Immunogenicity Assessment of Biotechnology-derived Therapeutic Proteins and its Relevance in Clinical Practice

The introduction of biotechnological therapies have significantly changed the prognosis of chronic inflammatory rheumatic diseases, such as Rheumatoid Arthritis (RA), Ankylosing Spondilytis (AS) and Psoriatic Arthritis (PsA). The first and most widely used anti-TNF α agents for the mentioned diseases are infliximab, adalimumab and etanercept. Infliximab is a chimeric antibody that contains mice variable regions while Adalimumab is a fully human antibody, both IgG1k. Etanercept is a fusion protein containing the human TNF receptor-2 linked to a human IgG1-constant region.

Asied from the clinical improvement that those biological agents bring to the majority of our patients, a considerable number of them fail to respond or cannot maintain those responses over time. An association between poor therapeutic outcomes and presence of antibodies against biologics has been verified. These antibodies can be anti-idiotype or just "binding antibodies", affecting the biologic bioavailability, efficacy and even safety profile. The assessment of sera antibodies as well as functional drug levels in circulation is technically challenging. Several methods are available, the majority having important limitations that have led to erroneous interpretations and contradictory results. We undertook a meta-analysis, which critically analyzed the results according to the assays used and we concluded that anti-biologic antibodies have a clear impact on therapeutic effectiveness (in press).

We have been monitored immunogenicity in a cohort of patients treated with anti-TNF alpha agents, using different assays, in order to select the most suitable for implementation in our clinical practice as a screening test, which also implies an economic evaluation (economic decision study on going).

Monitoring immunogenicity will allow us to identify potential non-responders early on and design strategies to optimize the current therapy or, in the case of switchers, to optimize further therapeutic decisions, which might include less immunogenic alternatives and/or drugs with different mechanism of action.

In parallel, we are developing a set of experiments, in human and mouse models, in order to clarify the mechanisms that determine the immunogenicity of anti-TNF alpha agents.

The routine assessment of immunogenicity in clinical practice will help us better understand the clinical heterogeneity among patients and to tailor more cost-effective therapies, with fewer side effects.

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This project has been developed in two Institutions: Instituto Gulbenkian Ciência (IGC), in Oeiras, and Sanquin Research Institute, in Amsterdam, with the supervision of Jocelyne Demangeot, head of the Lymphocyte Physiology Group at IGC and Lucien Aarden, head of the Immunopathology Department at Sanquin.

In this project my collaborators are: Elizabeth Benito-Garcia, from BioEpi, a Clinical & Translational Research Center in Oeiras; Miguel Gouveia, Professor of Pharmacoeconomy at Universidade Católica in Lisboa and Lurdes Barbosa, nurse at Day Care Center of Hospital Garcia de Orta.