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The research leading to these results has received support from the Innovative Medicines Initiative Joint Undertaking under grant agreement n° [115303], resources of which are composed of financial contribution from the European Union's Seventh Framework Programme (FP7/2007-2013) and EFPIA companies' in kind contribution.'
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INTRODUCTION

A growing number of medicines are based on biological molecules such as proteins and monoclonal antibodies. These novel drugs have resulted in new, more effective treatments for a number of serious conditions. Yet sometimes these medicines trigger a response from the patient's immune system, which can decrease the effectiveness of the drug or cause severe side effects.

The aim of the IMI-founded ABIRISK project **"Anti-Biopharmaceutical Immunization: Prediction and Analysis of Clinical Re to Minimize the Risk",** is to shed new light on the factors behind this immune response. The project, which represents the first concerted effort to solve this problem, officially kicked off March 1st, 2012. ABIRISK project will aid in the creation of new, safer **biopharmaceuticals (BPs)** and also generate tools to determine how individual patients are likely to respond to them both in clinical trials and after release to the market.

The ABIRISK consortium (presently made up of thirty-five partners, twenty-four of which are academic institutions, nine are EFPIA member companies and two are small and medium enterprises, with thirteen countries represented), has been designed to meet all of these requirements in order to target three types of disorders: **Hemophilia A, Multiple sclerosis and Inflammatory diseases: inflammatory rheumatisms (including rheumatoid arthritis) and inflammatory bowel diseases.**

ABIRISK Project will collect data both retrospectively from patients suffering from various types of diseases and treated with various BPs at European centers with a high level of experience in clinical research and will prospectively recruit additional patients in dedicated studies during the 5 years of this program. Guidelines and Standard Operating Protocols for the study of anti-drug immunization will be established and used to standardize the collection of prospective data from these patients.

ABIRISK Project thus represents a unique opportunity to create an interdisciplinary task force of clinical centers especially designed to study immune responses against biopharmaceuticals.

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WELCOME

Dear Reader,

We would like to welcome you to the February 2015 issue the **ABIRISK Scientific Newsletter**. The Scientific Newsletter gives you a monthly update on the most relevant literature related to ABIRISK topics published around the globe, both inside and outside ABIRISK consortium.

This month, we chose to draw attention to the study conducted by P. Aero's group of the T cell CD4+ repertoire in Rheumatoid Athritis patients treated with abatacept, particulary looking at the effect of treatment on the $CD28^{neg}$ subpopulation of CD4+ T cells.

In addition, you will find in this issue some regulatory news from biopharmaceuticals field

We look forward to your visit on **ABIRISK** website for more information and updates on the program.

Enjoy reading !

Best wishes

The ABIRISK management team

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LITERATURE

This month's selected article

Co-stimulatory CD28/CD80-CD86 interactions are central to T cell activation and expansion. In rheumatoid arthritis (RA) patients, increased persisting $CD28^{neg}$ sub-populations of CD4 T cells have been recurrently found in peripheral blood and synovial fluid. Several studies demonstrated that these cells were clonally expanded yet not anergic despite the lack of CD28-induced secondary signal. In RA patients treated with abatacept - a CTLA4-Ig fusion protein that competes with endogenous CTLA4 for binding to the CD28 ligands - a reduction of circulating $CD28^{neg}$ T cells has been observed. This reduction was concomitant with an improvement of RA disease activity, leading to formulate the hypothesis that abatacept might benefit patients through prevention of expansion and/or generation of $CD28^{neg}$ $CD4^{+}$T cell clonotypes.

In the current paper, Imberti et al. sought to investigate whether the decrease in $CD28^{neg}$ $CD4^{+}$ T cell clonotypes observed in abatacept-treated patient was accompanied by an improvement of global T cell receptor (TCR) diversity.

Forty-four RA patients treated with abatacept for at least 12 months were enrolled in the study and peripheral blood T cell repertoire diversity examined for 17 of them at T0 and T12 months, using complementarity-determining region 3 (CDR3) spectratyping of the TCR V β chain (TCRBV). Diversity of the T cell repertoire was reflected by CDR3 length variations and TCRBV usage perturbations. Thymic outpout and apoptosis modification were also investigated at the 2 time points. All RA patients were gender-matched with healthy controls (HC).

At T0, $CD28^{neg}$ $CD4^{+}$ T numbers were identical in treated and control groups but lower in the abatacep group at month 12. Similarly, TCRBV diversity alteration in total PBMCs was higher in treated patients than healthy controls and significantly decreased over the treatment period.

Abatacept treatment did not seem to affect thymic outpout of recent $CD4^{+}$ T emigrants ($CD45RA^{pos}CD31^{pos}$), nor did it influence the number of highly antigen experienced $CD4^{+}$ T cells ($CD45RA^{pos}CCR7^{neg}$) as absolute numbers of both sub-populations remained the same. Apoptosis activity assessed through telomerase reverse

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transcriptase activity (TERT) activity was also found comparable before and after treatment. Therefore, the reduction in clonotypes observed in the RA abatacept-treated group could not be explained or related to any of these events.

Taken together, the authors showed that abatacept treatment induced a decrease in $CD28^{neg}$ $CD4^{+}$ T cell clonotypes and improved overall TCRBV diversity. Nevertheless, no correlation was found between TCR repertoire modifications and disease activity variation. Further studies conducted on larger abatacept cohorts and also possibly including a control group of patients treated with another biopharmaceutical such as an anti-TNFα (known to induce similar reduction of $CD28^{neg}$ $CD4^{+}$ T cell sub-population) might help shed light on the mechanisms of action of abatacept and its potential role in $CD28^{neg}$ $CD4^{+}$ T cell clonotypes decline.

Reduced T-cell repertoire restrictions in abatacept-treated rheumatoid arthritis patients.
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Immunogenicity

Changes in serum trough levels of infliximab during treatment intensification but not in anti-infliximab antibody detection are associated with clinical outcomes after therapeutic failure in Crohn's disease.
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Systemic Lupus Erythematosus

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REGULATION

EMA

Work plan for the Rheumatology-Immunology Working Party 2014
Updated
January 2015

Human medicines European public assessment report (EPAR): RoActemra, tocilizumab
Revision: 15, Authorised
January 2015

Human medicines European public assessment report (EPAR): Cimzia, certolizumab pegol
Revision: 13, Authorised
January 2015

Scientific guideline: Guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance: non-clinical and clinical issues
Adopted
January 2015

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