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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the near future, establishing multicenter studies and using appropriate techniques, the determination of both the immunogenicity and drug levels will gain ground in the monitoring of patients on biological therapies.

The examples mentioned by Balsa et al., to highlight the difficulties that have existed in the standardization of the detection techniques for antiphospholipid antibodies (APA) and[3,4] anti granulocyte cytoplasmic antibodies and their application in clinical practice, are perfectly valid.However, both measurements and their interpretation are supported by international consensus groups, numerous publications and multicenter studies that have exchanged biological samples, with the aim of agreeing on detection ranges, establishing guidelines for testing and the use of calibration curves and appropriate cut points.[3,5,6]

In the specific case of the APL, which were described in 1983, the consensus of Sapporo, in 1999 helped to define the clinical and especially the laboratory data for the diagnosis of antiphospholipid syndrome (APS), which included the presence of lupus anticoagulant and the G and/or M anticardiolipin isotypes.[7] In view of the persistent variability of APL determinations by various research groups within APS, these criteria were reviewed in the consensus of Sydney in 2005, adding B2 glycoprotein determinations to the criteria I for laboratory diagnoses, criteria currently considered valid internationally.[3,8–10]

With respect to the regulated analysis of observational studies in epidemiology and the review of the literature cited by Balsa et al., both publications conclude that although the trends with respect to clinical response are clear, different studies evaluating the whole, the heterogeneity of the cohorts studied, using techniques not yet standardized and the imprecision of the assays makes the reliable correlations with clinical response to biologic therapy risky.[11,12] Especially noteworthy is the review by Vincent et al., detailing the great variability of results regarding drug-drug immunogenicity data.[12]

As discussed Balsa et al., for the detection of specific antibodies traits such as isotype and affinity, the technique known as acid dissociation procedure is very helpful in immunology and has already been used to determine anti-drug antibody and is likely to be integrated in the design these techniques.[13–15]

Finally, as authors, we would say that the highest motivation of this review was to highlight the complexity surrounding the determination of immunogenicity that other medical specialties have previously experienced and to understand and apply these important concepts in an effective way in the area of rheumatology. The editorial entitled "Understanding the concept of immunogenicity" has achieved the most important of our goals, to increase the interest and promote discussion on this topic among readers of Reumatología Clínica.

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