974 (2011).

14 Balsa A, Del Amo J, Blanco F *et al.* Prediction of functional impairment and remission in rheumatoid arthritis patients by biochemical variables and genetic polymorphisms. *Rheumatology (Oxford)* 49(3), 458–466 (2010).

15 Lillegraven S, Paynter N, Prince FH *et al.* Performance of matrix-based risk models for rapid radiographic progression in a cohort of patients with established rheumatoid arthritis. *Arthritis Care Res. (Hoboken)* 65(4), 526–533 (2013).