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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 Relevance 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 **May 2014** issue of 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 work by Núñez and collaborators exploring the potential of HLA typing in Multiple Sclerosis patients as a predictive biomarker of resistance to treatment with IFNβ due to immunogenicity.

In addition, you will find in this issue some regulatory news on biopharmaceuticals and a list of ABIRISK topics-related scientific meetings taking place in the first quarter of 2013.

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

Recombinant interferon β (IFNβ) remains as of today the most commonly used first-line therapy for multiple sclerosis (MS). A high percentage of patients will however develop anti-drug antibodies during therapy, most of them doing so within the first 12-18 months of treatment with some exhibiting high titers of Neutralizing antibodies (NAbs). Previous work conducted on MS patients samples predominantly of northern European heritage and recruited in Germany, had revealed a strong HLA-DRB1*04:01,*04:08, and *16:01 association with the development of binding and neutralizing antibodies to IFNβ (*Hoffmann* et al., 2008; *Buck* et al., 2011).

Likewise, in the present Núñez and collaborators paper sought to investigate a possible contribution of HLA alleles to the development of NAbs in 3 independent Southern Europe MS cohorts. To this aim, 610 MS patients diagnosed following the McDonald criteria were included at three different centres from Northern, Central and Southern Spain. Patients were treated for at least 2 years with either intramuscular or subcutaneous IFNβ-1a, or subcutaneous IFNβ-1b.

Combined analysis of genotyping data and NAbs measurement demonstrated an association of NAbs production with the DRB1*07 allele, but confined to individuals also carrying MHC class I A*26 or B*14 alleles. This combination was found in 20% of patients with high titres of NAbs, as opposed to 5.4% of NAb-negative patients. The DRB1*04:01 allele, as previously shown, was also significantly more frequently carried by patients with high titres of NAbs. On the contrary, HLA-DRB1*03:01, HLA-DQA1*05:01 and HLA-DQB1*02:01alleles were associated with protection.

Taken together, these data suggest that HLA genotyping in MS patients could be used as a predictive marker of resistance to treatment with IFNβ due to immunogenicity. As more than 50% of the patients enrolled in the present study only express one the five identified alleles/combination of alleles, this also suggest that a large

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proportion of MS patients of European heritage could benefit from such screening and be treated with alternative biopharmaceuticals, such as the monoclonal antibodies Natalizumab or Alemtuzumab.

HLA alleles as biomarkers of high-titre neutralising antibodies to interferon-β therapy in multiple sclerosis.

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REGULATION

EMA

Draft guideline on non-clinical and clinical development of similar biological medicinal products containing recombinant human insulin and insulin analogues
Draft : consultation open
Consultation end date : 31 July 2014

Draft guideline on process validation for the manufacture of biotechnology-derived active substances and data to be provided in the regulatory submission
Draft : consultation open
Consultation end date : 31 October 2014

Human medicines European public assessment report (EPAR): Rebif,interferon beta-1a
Revision: 27, Authorised
April 2014

Opinion/decision on a Paediatric Investigation Plan (PIP): Humira, adalimumab
Therapeutic area : Dermatology
April 2014

Opinion/decision on a Paediatric Investigation Plan (PIP): Stelara, ustekinumab
Therapeutic area: Immunology-Rheumatology-Transplantation/Gastroentology-Hepatology
April 2014

Human medicines European public assessment report (EPAR): Tysabri, natalizumab
Revision: 16, Authorised
April 2014

Human medicines European public assessment report (EPAR): Avonex, interferon beta-1a
Revision: 19, Authorised
April 2014

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