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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 the April 2013 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 selected a review by Choy et al. published in Nature Reviews Rheumatology recapitulating current and future biologic therapies for Rheumatoid Arthritis, highlighting difficulties faced by clinicians when given the opportunity to chose from several effective new options.

In addition, you will find in this issue some regulatory news on biopharmaceuticals and an update on forthcoming conferences of interest.

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

Rheumatoid arthritis (RA) patients failing to respond to conventional DMARD therapy are nowadays offered an alternative treatment by means of biologic therapy. Current approved biotherapeutics for RA treatment include cytokines blockers (anti-TNFα and TNFα receptor, anti-IL-6 and IL-6 receptor, anti-IL-1) and lymphocyte targeting agents (anti-CD20, CTLA4 fusion protein).

The list of putative biotherapeutic agents for RA treatment is rapidly expanding, with other cytokines such as IL-17, IL-23 and signal transduction pathway blockers (e.g. anti-JAK pathway) now reaching the late stages of clinical development. Small-molecule inhibitors of signal transduction pathway and cytokines blockers have indeed been the main focus of new therapies development efforts in the recent years.

However, in absence of reliable biomarkers and clear understanding of the molecular basis of efficacy or lack of thereof of each biotherapeutic agent, clinicians are faced with a difficult choice. In this paper, Choy et al. review the modes of action of each of these types of therapy and consider the challenges associated with their use in clinical practice.

The problem of choice: current biologic agents and future prospects in RA.
Choy EH, Kavanaugh AF, Jones SA.
Nat Rev Rheumatol. 2013 Feb 19
Immunogenicity

**Subcutaneous abatacept for the treatment of rheumatoid arthritis.**
Schiff M.

**Late immune tolerance induction in an adult with severe haemophilia A and high-responder inhibitor: 1-year outcome.**

**The frequency of anti-infliximab antibodies in patients with rheumatoid arthritis treated in routine care and the associations with adverse drug reactions and treatment failure**
*Rheumatology*. 2013 Mar 4

**Methods**

**External Quality Assessment of Factor VIII Inhibitor Assays.**
Bonar RA, Favaloro EJ, Marsden K.
*Semin Thromb Hemost*. 2013 Feb 22

**Monitoring of adalimumab and antibodies-to-adalimumab levels in patient serum by the homogeneous mobility shift assay.**

**Biomarkers**

**Biomarkers in Multiple Sclerosis: An Up-to-Date Overview.**
Katsavos S, Anagnostouli M.
*Mult Scler Int*. 2013;2013:340508

**The type I IFN signature as a biomarker of preclinical rheumatoid arthritis.**
**Rheumatoid factor does not predict response to TNF antagonists in rheumatoid arthritis: Three centers experience.**


### Systemic Lupus Erythematosus

**Persistent memory B cell down-regulation after 6-year remission induced by rituximab therapy in patients with systemic lupus erythematosus.**


**Belimumab: targeted therapy for lupus.**


**Down-regulation of interferon signature in systemic lupus erythematosus patients by active immunization with interferon α-kinoid.**


**B-Cell Targeted Therapies in Systemic Lupus Erythematosus : Successes and Challenges.**


**B-cell-targeted therapies in systemic lupus erythematosus.**

Rheumatoid Arthritis

Effects of subcutaneous and intravenous golimumab on inflammatory biomarkers in patients with rheumatoid arthritis: results of a phase 1, randomized, open-label trial.

Exposure-Exposure Relationship of Tocilizumab, an Anti-IL-6 Receptor Monoclonal Antibody, in a Large Population of Patients With Rheumatoid Arthritis.

Harms of TNF inhibitors in rheumatic diseases: a focused review of the literature.

Longterm Safety and Efficacy of Tocilizumab in Patients with Rheumatoid Arthritis: A Cumulative Analysis of Up to 4.6 Years of Exposure.

