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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 February 2016 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.

As each month, we are drawing your attention to a selection of articles that we think make a difference in their respective fields.

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 articles

1. A review proposed by our consortium that summarises the different strategies developed to enhance the half-life of FVIII:

**Immunogenicity of long-lasting recombinant factor VIII products.**

2. A discussion around the role of vitamin D in multiple sclerosis, a matter that is highly debated:

**Can vitamin D reduce inflammation in relapsing-remitting multiple sclerosis?**

3. A new demonstration that presence of ADA impairs clinical outcome in rheumatic diseases treated with adalimumab. And a new demonstration that ADA occur very early: in 90% of patients exhibit ADA in the first 4 weeks:

**The clinical relevance of early anti-adalimumab antibodies detection in rheumatoid arthritis, ankylosing spondylitis and psoriatic arthritis: A prospective multicentre study.**
Immunogenicity

Pre-existing Antibody: Biotherapeutic Modality-Based Review.

Secukinumab, a novel anti-IL-17A antibody, shows low immunogenicity potential in human in vitro assays comparable to other marketed biotherapeutics with low clinical immunogenicity.
Karle A, Spindeldreher S, Kolbinger F.
MAbs. 2016 Jan 28

Utility of a Bayesian Mathematical Model to Predict the Impact of Immunogenicity on Pharmacokinetics of Therapeutic Proteins.
AAPS J. 2016 Jan 19

Evaluating and Reporting the Immunogenicity Impacts for Biological Products—a Clinical Pharmacology Perspective.
AAPS J. 2015 Dec 31

Hypersensitivity reactions during treatment with biological agents.
Puxeddu I, Caltran E, Rocchi V, Del Corso I, Tavoni A, Migliorini P.

Using monoclonal antibodies as an international standard for the measurement of anti-adalimumab antibodies.
van Schouwenburg PA, Kruithof S, Wolbink G, Wouters D, Rispens T.

Full validation of therapeutic antibody sequences by middle-up mass measurements and middle-down protein sequencing.
MAbs. 2016 Jan 13:0.
Preventing Aggregation of Recombinant Interferon beta-1b in Solution by Additives: Approach to an Albumin-Free Formulation.

Biosimilars

Clinical data and regulatory issues of biosimilar products.
Stevenson JG.

Biosimilars: A consideration of the regulations in the United States and European union.
Daller J.
Regul Toxicol Pharmacol. 2015 Dec 28

Switching Between Infliximab Originator and Biosimilar in Paediatric Patients with Inflammatory Bowel Disease. Preliminary Observations.

Animal models

An Albumin-Free Formulation for Escherichia coli-Derived Interferon Beta-1b with Decreased Immunogenicity in Immune Tolerant Mice.
Haji Abdolvahab M, Fazeli A, Radmalekshahi M, Nejadnik MR, Fazeli MR, Schellekens H.
J Interferon Cytokine Res. 2016 Jan 29

Recombinant factor VIII Fc (rFVIIIFc) fusion protein reduces immunogenicity and induces tolerance in hemophilia A mice.
Cell Immunol. 2015 Dec 29
Old and new therapeutics for Rheumatoid Arthritis: in vivo models and drug development.
Sardar S, Andersson Å.

Active immunisation targeting soluble murine tumour necrosis factor alpha is safe and effective in collagen-induced arthritis model treatment.

Antibody response to recombinant human coagulation factor VIII in a new rat model of severe hemophilia A.
Lövgren KM, Søndergaard H, Skov S, Weldingh KN, Tranholm M, Wiinberg B.

Biomarkers

Differential methylation as a biomarker of response to etanercept in patients with rheumatoid arthritis.
Arthritis Rheumatol. 2016 Jan 27.

Reduced numbers of mucosal DR(int) macrophages and increased numbers of CD103(+) dendritic cells during anti-TNF-α treatment in patients with Crohn’s disease.

Serum Markers in Rheumatoid Arthritis: A Longitudinal Study of Patients Undergoing Infliximab Treatment.

Smolenska Z, Smolenksi RT, Zdrojewski Z.
Biomarkers. 2016 Jan 26:1-7

Higher expression of TNFα-induced genes in the synovium of patients with early rheumatoid arthritis correlates with disease activity, and predicts absence of response to first line therapy.
Systemic Lupus Erythematosus

**Treat-to-target in systemic lupus erythematosus: are we there yet?**
Mok CC.

**Self-reactive IgE exacerbates interferon responses associated with autoimmunity.**

Arthritis

**Effectiveness and safety of abatacept in elderly patients with rheumatoid arthritis enrolled in the French Society of Rheumatology’s ORA registry.**

**Agreements and Discrepancies between FDA Reports and Journal Papers on Biologic Agents Approved for Rheumatoid Arthritis: A Meta-Research Project.**
Amarilyo G, Furst DE, Woo JM, Li W, Bliddal H, Christensen R, Tarp S.

**Drug-induced hypereosinophilia related to tocilizumab therapy for rheumatoid arthritis.**
Morrisroe K, Wong M.

**Factors associated with choice of biologic among children with juvenile idiopathic arthritis: results from two UK paediatric biologic registers.**
Kearsley-Fleet L, Davies R, Baildam E, Beresford MW, Foster HE, Southwood TR, Thomson W, Hyrich KL.

**Anti-TNFα agents curb platelet activation in patients with rheumatoid arthritis.**
Recent advances in the use of Anti-TNFα therapy for the treatment of juvenile idiopathic arthritis.

Evaluation of golimumab for the treatment of patients with active rheumatoid arthritis.

