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Letters to the Editor

Reply to: "Understanding the Immunogenicity Concept"☆

Respuesta a: «Comprender el concepto de inmunogenicidad»

Dear Editor,

We read with interest the editorial by Drs. Valor and de la Torre entitled "Understanding the concept of immunogenicity"[1] and we would like to provide some comments and considerations.

Immunogenicity is defined as the formation of antibodies directed against a protein and all therapeutic proteins may trigger an unwanted immune response, which is highly dependent on the structure.[2] There are 2 types of antibodies[3] non-neutralizing antibodies, formed against recombinant structures and immunoglobulin receptors and which bind to the drug through an area different from that used to bind to the ligand, so they theoretically do not affect its mechanism of action. These antibodies form immune complexes bound to the drug that are slowly removed from the circulation decreasing its bioavailability. Another type of antibodies are neutralizing, recognizing idiotypes of therapeutic antibodies, such as infliximab and adalimumab, inhibiting the binding of the drug to its ligand, leading not only to a decrease in the concentration of free drug but also reduced efficacy.[4] The difference between them lies not only in their clinical consequences, but also in the difficulty for their detection.[5]

Treatment with anti-TNF follows the rules of the classical pharmacokinetic,[3] in which circulating drug levels are related to efficiency, with very high levels (above threshold) associated with toxicity and[5] inefficiency. Serum concentrations of anti-TNF drugs are variable due to a variety of factors, the presence of antibodies against the drug, the main cause of evident suboptimal concentrations, which is related to the loss of efficiency, a need to increase the dose and the occurrence of infusion reactions.[6] A meta-analysis and systematic review of the recent literature, which analyzes all articles published to date on the immunogenicity of anti-TNF treatment, reaches these conclusions.[4]

There are still many clinicians, probably supported by clinical trial data,[7–9] considering immunogenicity as an unimportant issue and have the idea that antibody formation to TNF blockers has limited clinical consequences, and there are several reasons that may explain this view. First, the use of very sensitive techniques[10] limits the detection of antibodies in many patients and does not give a real idea of their frequency. Second, the different incidence of immunogenicity, even with the same drug and the same disease, reduces clinical credibility from immunogenicity, but this may be due to serum collection time, the various methods used for the determination of antibodies, drug exposure and other undefined variables. Third, the impact of immunogenicity in clinical practice can not be measured in all its consequences while its determination is not used routinely and does not obtain enough data to relate the different clinical events with drug levels and the presence of anti-drug antibodies.

Immunogenicity is a dynamic process,[11–13] and anti-drug antibodies can appear even at 2 years or more after biological treatment, so the determination of the frequency of immunogenicity in clinical trials, usually of short duration, and in extension studies, which only include completers, is obviously underestimated. The fact that a patient has not been shown to have antibodies after treatment does not mean that they can not be detected months later, because this involves various factors such as the duration of treatment, concomitant treatment and dosing schedules, among others. For example, a patient who has produced a small amount of antibodies that then bind to drug and are undetected, may result positive for these if drug administration is spaced so as to disappear from circulation following the usual patterns of pharmacokinetics.

One of the biggest obstacles to assess immunogenicity is the difficulty of measuring antidrug antibodies. As the immunogenic epitopes of each drug are not yet identified, assays have been developed to evaluate the binding of labeled drug (enzymatically or radioactively) with the antibody present in the serum. The most commonly used tests to date, and which are reflected in some.[4,6] 2 good reviews are grouped mainly into two methods: ELISA and RIA, as is well mentioned in the editorial that we are commenting upon. The fact that there are no standard or known concentration patterns, that would permit us to establish threshold values of positivity, does not mean that the tests are not validated, not reproducible or not useful to obtain clinically relevant conclusions. The ELISA and RIA methods have ample evidence, throughout the history of immunology, including the field of rheumatology, that show them to be extremely useful to obtain data for diagnosis and prognosis. Even so, poorly standardized ELISA is used to detect antiphospholipid antibodies, which 25 years since its description still shows no consensus on the nature of the antigenic epitopes, or on the specific assay conditions of,[14] but are used in daily clinical and gives a clear diagnostic and prognostic value. There is, in addition, little uniformity between the methods for detecting antibodies against granulocyte cytoplasm,[15] a field in which there is still no standardization to establish whether it is more appropriate or more relevant to perform granulocyte immunofluorescence or enzyme assays with specific purified antigens. However, these tests produce very useful clinical information, with both the laboratory and the clinician aware of their limitations. In our opinion, the tests that are being used today to evaluate immunogenicity do not lack sensitivity, specificity or reproducibility, but rather we need to learn to interpret the results in the context of the circumstances of the patients being treated.

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All these tests have the problem of interference from the presence of the drug when detecting the antibodies. If any drug is present in the serum antibodies, it forms immune complexes, and the complexes are not detected by standard ELISA and RIA. Some authors have described[16,17] acid dissociation methods to detect low levels of antibodies to immune complexes present in early stages of treatment, but with little or no clinical significance, since they fail to neutralize circulating drug levels. A bridge ELISA assay, which detects only antibody levels in excess of the concentration of drug, is currently used[17] as it best reflects the clinical impact of immunogenicity, since a positive result in this test means a total absence of free drug and, therefore, a lack of clinical efficacy.

In conclusion, we could say that, in our opinion, the immunogenicity of biologics is an alarm signal, which can be very useful when making treatment decisions. However, according to the authors of the editorial, the clinical efficacy of the drugs is in circulating therapeutic levels, with immunogenicity being a minor player that has to be taken into account mainly because it causes an abnormal decrease or disappearance of the drug and, therefore, the loss of its effectiveness.

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Reply to Balsa et al. Relative With the Review "Understanding the Concept of Immunogenicity"☆

Respuesta a Balsa et al. en relación con la revisión «Entendiendo el concepto de inmunogenicidad»

Dear Editor,

We would like to thank Balsa et al. their interest and comments on the review "Understanding the concept of immunogenicity",[1] in giving their opinion on the concept of immunogenicity, more specifically when applied to biological therapies in rheumatology. We would also like to thank the editor of Reumatología CLínica the opportunity to reply, which manifests the commitment of this journal in the settlement of very current controversies. With these lines we would like to mention some of the comments made.

It is well known that both standardizing and validating assays in immunology, especially in the area of autoimmunity, are an extremely difficult and complex task. Therefore, determinations made over time have high inter and/or intra laboratory methodological variability which always requires consensus to establish the steps to be followed in order to standardize results and to optimize techniques in order to have an adequate sensitivity, specificity and reproducibility. In the case of the determination of immunogenicity in biological therapies, such procedures have not been well documented in the field of rheumatology. Our duty is to promote the validation and standardization of techniques and when this is not possible, the next step is to establish rules among the relevant stakeholders and build consensus.

Fortunately, the international scientific community has recognized the need to work together and in 2012 created the group Anti-Biopharmaceutical Immunization: prediction and analysis of clinical relevance to minimize the risk. European Union Innovative Medical Initiative (ABIRISK).[2] Its main objective is the establishment of international standards, internal standards and consistent detection techniques applied to each biologic drug marketed. In

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