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EDITORIAL

Biologic therapies for systemic autoimmune diseases. Are expectations met?

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Systemic autoimmune diseases (SAD) covers a group of disorders including the previously named "collagenosis," vasculitis, antiphospholipid syndrome, and a series of processes with an anti-inflammatory base, which are not always well-defined. The aetiology of all of these disorders is multiple and is related to a combination of determining genetic factors, environmental factors, hormonal factors and the presence of antigenic structures, which are possibly linked to infective agents. The formation of autoantibodies plays a predominant role in the pathogenesis of some of these pathologies, while in others inflammatory molecules are involved, such as the tumour necrosis factor (TNF) and other cytokines and soluble mediators. Although the introduction in the middle of the last century, first of corticosteroids and subsequently immunosuppressive drugs, has changed the evolution and prognosis of these diseases, not all patients benefit from these treatments. On the one hand, a significant proportion of patients present lack of response or partial or incomplete response, despite starting treatment with the drugs and their proper associated treatments. However, in other patients, the disease cannot be controlled using normal doses of these drugs, either due to the appearance of adverse effects or because they require higher doses during an excessively prolonged period. As a result, it is not uncommon in clinical practice to have a patient in which the traditional therapeutic measures do not work or cannot be applied. Biological therapies are therapies aimed at biological targets and are based on the exogenous administration of several types of synthetic molecules related to the immune response (antibodies, soluble receptors, cytokines, or cytokine antagonists). The therapeutic indications currently approved for the use of biological therapies focus on rheumatic diseases and inflammatory diseases of the digestive system and the skin. In SAD their indication is restricted to clinical trials and refractory cases of conventional treatment, the so-called compassionate use. Even so, the use of biological therapies in SAD has grown in recent years due to the observation of a good response in certain patients and since these therapies have been suggested as an alternative treatment in certain clinical situations. However, it is important to remember their use is associated with patients who have been selected due to a poor response to conventional treatment (compassionate use) and they are only used in a very small number of cases. Therefore, to accumulate experience and knowledge in the use of these therapies in SAD, it is important to record each and every patient receiving these treatments in the different hospitals.

For this purpose, at the start of 2006 a register was designed for patients with SAD receiving biological treatment. This is called the BIOGEAS register (www.biogeas.org) and a total of 25 GEAS members representing 19 hospitals in Spain collaborate in this project. This project has managed to record almost 300 patients with SAD who have received one or several biological therapies, and has facilitated very accurate information on the reasons and clinical circumstances that influence the decision to use these therapies. It also provides information on the doses,

responses obtained and the associated secondary effects. Although experience of 15 different types of SAD has been accumulated, 80% of the cases include patients with systemic lupus erythematosus, Sjögren's syndrome, systemic vasculitis, inflammatory myopathies, and Behçet disease. In 75% of cases a favourable response was obtained, and rituximab (anti-CD20 therapy) was the most frequently used drug, followed by anti-TNF therapies. As is the case with conventional therapies, a percentage of patients do not respond, or do not respond completely. In 10% of cases a favourable response was not obtained with the initial biological therapy and this was therefore replaced by a second drug. In the majority of these cases, the response was also favourable. With respect to adverse effects, these were observed in 16% of cases, in particular infections, although in some cases it was not possible to determine with any certainty that these were directly related with the administration of the biological therapy.

An undesirable effect which requires particular attention in relation to the use of biological therapies is the development of clinical changes compatible with an autoimmune disease, which could complicate matters and lead to errors and diagnostic confusion. On reviewing the literature, more than 240 cases of patients who developed clinical and/or laboratory alterations that were compatible with a SAD on receiving biological therapy were found; the majority of cases were lupus and vasculitis. As was the case with the introduction of corticosteroids and immunosuppressive drugs, expectations of biological therapies for the treatment and control of SAD have been high, with an initial phase of contained euphoria. The results obtained from the BIOGEAS register, although observational and for patients with a poorer clinical picture having failed with conventional therapies, allow us to maintain expectations for future therapies. This is indeed the case, without losing sight of the fact that they do produce the same patterns as those already seen with conventional treatments, that is, that there is a high percentage of patients who fail and do not respond to these therapies and they are not exempt from the associated secondary effects.

There is still a lot to be done, starting with the establishment of SAD as one of the indications of these therapies, therefore reducing the gradual increase in their compassionate use. A proper role for these therapies in the therapeutic strategies related to these diseases must be determined, along with their indications. We must also stop administering such therapies to patients who fail with conventional treatment only (compassionate use), which may reduce or hide their true potential. Nor is it clear whether these therapies should replace base treatment or whether they should be used as a specific supplement to said treatment and, therefore, whether they should be administered in conjunction with these. Nor do we have a response to the eternal questions asked by those who treat such patients, such as: how long should treatment be maintained? Or at what point can we stop treatment? The answers are not known with respect to conventional treatment, and even less so for these new therapies.

To be able to respond to all these questions, we have to continue to accumulate real experience, as has been the case for the last 3 years, with the inclusion of these patients in a general national multicentre register (BIOGEAS register). It is only in this way that we can be sure that we are working on what occurs on a day to day basis in real-life clinical practice, without the communication errors that always accompany the publication of results of specific cases, and we await controlled and well-designed studies that help define the role that these promising therapies could have on improving the quality of life and the survival of patients with SAD.

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