Biologics beyond TNF-α inhibitors and the effect of targeting the homologues TL1A-DR3 pathway in chronic inflammatory disorders.

A longitudinal genome-wide association study of anti-tumor necrosis factor response among Japanese patients with rheumatoid arthritis.

Rheumatoid factor and anti-citrullinated protein antibody positivity are associated with a better effectiveness of abatacept: Results from the Pan-European registry analysis.

Inflammatory Bowel Diseases

Anti-TNF monotherapy for Crohn’s disease: a 13-year multicentre experience.

Eldelumab [Anti-IP-10] Induction Therapy for Ulcerative Colitis: A Randomised, Placebo-Controlled, Phase 2b Study.
Papamichael K, Mantzaris GJ, Peyrin-Biroulet L.
Expert Opin Drug Saf. 2016 Jan 22

Expert consensus paper on the use of Vedolizumab for the management of patients with moderate-to-severe Inflammatory Bowel Disease.
Armuzzi A, Gionchetti P, Daperno M, Danese S, Orlando A, Lia Scribano M, Vecchi M, Rizzello F; GIVI (Gruppo Italiano su Vedolizumab nelle IBD) Group; GIVI Gruppo Italiano su Vedolizumab nelle IBD Group.
Dig Liver Dis. 2016 Jan 7

Meta-analysis of the effectiveness and safety of vedolizumab for ulcerative colitis.
World J Gastroenterol. 2015 May 28;21(20):6352-60

Integrin-based therapeutics: biological basis, clinical use and new drugs.

Disrupted regulatory T cell homeostasis in inflammatory bowel diseases.
Pedros C, Duguet F, Saoudi A, Chabod M.

Direct effect of infliximab on intestinal mucosa sustains mucosal healing: exploring new mechanisms of action.
Dig Liver Dis. 2015 Dec 19.

Identifying patients at high risk of loss of response to infliximab maintenance therapy in paediatric Crohn's disease.

Adalimumab in pediatric Crohn's disease.
Patel AS, Suarez LD, Rosh JR.

Next-Generation Therapeutics for IBD.
Löwenberg M, D'Haens G.
Multiple Sclerosis


Association of Immunotherapies With Outcomes in Relapsing-Remitting Multiple Sclerosis. Tramacere I, Del Giovane C, Filippini G. JAMA. 2016 Jan 26;315(4):409-10


Cytokine-Defined B Cell Responses as Therapeutic Targets in Multiple Sclerosis.

Hemophilia

B-cell memory against factor VIII
Reipert BM. Cell Immunol. 2016 Jan 6

A subset of high titer anti-factor VIII A2 domain antibodies are responsive to treatment with factor VIII.

Molecular design and downstream processing of turoctocog alfa (NovoEight), a B-domain truncated factor VIII molecule.


Basic immunology

Polysialylation controls dendritic cell trafficking by regulating chemokine recognition.

Autophagy enforces functional integrity of regulatory T cells by coupling environmental cues and metabolic homeostasis.

CD4+T cell anergy prevents autoimmunity and generates regulatory T cell precursors.
Opinions/Commentaries/Across diseases reviews

The thymus and rheumatology: should we care?
Cosway E, Anderson G, Garside P, Prendergast C.

Is rheumatoid arthritis an autoimmune disease?
Chemin K, Klareskog L, Malmström V.
Curr Opin Rheumatol. 2016 Mar;28(2):181-8

Subgroup analysis in MS trials.
Sormani MP.

Alterations in immune function with biologic therapies for autoimmune disease.
Her M, Kavanaugh A.

The biology behind interleukin-6 targeted interventions.
Liu X, Jones GW, Choy EH, Jones SA.

MS arising during Tocilizumab therapy for rheumatoid arthritis.
Beauchemin P, Carruthers R.

Comabella M.

AVX-470, an Orally Delivered Anti-TNF Antibody for Treatment of Active Ulcerative Colitis: Results of a First-in-Human Trial.
Harris MS, Hartman D, Lemos BR, Erlich EC, Spence S, Kennedy S, Ptak T, Pruitt R, Vermeire S, Fox BS.

Market watch: Upcoming market catalysts in Q4 2015.
Liu M.
Make journals report clinical trials properly.
Goldacre B.

Authorized manufacturing changes of therapeutic monoclonal antibodies (mAbs) in European Public Assessment Report (EPAR) documents.
Vezér B, Buzás Z, Sebeszta M, Zrubka Z.

REGULATION

EMA

Human medicines European public assessment report (EPAR): Humira, adalimumab
Revision: 43, Authorised
January 2016

Human medicines European public assessment report (EPAR): Benepali, etanercept
Revision: 0, Authorised
January 2016

Human medicines European public assessment report (EPAR): Inflectra, infliximab
Revision: 9, Authorised
January 2016

Workshop on immunogenicity assessment of biotechnology-derived therapeutic proteins

Human medicines European public assessment report (EPAR): Plegridy, peginterferon beta-1a
Revision: 7, Authorised
January 2016
Recombinant porcine factor VIII (B-domain-deleted)
Orphan designation:
Updated
January 2016

Recombinant fusion protein consisting of human coagulation factor VIII attached to the Fc domain of human IgG1 for the: Treatment of haemophilia A
Orphan designation
Updated
January 2016

Human medicines European public assessment report (EPAR): Enbrel, etanercept
Revision: 47, Authorised
January 2016

Opinion/decision on a Paediatric investigation plan (PIP): RoActemra, tocilizumab
Therapeutic area: Immunology-Rheumatology-Transplantation
Updated
January 2016