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Predictors of response to biologic therapies in rheumatoid arthritis

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ABSTRACT

The advent of biological therapies has revolutionized the management of rheumatoid arthritis, demonstrating effectiveness in controlling clinical and radiological damage. However, 20% to 40% of the patients will not respond to these therapies, which are associated to a very high cost. In addition, non-responder patients are exposed to possible adverse effects. For these reasons, we need to identify predictors of response to these treatments. These predictors are reviewed in this evidence-based paper and classified into genetic and non-genetic. Despite extensive search, nowadays there are no predictors powerful enough to be used in regular clinical practice. Serum factors, the presence of rheumatoid factor and anti-cyclic citrullinated peptide antibodies, are the only factors currently being used to predict the response to specific biological therapy. In the future, probably thanks to new technologies based on genomics, transcriptomics and proteomics, it will be possible to identify genetic predictors of response to biological drugs that will allow us to select suitable patients for a specific biological therapy.

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Factores predictores de respuesta a terapias biológicas en la artritis reumatoide

RESUMEN

El desarrollo de las terapias biológicas ha supuesto un gran avance en el manejo de la artritis reumatoide (AR) al haber demostrado efectividad en el control de la clínica y daño radiológico. Sin embargo, entre un 20-40% de los pacientes no van a responder a estas terapias, lo que determina un alto coste económico a la vez que los expone a posibles efectos adversos, por lo que se precisa de la identificación de factores predictores de respuesta a ellos. Estos se revisan en el actual trabajo en función de su evidencia científica y se clasifican en genéticos y no genéticos. A pesar de su extensa búsqueda, en la actualidad no disponemos de potentes predictores que puedan ser utilizados en la práctica clínica diaria. Posiblemente a día de hoy sólo los factores séricos, positividad del factor reumatoide (FR) y anticuerpos antipeptido citrulinado (anti-CCP) permiten predecir la respuesta a determinados biológicos. En un futuro, probablemente gracias a las nuevas tecnologías basadas en la genómica, transcriptómica y proteómica se identificarán predictores genéticos que permita seleccionar pacientes idóneos para una determinada terapia biológica.

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Palabras clave:

Terapias biológicas
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Introduction

Rheumatoid arthritis (RA) is a chronic, systemic, inflammatory disease with a genetic predisposition, of unknown aetiology, characterized by symmetrical erosive synovitis.

The advent of biological therapies has led to a breakthrough in our therapeutic arsenal which allows control of the signs and symptoms with less radiological deterioration whilst providing a

better quality of life for our patients. We currently have 8 biological agents for RA with different action targets (Figure 1): **1) 5 against tumour necrosis factor (anti-TNF)** which are: soluble receptor etanercept (ETN) and 4 monoclonal antibodies; infliximab (IFX), golimumab, pegylated certolizumab and adalimumab (ADA); 2) a monoclonal antibody against B lymphocytes, rituximab (RTX); 3) a fusion protein which modulates T cell activation, abatacept (ABA); 4) a monoclonal antibody against the receptor of interleukin 6 (IL-6), tocilizumab (TCZ), and 5) an inhibitor of interleukin 1 (IL-1), anakinra. One problem which we encounter in daily practice is the great variability presented by patients in response to the various biological therapies, to the point that between 20% and 40% will have no response.¹ Clearly, this represents a high economic cost which at

