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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 November 13 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 are extremely pleased to highlight a **recent publication in *Gut* by our partners from the RAMBAM and SHEBA medical centers on behalf of ABIRISK consortium.** Exploring the temporal evolution of anti-drug antibody (ADA) production in Inflammatory Bowel Disease patients treated with anti-TNFalpha Ungar et al. notably observed that 90% of the patients who develop ADA do so within the first 12 months of therapy, indicating that patients remaining ADA negative for 12 months might be at low risk of developing ADA at a later stage. Go to the section *'This month's selected article'* to find out more !

In addition, you will find in this issue some regulatory news and recommendations from the Biopharmaceutical 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

Approximately 60% of Crohn's disease patients will develop anti-drug antibodies (ADA) when sporadically treated with the anti-TNFalpha therapeutic antibody infliximab, and this proportion scatters from 6 to 25% in patients that receive scheduled therapy. The presence of ADA is accompanied with lower Infliximab trough levels and in most cases associated with a loss of clinical response. However, the full impact of ADA development on clinical efficacy of the drug remains ambiguous, as for some patients ADA development does not translate into resistance to treatment.

In this study published in the September issue of Gut, our ABIRISK partners from the SHEBA and RAMBAM medical centres in Israel sought to determine the temporal evolution of ADA in the serum of inflammatory bowel disease (IBD) patients treated with infliximab, and to investigate the alleged correlation between infliximab immunogenicity kinetics and the onset of clinical response loss.

To this aim, 98 patiens with Crohn's disease and 27 patients with ulcerative colitis were included to receive infliximab therapy and infliximab trough levels together with ADA presence were assessed in serum. Of note for ADA measurement, an in-house assay was used, Details of the method can be found in Ben-Horin et al. 2011 and Kopylov et al. 2012 publications. The median follow-up of enrolled patients was 11.5 months, and physicians were not blinded to ADA results allowing them to integrate this parameter in their approach to treatment. Addition of an immunomodulator during the study was permitted and analyses later showed that it significantly extended ADA-free survival compared to monotherapy.

The study revealed that 46% developed infliximab-specific ADA. Interestingly, 90% of the patients who develop ADA did so within the first 12 months of therapy, indicating that patients remaining ADA negative for 12 months might be at low risk of developing ADA at a later stage.

Assessing the temporal evolution of ADA formation, the authors found that in 54% of patients the detection of infliximab-specific ADA in serum preceded the manifestation of loss of clinical response. For 30% of patients,

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the two events were concomitant, and in 16% of patients the onset of loss of clinical response occurred before serum ADA detection. The prevalence of low infliximab trough levels and high ADA titres was indeed significantly elevated among patients with loss of response. However, the rate of loss of response was similar for patients with low or high ADA titres.

As previously reported, transient ADA secretion was observed throughout the duration of infliximab therapy and did not impact the course of treatment.

The temporal evolution of antidrug antibodies in patients with inflammatory bowel disease treated with infliximab.
Ungar B, **Chowers** Y, Yavzori M, Picard O, Fudim E, Har-Noy O, Kopylov U, Eliakim R, **Ben-Horin** S; **on behalf of ABIRISK consortium.**
Gut. 2013 Sep 16.

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Immunogenicity

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Pashov AD, Calvez T, Gilardin L, **Maillère B**, Repessé Y, Oldenburg J, Pavlova A, Kaveri SV, **Lacroix-Desmazes S.**

Haemophilia. 2013 Oct 14.

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Moss AC, Brinks V, Carpenter JF.

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The when and how of biologic agent withdrawal in rheumatoid arthritis: learning from large randomised controlled trials.

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Opinions/Commentaries/Across diseases reviews

Is Extrapolation of the Safety and Efficacy Data in One Indication to Another Appropriate for Biosimilars?
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Is CD69 an effective brake to control inflammatory diseases?
González-Amaro R, Cortés JR, Sánchez-Madrid F, Martín P.
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Costs of adalimumab versus infliximab as first-line biological therapy for luminal Crohn's disease.
Choi GK, Collins SD, Greer DP, Warren L, Dowson G, Clark T, Hamlin PJ, Ford AC.
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Drug safety evaluation of certolizumab pegol.
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Frequency of the off-label use of monoclonal antibodies in clinical practice: a systematic review of the literature.

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REGULATION

EMA

Opinion/decision on a Paediatric Investigation Plan (PIP): Recombinant fusion protein consisting of human coagulation factor VIII attached to the Fc domain of human IgG1 (rFVIIIFc)
Therapeutic area: Haematology-Hemostaseology (updated)

Human medicines European public assessment report (EPAR): Inflectra, infliximab
Revision: 1, Authorised
October 2013

Pending EC decision: Cimzia, certolizumab pegol
Opinion date: 24-Oct-2013

Human medicines European public assessment report (EPAR): Simponi, golimumab
Revision: 15, Authorised
October 2013

Human medicines European public assessment report (EPAR): Cimzia, certolizumab pegol
Revision: 8, Authorised
October 2013

Scientific guideline: Concept paper on the revision of the note for guidance on the approach towards harmonisation of withdrawal periods, draft: consultation open
Consultation end date : 31/01/2014

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Human medicines European public assessment report (EPAR): Ilaris, canakinumab
Revision: 7, Authorised
October 2013

Human medicines European public assessment report (EPAR): RoActemra, tocilizumab
Revision: 12, Authorised
October 2013

Recommendations

EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs: 2013 update.

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