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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.
Dear Reader,

We would like to welcome you to March 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 highlight a proof of concept study conducted by Gavasso and colleagues in Norway and published in Plos One, demonstrating the possible use of phosphorylation of Stat1 protein as a surrogate marker of anti-IFNβ neutralizing antibodies effect on INFβ treatment in multiple sclerosis patients.

We are also very pleased to have inserted in the Literature Immunogenicity section, a link to publication by the group of Anna Fogdell-Hahn, from the ABIRISK partner Karolinska Institute in Sweden!

In addition as usual, you will find in this issue some news from the regulatory field of Biotherapeutics, and in particular the consultation is open for the Draft Scientific guideline: Concept paper on the revision of the guideline on immunogenicity assessment of biotechnology-derived therapeutic proteins.

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
This month's selected article

In multiple sclerosis (MS) IFNβ-treated patients, dissecting what leads to the formation of anti-IFNβ neutralizing antibodies (NAbs) from what is the consequence of reduced treatment effect remains a challenge. However, it is possible to measure the grade of biological relevance the presence of different titres of NAbs has at the cellular level. Using a phospho-specific flow cytometry approach (phosphoflow), Gavasso et al. previously identified pStat1 as a possible biomarker of anti-IFNβ NAbs impact on immune cells responsiveness ex vivo (Multiple Sclerosis 2012).

In this proof of concept study, published in PloS One in March, blood samples were taken before and 4, 6 and 8 hours after IFNβ injection, from MS patients who had been treated for 1-5 years and were either negative, low/medium or high IFNβ NAbs positive. IFNβ-specific NAbs, IFNβ serum concentration, gene expression and phosphorylation of Stats were assessed as depicted in the workflow below:
Principal Component (PCA) and Statistical analyses revealed that the phosphorylation of Stat1 was clearly blocked by anti-IFNβ NAbs. Phosphorylation status assessment was more reliable than gene expression. Moreover, PCA could separate high NAb-positive from medium positive and negative patients. The authors rightly concluded that “Measurements of pathway-specific activation levels of signalling molecules after in vivo IFNβ injection are possible, and phosphorylation patterns of Stat proteins are clearly affected by NAbs.”

In light of this paper, assessment of phosphorylation patterns of Stat proteins might be a better way to measure biological relevance of NAbs compared to Mx1 in vivo expression, since Stat phosphorylation exhibited both less individual variation and less variation with time after injection.

Deficient phosphorylation of stat1 in leukocytes identifies neutralizing antibodies in multiple sclerosis patients treated with interferon-Beta.
**Immunogenicity**

*ABIRISK PUBLICATION!*

**Human leukocyte antigen genes and interferon Beta preparations influence risk of developing neutralizing anti-drug antibodies in multiple sclerosis.**


**Trough s-infliximab and antibodies towards infliximab in a cohort of 79 IBD patients with maintenance infliximab treatment.**


**Methods**

**Innovative Use of LC-MS/MS for Simultaneous Quantitation of Neutralizing Antibody, Residual Drug, and Human Immunoglobulin G in Immunogenicity Assay Development.**


**Analyzing Subvisible Particles in Protein Drug Products: a Comparison of Dynamic Light Scattering (DLS) and Resonant Mass Measurement (RMM).**

Panchal J, Kotarek J, Marszal E, Topp EM.

**Animal models**

**Interleukin-6 Receptor Blockade Enhances CD39+ Regulatory T Cell Development in Rheumatoid Arthritis and in Experimental Arthritis.**

**Interleukin-10 produced by B cells is crucial for the suppression of Th17/Th1 responses, induction of T regulatory type 1 cells and reduction of collagen-induced arthritis.**
Carter NA, Rosser EC, **Mauri C.**

**Biomarkers**

**A1.25 B-Cell profile in RA patients treated with two different biological therapeutic targets: anti-TNF and anti-IL6R, a cross-sectional study.**
Hernández D, Valor L, de la Torre I, Del Río T, Martínez L, Naredo E, González C, Lopez-Longo J, Monteagudo I, Montoro M, Carreño L.

**IL2/IL21 region polymorphism influences response to rituximab in systemic lupus erythematosus patients.**
**Systemic Lupus Erythematosus**

*Lupus clinical development: will belimumab's approval catalyse a new paradigm for SLE drug development?*

Runkel L, Stacey J.

**Therapeutic targeting of the BAFF/APRIL axis in systemic lupus erythematosus.**

Stohl W.

*Systemic lupus erythematosus: a therapeutic challenge for the XXI century.*

Ugarte-Gil MF, Alarcón GS.

*In-/off-label use of biologic therapy in systemic lupus erythematosus.*

Gatto M, Kiss E, Naparstek Y, Doria A.

