LE STUDIUM
CONSORTIUM

MONITORING OF MONOCLONAL ANTIBODIES GROUP IN EUROPE (MAGE) FOR INFLAMMATORY DISEASES

4-7 May 2015 & 19-22 October 2015 | LOCATION | CESR, Tours

Pr Denis Mulleman

Consortium coordinator

Denis Mulleman is Professor of Rheumatology at the University François-Rabelais of Tours, member of the joint research unit of CNRS, UMR 7292 in the team — Antibodies, Fc receptors and clinical responses. His research aims to characterise the concentration-response relationship of monoclonal antibodies used in inflammatory diseases, to help clinicians to individualise dosages, enabling personalised therapeutic drug monitoring. He is involved in numerous research projects using anti-TNF mAbs and Fc-containing fusion proteins, among them an Innovative Medicine Initiative (IMI) European project dedicated to the immunogenicity of biopharmaceuticals. His group (head: Gilles Paintaud) has been deeply involved in the development of validated ELISA techniques allowing the quantification of serum concentrations of therapeutic antibodies. He is coordinator of designed clinical drug trials enabling population pharmacokinetic and pharmacokinetic-pharmacodynamic (PK-PD) modelling to quantify the different sources of the response interindividual variability.

PROJECT

Biopharmaceuticals, in particular monoclonal antibodies, have radically transformed the course of various conditions, from malignancies to inflammatory diseases. Considerable inter-individual variability in the clinical response has been documented. It has been shown that pharmacokinetics (drug concentration versus time) is highly variable between patients and is related to clinical response, patients with high concentrations of the drug being more likely to respond than those who have low concentrations. Pharmacokinetic and pharmacokinetic-pharmacodynamic (PK-PD) modelling allows a description of the dose-response relationship to identify the sources of inter-individual variability, for both PK and PD-PD relationship. The team is seeking to explain this variability by studing the sources of the inter-individual variability that is observed in the response to monoclonal antibodies. Our work is based on both *in vitro* and preclinical models and on patient studies. Mathematical models are also used to quantify the influence of the individual sources of variability, to describe biological phenomena, and to design personalized dosage regimens for therapeutic antibodies.

Over the last few years, academic groups have developed tools to monitor the pharmacological effect of therapeutic antibodies by means of measuring trough concentrations and biomarkers of disease activity. This practice called therapeutic drug monitoring (TDM), involves the measurement *in sera* of the concentration of the drug, often in combination with anti-drug antibodies (ADA) detection on the one hand, and the disease activity of patients on the other hand. TDM may help clinicians to adjust the dose regimen according to individual characteristics to improve clinical outcomes and avoid adverse events related to unnecessary overexposure. This strategy is relevant considering the economic burden of inflammatory chronic disease such as rheumatoid arthritis, Crohn's disease and multiple sclerosis. However, although TDM of biopharmaceuticals seems promising, its implementation in clinical settings deserves further research to develop reliable and standardized assays, mathematical modelling (population approaches to analyze databases, mechanistic PK-PD modelling, clinical trial simulation) and clinical expertise.

The main aim of the MAGE consortium is to examine the scientific bases of the TDM of monoclonal antibodies in inflammatory diseases. This will be facilitated

1. to standardize assays for drug measurement,
2. to perform analyses in partnership to develop algorithms for TDM
3. to design comparative effectiveness research to validate these tools.

PARTNERS

The partners of the MAGE (Monitoring of Antibodies academic Group in Europe) have experience in clinical research on monoclonal antibodies and develop their research in academic laboratories. Given a strong expertise in pharmacology, immunology, and applied mathematics, the MAGE is gathering increasing scientific evidence to support a therapeutic drug monitoring of particular molecules in the field of inflammatory diseases. The MAGE consortium participants are at the crossover between

1. biology (assays, biomarkers),
2. clinic (patient cohorts and clinical trials),
3. mathematics (modelling).

Five institutions/laboratories constitute the MAGE whose representative are listed below

Dr Antonio Bertolotto
is Direttore dell'Unità Operativa di Neurologia 2 - Centro di Riferimento Regionale per la Sclerosi Multipla, Orbassano, Turin, Italy a large tertiary centre in charge of the clinical management of multiple sclerosis patients. The laboratory has an extensive experience in detection of binding antibodies in samples of patients treated with IFN beta and/or Natalizumab. This centre holds a large sample collection in a biobank as well as clinical and imaging data (MRI) of multiple sclerosis and related diseases.

Pr Ann Gils
is a PI in the Department of Pharmaceutical and Pharmacological Sciences, KU Leuven Belgium, Laboratory for Therapeutic and Diagnostic Antibodies. The core business of the laboratory is the generation, characterisation and application of monoclonal antibodies. The laboratory has developed a number of assays to perform therapeutic drug monitoring and immunogenicity of biologicals, has an intensive collaboration with both the department of dermatology and of gastroenterology of University Hospital of Leuven and is involved in pharmacometrics.

Dr Dora Pascual-Salcedo
is the head of autoimmune section in one of the biggest Hospitals in Spain, is an expert in autoimmunity at the University Hospital La Paz, Madrid. In her lab they perform test to identify and quantify autoantibodies in sera of patients with autoimmune diseases. She has excellent connections with rheumatologists, dermatologists and gastroenterologists. She has introduced in La Paz Hospital the systematic determination of drug and anti-drug antibody levels for all patients at every visit, for most used biological drugs. She will contribute with her expertise in performance and interpretation of drug and anti-drug antibody levels, her knowledge of the clinical response associated with these parameters, her capacity to provide serum samples (more than 30.000 stored), her expertise in guiding Therapeutic Drug Monitoring in her Hospital, her collaboration with the pediatric rheumatology department.

Dr Gert Jan Wolbink
is a rheumatologist and the PI of the Biologicals Research Unit at Jan van Breemen Research Institute/Reade, Amsterdam, The Netherdands, in the Rheumatology and Immunology Center investigating clinical strategies including therapeutic drug monitoring (TDM) for optimisation of treatment with biologicals. Together with Theo Rispens he heads the Biologicals Research Group at Sanquin Immunopathology, which focusses on basic and translational research in the field of immunogenicity and TDM.

AROUND THE PROJECT

Posters

- Pouw, M. F.; Mulleman, D.; Nurmohamed, M. T.; Rispens, T.; Paintaud, G.; Wolbink G.; Ternant D. Adalimumab Concentration at 16 Weeks of Treatment Is Associated with Treatment Discontinuation within One Year, ACR/ARHP Annual Meeting, San Francisco (USA), November 6-11, 2015.

Scientific publications

- Ternant, D. ; Bejan-Angoulvant, T. ; Passot, C. ; Mulleman, D. ; Paintaud, G. Clinical Pharmacokinetics and Pharmacodynamics of Monoclonal Antibodies Approved to Treat Rheumatoid Arthritis, *Clin. Pharmacokinet.*, **2015**, *54*, 11071123