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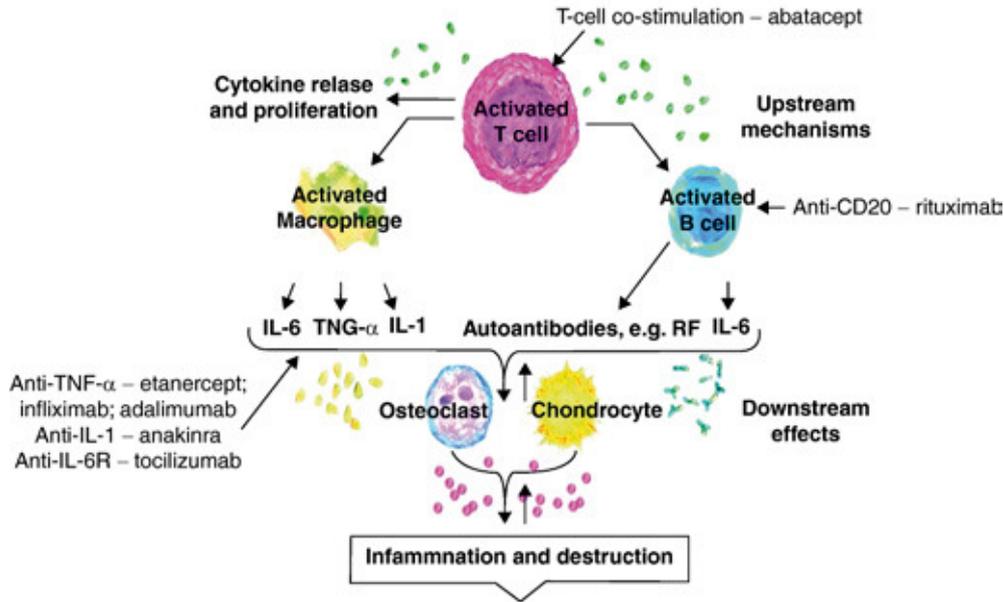


Figure 1. Action targets of some of the biological agents used in rheumatoid arthritis.

the same time exposes non-responding patients to adverse effects unnecessarily. This determines the importance of finding predictors of both response to these therapies and their side effects, in the hope that a personalized application of drugs based on the genotype of each patient will be possible in the future. However, our review has found no studies evaluating the existence of factors which can predict side effects of different biological agents.

Classification of predictors of response to biological agents

In a simple manner, we can classify the predictors of response into genetic and non-genetic (Figure 2); the latter, identified by genomic medicine, encompass genomics, transcriptomics and proteomics. The non-genetic, in turn, can be classified into clinical, serological, imaging and histological.

Starting from a heterogeneous population with RA, we may find differences in the distribution of proteins and antibodies (rheumatoid factor [RF], anti-CCP, etc.), RNA (transcription of genes), DNA (polymorphisms, microsatellites), response to drugs and clinical manifestations. From these differences we can define predictors.

Clinical predictors

Although the medical literature contains many studies regarding their prognostic value in RA, few studies have examined their value as

predictors of response. Possibly the most important has been the study by Hyrich et al² which analyzed this association in a cohort of 3,646 patients. It concluded that low physical disability at the beginning of treatment, estimated by HAQ (Health Assessment Questionnaire), behaves as a predictor of response to anti-TNF therapy while a high baseline HAQ is a strong predictor of its absence. Regarding gender, women achieved a lower remission rate, as was also the case with smoking in relation to the response to IFX. On the other hand, neither age nor duration of the disease nor DAS 28 prior to therapy were found to be predictors of response. The same study highlighted that the use of methotrexate associated with anti-TNF therapy (ETN or IFX) acted as a strong predictor of response, whereas the previous failure of several disease-modifying antirheumatic drugs (DMARDs) was accompanied by a lower rate of remission.

Serological predictors

Rheumatoid factor

Among these predictors, positive RF and a better response to it was the most important association described. In a study by Hyrich et al⁴ the presence of RF was associated with a poorer response to anti-TNF. Another previous study⁵ reached the same conclusion in relation to the IgA isotype, so that patients with higher levels presented a poor response.

Anti-cyclic citrullinated peptide antibodies

Currently, it seems established that their presence in blood is associated with a better response to RTX.⁴ An “enhanced B lymphocyte activity”, whose serum expression would be RF and anti-CCP would explain the better response to RTX observed in these patients. In contrast, the positivity of this antibody was associated with a lower response to anti-TNF and low levels to a better response to combination therapy with IFX + DMARD.^{4,6}

Cytokines

Although seemingly attractive as predictors of response given that they are targets for biologic therapies, none of the studies have

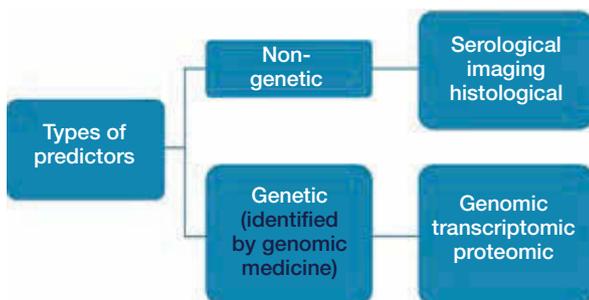


Figure 2. Classification of predictors of response to biological therapy.