**Arthritis**

*Switching of biologic disease modifying anti-rheumatic drugs in patients with rheumatoid arthritis in a real world setting.*

Meissner B, Trivedi D, You M, Rosenblatt L.
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The early clinical course of infliximab treatment in rheumatoid arthritis: results from the REMARK observational study.

A1.54 Development of a novel bispecific therapeutic for rheumatoid arthritis.
Ferrari M, Onuoha S, Sblattero D, Pitzalis C.

Applying biologic therapies to the management of patients with rheumatoid arthritis.
Epstein AA, Kremer JM, Siegel E.

Safety, effectiveness, and pharmacokinetics of adalimumab in children with polyarticular juvenile idiopathic arthritis aged 2 to 4 years.
Kingsbury DJ, Bader-Meunier B, Patel G, Arora V, Kalabic J, Kupper H.

Inflammatory Bowel Disease

Novel concepts in inflammatory bowel disease.
Moran GW, Dubeau MF, Kaplan GG, Panaccione R, Ghosh S.

Subcutaneous golimumab therapy for ulcerative colitis.
Lowe AW, Moseley RH.
When combination therapy isn't working: Emerging therapies for the management of inflammatory bowel disease.
Krishnareddy S, Swaminath A.

Moving towards disease modification in inflammatory bowel disease therapy.
Allen PB, Peyrin-Biroulet L.

Combination therapy with infliximab and azathioprine is superior to monotherapy with either agent in ulcerative colitis.

Systematic review with network meta-analysis: the efficacy of anti-tumour necrosis factor-alpha agents for the treatment of ulcerative colitis.
Stidham RW, Lee TC, Higgins PD, Deshpande AR, Sussman DA, Singal AG, Elmunzer BJ, Saini SD, Vijan S, Waljee AK.


Adalimumab versus infliximab for the treatment of moderate to severe ulcerative colitis in adult patients naive to anti-TNF therapy: An indirect treatment comparison meta-analysis.
Thorlund K, Druyts E, Mills EJ, Fedorak RN, Marshall JK.
Early Trough Levels and Antibodies to Infliximab Predict Safety and Success of Re-initiation of Infliximab Therapy.

Crohn's disease: a review of treatment options and current research.
Bandzar S, Gupta S, Platt MO.

New biologic therapeutics for ulcerative colitis and Crohn's disease.
Mozaffari S, Nikfar S, Abdolghaffari AH, Abdollahi M.

In vitro assessment of the effects of vedolizumab binding on peripheral blood lymphocytes.
Wyant T, Yang L, Fedyk E.

Multiple Sclerosis

Atorvastatin Added to Interferon Beta for Relapsing Multiple Sclerosis: 12-Month Treatment Extension of the Randomized Multicenter SWABIMS Trial.

Treatment satisfaction, adherence and behavioral assessment in patients de-escalating from natalizumab to interferon beta.
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Efficacy and safety of natalizumab in multiple sclerosis: interim observational programme results.

Hemophilia

Rates of Inhibitor Development in Previously Untreated Patients with Severe Hemophilia A Treated with Plasma-Derived or Recombinant Factor VIII: No Proof of Difference or Proof of No Difference?
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Response to "Rates of Inhibitor Development in Previously Untreated Patients with Severe Hemophilia A Treated with Plasma-Derived or Recombinant Factor VIII: No Proof of Difference or Proof of No Difference?", Franchini M, Mengoli C.

Basic immunology

Circadian Clock Proteins and Immunity.
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Opinions/Commentaries

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Semin Oncol. 2014 Feb;41 Suppl 1:S3-S14.
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Draft: consultation open
Consultation end date: 31 May 2014

Scientific guideline: Concept paper on the revision of the guideline on immunogenicity assessment of biotechnology-derived therapeutic proteins
Draft consultation open
Consultation start date: 25/03/2014
Consultation end date: 30/06/2014

Scientific guideline: Draft guideline on the investigation of subgroups in confirmatory clinical trials
Draft: consultation open
Consultation end date: 31 July 2014

Work plan for the Gastroenterology Drafting Group 2014
Updated
February 2014

Opinion/decision on a Paediatric Investigation Plan (PIP): Secukinumab, Therapeutic area: Immunology-Rheumatology-Transplantation
Updated
February 2014
Work plan for the Rheumatology-Immunology Working Party 2014
Updated
February 2014

Opinion/decision on a Paediatric Investigation Plan (PIP): Simponi, Golimumab, Therapeutic area: Immunology-Rheumatology-Transplantation
Updated
February 2014

Opinion/decision on a Paediatric Investigation Plan (PIP): Humira, Adalimumab, Therapeutic area: Immunology-Rheumatology-Transplantation/Dermatology/Gastroentology-Hepatology
Updated
February 2014

Human medicines European public assessment report (EPAR): Avonex, interferon beta-1a
Revision: 18, Authorised
February 2014

Human medicines European public assessment report (EPAR): Enbrel, etanercept
Revision: 39, Authorised
February 2014