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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 Re 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 2015 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 Deehan et al. on the management of unwanted immunogenicity of therapeutic proteins, mainly reporting on discussions that took place at the European Immunogenicity Platform annual symposium in February 2014.

In addition, you will find in this issue some regulatory news on biopharmaceuticals.

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
LITERATURE

This month’s selected article

The introduction of biopharmaceuticals products (BPs) has been a critical step forward in the treatment of many severe diseases. A major limitation to the use of BPs remains the development of anti-drug antibodies (ADA) in a subset of patients. ADA may decrease the efficacy of BPs by neutralizing them or modifying their clearance, and they may be associated with BP-specific hypersensitivity reactions. The prediction, prevention and cure of anti-drug immunogenicity are thus major goals in biopharmaceutical drug development and patient safety.

In this paper, Deehan et al. review the critical topics discussed at the February 2014 European Immunogenicity Platform Symposium around unwanted BPs immunogenicity.

Namely, they report that a better understanding of BPs immunogenicity and a potential reduction of its clinical consequences may rely upon: 1) the use of innovative in silico, in vitro and in vivo immunogenicity prediction tools; 2) further improvement of ADA assays performance, in particular with respect to sensitivity and drug tolerance thresholds; 3) refined analysis of the clinical relevance of ADA in treated patients.

Such multidisciplinary and integrated approach is the one chosen by the ABIRISK consortium to analyze the mechanisms and consequences of immunization against biopharmaceutical products in Hemophilia A, Multiple sclerosis and in Inflammatory diseases: inflammatory rheumatism -including adult and juvenile rheumatoid arthritis- and inflammatory bowel diseases.

Managing unwanted immunogenicity of biologicals.
Deehan M, Garcês S, Kramer D, Baker MP, Rat D, Roettger Y, Kromminga A.
Immunogenicity

**Antidrug antibodies against TNF-blocking agents: correlations between disease activity, hypersensitivity reactions, and different classes of immunoglobulins.**

**Do neutralising antibodies against exogenous interferon-beta inhibit endogenous signalling pathways?**

**Evaluation of the impact of neutralizing antibodies on IFNβ response.**

**Antibodies to infliximab and adalimumab in patients with rheumatoid arthritis in clinical remission: a cross-sectional study.**

**A case of Crohn's disease that developed anti-infliximab and anti-adalimumab antibodies.**

Methods

**Statistical approaches for the determination of cut points in anti-drug antibody bioassays.**

**Protein aggregation and its impact on product quality.**
Roberts CJ. Curr Opin Biotechnol. 2014 Dec;30:211-7

**Thermally induced degradation pathways of three different antibody-based drug development candidates.**
Structure-based development and optimization of therapy antibody drugs against TNFα.

Expression of anti-Tumor Necrosis Factor alpha (TNFα) Single Chain Variable Fragment (scFv) in Spirodea punctata plants transformed with Agrobacterium tumefaciens.
Parthasarathy B, P K S, Venkataraman K, Vijayalakshmi MA.

Animal models

Animal models of rheumatoid arthritis: How informative are they?
McNamee K, Williams R, Seed M.
Eur J Pharmacol. 2015 Mar 27.

Mouse Models of Multiple Sclerosis: Lost in translation?
Baker D, Amor S.
Curr Pharm Des. 2015 Mar 16.

Cathepsin S inhibition suppresses systemic lupus erythematosus and lupus nephritis because cathepsin S is essential for MHC class II-mediated CD4 T cell and B cell priming.

Biomarkers

HLA-DRB1 does not have a role in clinical response to interferon-beta among Iranian multiple sclerosis patients.
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FCGR polymorphisms in the treatment of rheumatoid arthritis with Fc-containing TNF inhibitors.

Neurology. 2015 Mar 11.

Experimental colitis models: Insights into the pathogenesis of inflammatory bowel disease and translational issues.
Valatas V, Bamias G, Kolios G.

Systemic Lupus Erythematosus

Emerging biological therapies for systemic lupus erythematosus.
Mok CC.

Progress with the use of monoclonal antibodies for the treatment of systemic lupus erythematosus.
Jordan N, Lutalo PM, D'Cruz DP.

T cells as a therapeutic target in SLE.
Comte D, Karampetsou MP, Tsokos GC.
Lupus. 2015 Apr;24(4-5):351-63.

First-in-human trial of the safety, pharmacokinetics and immunogenicity of a PEGylated anti-CD40L antibody fragment (CDP7657) in healthy individuals and patients with systemic lupus erythematosus.
Lupus. 2015 Mar 16.
Rheumatoid Arthritis

Canakinumab: A Review of Its Use in the Management of Systemic Juvenile Idiopathic Arthritis.
Hoy SM.

Comparable efficacy and safety between tacrolimus and methotrexate in combination with abatacept in patients with rheumatoid arthritis; a retrospective observational study in the TBC Registry.