Table
Main polymorphisms in rheumatoid arthritis

| Gene | Location of polymorphism | Alleles | Possible effect of the polymorphism |
|---------------|---|----------------------------------|--|
| TNF- α | -238 | G | More severe articular erosions |
| | | A | Less severe articular erosions |
| | -308 | G | Normal production of TNF- α |
| | | A | Positive regulation of TNF- α production |
| | | C | May contribute to susceptibility to RA |
| -857 | T | High production of TNF- α | |
| | G > A | Unknown | |
| IL-1RN | -1087 | G > A | Unknown |
| IL-1 | IL-1 α + 4845 (exon 5) | G | Altered production of IL-1 α . Increase of susceptibility to RA |
| IL-10 | -1082 | T | Unknown |
| | | G | Positive regulation of IL-10 production in lymphocytes |
| BAT2 | Microsatellites | A | Low concentrations of IL-10. Associated to RA in women |
| | | | Unknown |
| HLA | Specific alleles of the shared epitope (HLA-DR) | | May contribute to susceptibility and severity of RA |
| TNFRSF1A | -609 | G > T | Unknown |
| TNFRSF1B | 676 | T > G | Unknown |

A indicates adenine; BAT2, transcript 2 associated to allele HLA-B; C, cytosine; G, guanine; HLA, histocompatibility antigen; IL-1, interleukin 1; IL-10, interleukin 10; IL-1RN, antagonist of IL-1 receptor; IL-6, interleukin 6; T, thymine; TNFRSF, TNF- α receptor; TNF- α , tumour necrosis factor alpha.

conclusively and uniformly shown them to be a predictor of response. There are several studies in this line, among which we highlight that by Fabre et al,⁷ in which high baseline values of monocyte chemoattractant protein 1 (MCP-1), epidermal growth factor (EGF), as well as the combination of the latter with high baseline CRP values, were associated with response to ETN at 3 months of treatment.

Cartilage oligomeric matrix protein

Cartilage oligomeric matrix protein (COMP) is considered as a marker of articular cartilage replacement and thus could predict the bone damage that occurs in RA. In this sense, one study⁸ showed that patients with low baseline COMP responded better to ADA at 3 months, with over 50% of them reaching an ACR70. On the other hand, Lequerre et al did not find that baseline levels of this protein were associated with a clinical response to IFX.

Imaging predictors

Theoretically, it is postulated that synovial vascularization assessed by Doppler ultrasound prior to biological treatment could be associated with variations in response. In our review we found no studies which specifically assessed image data as predictors of response.

Histological predictors

Although we have very limited results regarding histological predictors of response to biological therapy, Klaasen et al⁹ recently identified the presence of synovial lymphocytic aggregates as a predictor of response to IFX.

Genetic predictors or predictors identified by genomic medicine

The genetic region major histocompatibility complex (HLA) explains about a third of the genetic component of RA. However, the rest of the genetic component responsible for displaying RA is very difficult to identify. Pharmacogenomics investigates changes in DNA and RNA related to the response to a given drug. Within the human genome, the main changes are: microsatellites (short sequence repeats), minisatellites (repeats of a long sequence), variations in the number of copies (large fragments of DNA), insertion or deletion (loss or addition of a small nucleotide sequence) and single nucleotide polymorphisms (SNPs). SNPs are the most common variations of the

genome and therefore the subject of many studies in various diseases, logically comprising RA patients (Table).

