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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 **February 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, alongside with some news from the Biopharmaceuticals regulatory field.

This month, we chose to draw attention to the results reported by Genovese et al. in *Arthritis and Rheumatism*, of two phase II clinical trials carried out in patients with rheumatoid arthritis and designed to assess the efficacy and safety of Tabalumab, a fully humanized monoclonal antibody targeting the B cell activating factor BAFF (also known as BLys),

We are also very pleased to announce on page 9 the publication in *Therapeutic Advances in Neurological Disorders* of a paper by our **partner Queen Mary University London on behalf of ABIRISK consortium.** In this review, Paul Creeke discusses the use of IFNb to treat multiple sclerosis, the biological and clinical relevance of binding and neutralizing anti-IFNb antibodies and the introduction of anti-drug antibody testing in clinical practice.

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

NB: All previous ABIRISK Scientific Newsletter issues are now available on our website at www.abirisk.eu

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LITERATURE

This month's selected article

Tabalumab in patients with rheumatoid arthritis with an inadequate response to methotrexate and naive to biologic therapy.
Genovese MC, Bojin S, Biagini I, Mociran E, Cristei D, Mirea G, Georgescu L, Sloan-Lancaster J.
Arthritis Rheum. 2013 Jan 28

B cells are known to play a pathogenic role in some autoinflammatory diseases. With the aim of hampering deleterious B cell compartment in such diseases, an immunotherapeutic approach has been proposed by means of monoclonal antibodies targeting either B cell surface markers (rituximab, alemtuzumab, ocrelizumab, epratuzumab), B cell activation factor BAFF (belimumab, tabalumab, briobacept) or both BAFF and the proliferation-inducing ligand APRIL (atacicept).

In the present study, Genovese and colleagues report on a phase II, randomized, double-blind, placebo-controlled, parallel, multiple-dose study designed to assess the efficacy, safety, pharmacokinetic and pharmacodynamic parameters of tabalumab in RA patients with active disease despite the use of methotrexate. Tabalumab (formerly LY2127399), is a fully human IgG4 monoclonal antibody which binds and neutralizes both soluble and membrane-bound forms of BAFF. Indeed it had been previously observed that RA patients exhibit an enhanced expression of factor BAFF in sera and synovial fluid, possibly linked to a pathogenic increase in B-cells survival rate.

The study was conducted between March 2006 and October 2007 at 20 sites in Romania, where placebo or tabalumab were administered intravenously at weeks 0, 3, and 6. The primary endpoint of the trial was the proportion of subjects with an ACR20 response at week 16.

At week 16, the proportion of tabalumab-treated patients achieving the primary endpoint in the 30 mg, 60 mg and 160 mg groups was respectively 57.6% ($p=0.01$), 67.6% ($p<0.001$), and 51.5% ($p<0.03$), compared with 29.4% in the placebo group. Significant differences in response rates were similarly seen in secondary endpoints (ACR50/70, DAS28-CRP and EULAR) responses, however no dose-response relationship was observed. This was accompanied by a transient increase in naive and memory B cells, followed by a strong reduction in naive B cells albeit not reaching complete depletion. Memory B cells returned to base-line at week 24. Serum IgM but not IgG or IgA were decreased during treatment.
In terms of immunogenicity, 3/100 patients developed antibodies to tabalumab : 2 patients (1, 30 mg; 1, 160 mg) had antibody titers of 1:2 at week 36, and 1 patient (160 mg) had a 1:4 antibody titer at week 4.

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Overall, the effects of tabalumab on the symptoms of RA were significant with respect to ACR20 in alltabalumab-treatment groups compared with placebo with a safety profile similar to that seen in the placebo group. Anti-drug antibody development was not associated with loss efficacy or onset of adverse events.

Interestingly, Genovese et al. also reported in *the Annals of the Rheumatic Diseases* last December (see the January issue of ABIRISK Scientific Newsletter), the results of an analogous trial (NCT00689728) from which substantially divergent conclusions could be drawn, as no significant differences were observed in ACR20 responses at week 16 in tabalumab-treated versus placebo groups. The authors suggested that patient biotherapy history and origin together with the one-time rescue dose at week present in the NCT00689728 trial could account for the disparate outcomes.

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Immunogenicity risk management for commercial advantage.
Schwabe N, Lawson V.
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In Vitro and In Vivo Studies of IgG-derived Treg Epitopes (Tregitopes): A Promising New Tool for Tolerance Induction and Treatment of Autoimmunity.
Cousens LP, Najafian N, Mingozzi F, Elyaman W, Mazer B, Moise L, Messitt TJ, Su Y, Sayegh M, High K, Khoury SJ, Scott DW, De Groot AS.
J Clin Immunol. 2013 Jan;33 Suppl 1:43-9.

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Rheumatoid Arthritis

Tocilizumab in rheumatoid arthritis: efficacy, safety and its place in therapy.
Kaneko A.
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Schwaab R, Pavlova A, Albert T, Caspers M, **Oldenburg J.**
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Opinions/Commentaries/Across diseases reviews

Of Mice and Men: The Need for Humanized Mouse Models to Study Human IgG Activity in Vivo
Anja Lux, Falk Nimmerjahn
J Clin Immunol. January 2013, Volume 33, Issue 1 Supplement, pp 4-8

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Ken Garber
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Andrew C Chan, Timothy W Behrens
Nature Immunology 14, 106-109 (2013)

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REGULATION

EMA

Human medicines European Public Assessment Report (EPAR): Simponi, golimumab
Revision: 12, Authorised
January 2013

Pending EC decision: Humira, adalimumab
Opinion date: 17-Jan-2013

Human medicines European Public Assessment Report (EPAR): Enbrel, etanercept
Revision: 36, Authorised
January 2013

Human medicines European Public Assessment Report (EPAR): Avonex,interferon beta-1a
Revision: 17, Authorised
February 2013

Opinion/decision on a Paediatric Investigation Plan (PIP): Stelara, ustekinumab
Updated
February 2013

Human medicines European Public Assessment Report (EPAR): Betaferon,interferon beta-1b
Revision: 22, Authorised
February 2013

Human medicines European Public Assessment Report (EPAR): Humira, adalimumab
Revision: 32, Authorised
February 2013

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FDA

Draft guidance for Industry : Immunogenicity Assessment for Therapeutic Protein Products

9468 Immunogenicity draft guidance for po

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Announcements

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BMJ. 2013 Jan 18;346:f275.

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