Targeting Interleukin-6 in Rheumatoid Arthritis

Anti-TNF Therapy Reduces Serum Levels of Chemerin in Rheumatoid Arthritis: A New Mechanism by Which Anti-TNF Might Reduce Inflammation.

Inflammatory Bowel Disease

Certolizumab pegol in the treatment of Crohn's disease.
Elective switching from infliximab to adalimumab in stable Crohn's disease.
Hoentjen F, Haarhuis BJ, Drenth JP, de Jong DJ.

Cost-per-remission analysis of infliximab compared to adalimumab among adults with moderate-to-severe ulcerative colitis.
Lofland JH, Mallow P, Rizzo J.
*J Med Econ.* 2013 Feb 27.

**Multiple Sclerosis**

Immunotherapy of Multiple Sclerosis: The State of the Art.
Karussis D.
*BioDrugs.* 2013 Feb 20

Deiß A, Brecht I, Haarmann A, Buttmann M.

Natalizumab treatment decreases serum IgM and IgG levels in multiple sclerosis patients.

The benefits and risks of alemtuzumab in multiple sclerosis.
Ontaneda D, Cohen JA.

**Hemophilia**

Identification and Multidimensional Optimization of an Asymmetric Bispecific IgG Antibody Mimicking the Function of Factor VIII Cofactor Activity.
Current status and future prospects for the prophylactic management of hemophilia patients with inhibitor antibodies.
Teitel JM, Sholzberg M.

**Basic immunology**

The signal peptide of the tumor-shared antigen Midkine hosts CD4+ T cell epitopes.
Kerzerho J, Schneider A, Favry E, Castelli FA, *Maillère B.*
*J Biol Chem.* 2013 Apr 3

**Opinions/Commentaries**

To target or not to target APRIL in systemic lupus erythematosus: that is the question!
Morel J, Hahne M.

First-line therapy in adult Crohn's disease: who should receive anti-TNF agents?
Danese S, Colombel JF, Peyrin-Biroulet L, Rutgeerts P, Reinisch W.
*Aliment Pharmacol Ther.* 2013 Mar 13

Canakinumab in pediatric rheumatic diseases
Wulffraat NM, Woo P.

Letter: are infliximab and adalimumab similar for Crohn's disease in clinical practice?
Tursi A, Elisei W, Picchio M, Penna A.
*Aliment Pharmacol Ther.* 2013 Apr;37(7):763-4

Letter: should immunosuppressive therapy be started with adalimumab in Crohn's disease?
Tursi A, Elisei W, Picchio M, Penna A.
*Aliment Pharmacol Ther.* 2013 Apr;37(7):763-4

Letter: should immunosuppressive therapy be started with adalimumab in Crohn's disease? Authors' reply.
Reenaers C, Louis E, Belaiche J, Seidel L, Keshav S, Travis S.
*Aliment Pharmacol Ther.* 2013 Apr;37(7):752-3
Regulatory T cells: recommendations to simplify the nomenclature.
Abbas AK, Benoist C, Bluestone JA, Campbell DJ, Ghosh S, Hori S, Jiang S, Kuchroo VK, Mathis D, Roncarolo MG, Rudensky A, Sakaguchi S, Shevach EM, Vignali DA, Ziegler SF.
REGULATION

EMA

Human medicines European Public Assessment Report (EPAR): Orencia, abatacept
Revision: 13, Authorised
March 2013

Scientific guideline: Reflection paper on Immune Tolerance Induction in haemophilia A patients with inhibitors, adopted
Adopted
March 2013

Overview of comments received on 'Reflection paper on Immune Tolerance Induction in haemophilia A patients with inhibitors
March 2013

Pending EC decision: MabThera, rituximab
Opinion date: 21-Mar-2013
Guidance for Industry: Enrichment Strategies for Clinical Trials to Support Approval of Human Drugs and Biological Products

OTHER NEWS

The IMI-founded is now open for business! For more information, please visit: Nature

Forthcoming conferences

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<tr>
<td>September</td>
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<td>21-26 Vienna, Austria</td>
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