Genetic predictors identified by genomics

The technique of studying associations throughout the whole genome (genome-wide association or GWAS) has represented a breakthrough by allowing analysis of hundreds of thousands of SNPs across the genome, whereas classical techniques only studied certain SNPs within a small region of the human genome.¹¹ GWAS studies identify the distribution of SNPs in cases and controls to further observe if there were statistical differences in distribution in both groups. This has allowed the identification of SNPs in different populations and individuals and thus polymorphisms which correlate with susceptibility to diseases or drug response.

Although there are few such studies in patients with RA, the first study evaluating the response to anti-TNF was conducted in 2008.¹² Among its findings we highlight the association of SNP2985 with changes in DAS28, of the rs1800896 gene (allele G) in the IL-10 promoter and the locus of paraoxonase (PON1) with a good response to anti-TNF. Paraoxonase is an enzyme associated with high density lipoprotein which appears to play an important role in the inflammatory response.

With respect to ETN, Padyukow¹⁰ in a retrospective observational study found no association between the shared epitope and the response. However, patients with genotype IL-10-1087 G/G and TNF α -308 G/G (subjects with low inflammatory response) presented a better response.

Another 3 works¹³ obtained similar results for the association between TNF- α -308G polymorphisms and a better response to ETN compared with genotype -308 A/G.

Among the studies which measured the response to IFX, Marotte et al in their prospective, longitudinal study in 198 patients found no association between shared epitope alleles and response. Several groups¹⁴ have coincided that the SNP -308 G/A in the TNF- α promoter region influences the response to IFX, in a similar manner to what has been commented about ETN, the GG genotype would determine a better response to IFX while the AA would have a worse response.

Despite all these relatively consistent studies, a very recent metaanalysis,¹³ which included 13 studies and 1,817 patients, concluded that neither the TNF α -308 A/G polymorphism nor the shared epitope alleles were associated with response to anti-TNF therapy (ETN, IFX, ADA) and only found an association between

polymorphism TNF α -238 A/G and response to IFX (association between A allele and poor response).

Genetic predictors identified by transcriptome analysis

The development of microarrays enables the study of all transcriptional activity within a given cell or tissue type. It represents an important advance because, previously, it was only possible to study the expression of a small number of genes simultaneously.

Using this technique, Julià et al¹⁵ analyzed blood cell gene expression from the RNA of 44 patients with RA before starting IFX treatment and assessed the response at 14 weeks according to EULAR criteria. They concluded that 8 genes (HLADRB3, SH2D1B, GNLY, CAMP, SLC2A3, IL2RB, MXD4 and TLR4) predict the response to IFX. Another recent study¹⁶ by the same group analyzed gene expression in blood cells, CD4 T cells and B cells using microarrays in 9 patients with RA before starting RTX treatment and assessed the response at 24 weeks (DAS28). An overexpression of the TRAF1 gene was associated with a favourable response while that of the ARG1 gene was associated with a poor response to RTX.

Genetic predictors identified by proteomic analysis

Proteomics will become an important line in future research to identify predictors of response to biological therapy, although at present there are few published studies and with small series.

Conclusions

In order to carry out personalized medicine, which enables a better selection of patients who respond to treatment and thus avoid potential side effects associated with these therapies, it is necessary to identify predictors of response. These can be classified into genetic and non-genetic. At present, only serum factors, RF positivity and anti-CCP offer the possibility of predicting the response to such biological agents. However, further studies are needed in order to unequivocally define predictors of response to different biological therapies and discover new ones. This will require minimizing the heterogeneity of the studies in regard to: design, sample size—most published genetic studies consist of less than 100 patients—,baseline clinical characteristics, response criteria (EULAR/ACR), time of assessment of response to treatment and technology used, especially in those identified by transcriptomic or proteomic analysis.

In a near future, widespread GWAS studies using whole genome sequencing and second generation techniques in large populations of patients with RA will probably allow us to obtain a combination of multiple SNPs and possibly a score to predict the response to a specific biological treatment. There is hope in the horizon for a combination of these SNPs with various non-genetic predictors, mostly identified by transcriptomic and proteomic analysis, which

will allow us to select the biological treatment which is best suited to each patient.

Conflict of interest

The authors declare no conflict of interest.

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