Rheumatoid Arthritis: an Evolutionary Force in Biologics.
Brown PM, Isaacs JD.

An examination of the mechanisms involved in secondary clinical failure to adalimumab or etanercept in inflammatory arthropathies.

FcGR genetic polymorphisms and the response to adalimumab in patients with rheumatoid arthritis.
Dávila-Fajardo CL, van der Straaten T, Baak-Pablo R, Medarde Caballero C, Cabeza Barrera J, Huizinga TW, Guchelaar HJ, Swen JJ.
Pharmacogenomics. 2015 Mar;16(4):373-81.

Towards optimal cut-off trough levels of adalimumab and etanercept for a good therapeutic response in rheumatoid arthritis. Results of the INMUNOREMAR study.

Novel therapeutic targets in rheumatoid arthritis.
Koenders MI, van den Berg WB.
Inflammatory Bowel Diseases


PRISMA--efficacy and safety of vedolizumab for inflammatory bowel diseases: a systematic review and meta-analysis of randomized controlled trials.

Safety of infliximab for the treatment of inflammatory bowel disease: current understanding of the potential for serious adverse events.
Khanna R, Feagan BG.

Comparative efficacy of golimumab, infliximab, and adalimumab for moderately to severely active ulcerative colitis: a network meta-analysis accounting for differences in trial designs.
Thorlund K, Druyts E, Toor K, Mills EJ.

Current, new and future biological agents on the horizon for the treatment of inflammatory bowel diseases.
Amiot A, Peyrin-Biroulet L.

Efficacy and safety of antiintegrin antibody for inflammatory bowel disease: a systematic review and meta-analysis.

Adalimumab trough levels and response to biological treatment in patients with inflammatory bowel disease: a useful cutoff in clinical practice.
Bodini G, Giannini EG, Savarino EV, Savarino V.
Multiple Sclerosis

Update on the Autoimmune Pathology of Multiple Sclerosis: B-Cells as Disease-Drivers and Therapeutic Targets.
von Büdingen HC, Pananichamy A, Lehmann-Horn K, Michel BA, Zamvil SS.

Switching therapies in MS: what are the options?
Markowitz CE.

Endogenous Interferon-β-Inducible Gene Expression and Interferon-β-Treatment Are Associated with Reduced T Cell Responses to Myelin Basic Protein in Multiple Sclerosis.

TRAIL and TRAIL receptors splice variants during long-term interferon β treatment of patients with multiple sclerosis: evaluation as biomarkers for therapeutic response.
J Neurol Neurosurg Psychiatry. 2015 Mar 3.

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Mahad DH, Trapp BD, Lassmann H.

A critical appraisal of daclizumab use as emerging therapy in multiple sclerosis.
D'Amico E, Messina S, Caserta C, Patti F.

Mult Scler. 2015 Feb 19.
Genome-Wide DNA Methylation Profiles Indicate CD8+ T Cell Hypermethylation in Multiple Sclerosis.
Bos SD, Page CM, Andreassen BK, Elboudwarej E, Gustavsen MW, Briggs F, Quach H, Leikfoss IS, Bjølgerud A, Berge T, Harbo HF, Barcellos LF.

Evaluating response to disease-modifying therapy in relapsing multiple sclerosis.
Freedman MS, Abdoli M.

Hemophilia

Biological therapies for inherited diseases: social and bioethical considerations. Hemophilia as an example.
Liras A.

Role of enhanced half-life factor VIII and IX in the treatment of haemophilia.
Mahdi AJ, Obaji SG, Collins PW.

Acquired hemophilia a successfully treated with rituximab.
D'Arena G, Grandone E, Di Minno MN, Musto P, Di Minno G.

Basic immunology

Differentiation and maintenance of long-lived plasma cells.
Kometani K, Kurosaki T.

Primary immunoglobulin repertoire development: time and space matter.
Granato A, Chen Y, Wesemann DR.
The ins and outs of MHC class II-mediated antigen processing and presentation.
Roche PA, Furuta K.

Opinions/Commentaries/Across diseases reviews

Therapeutics to block autoantibody initiation and propagation in systemic lupus erythematosus and rheumatoid arthritis.
Suurmond J, Zou YR, Kim SJ, Diamond B.

Hypersensitivity to biological agents-updated diagnosis, management, and treatment.
Galvão VR, Castells MC.

Regulatory B Cells and Mechanisms.
Rincón-Arévalo H, Sanchez-Parra CC, Castaño D, Yassin L, Vásquez G.
REGULATION

EMA

Scientific guideline: Final guideline on adjustment for baseline covariates in clinical trials
Adopted
March 2015

Adopted
March 2015

Overview of external comments received on the 'Guideline on clinical investigation of medicinal products for the treatment of systemic lupus erythematosus, and lupus nephritis'
March 2015

Human medicines European public assessment report (EPAR): MabThera, rituximab
Revision: 35, Authorised
March 2015

Orphan designation: Vatreptacog alfa (activated)
Updated
March 2015