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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 August 2016 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.

Each month we draw 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
This month's selected articles

1. There is a scaring paucity of evaluation of the socio-economic impact of NAB. This paper addresses this issue and should encourage others to do similar, not only in the field of IFNb

The Cost of Relapsing-Remitting Multiple Sclerosis Patients Who Develop Neutralizing Antibodies during Interferon Beta Therapy.

2. Ettinger et al demonstrate the immunodominant T cell response to a single peptide from FVIII in an inhibitor positive subject. They show that this epitope is also recognized by two other patients with inhibitors. Additionally, TCR sequencing demonstrated that all high-avidity clones and 94% of all clones expressed the same TCRB gene. The authors suggest the limited breadth of the immune response should facilitate the induction of tolerance. Additional note: In silico predictions for this epitope were: IEDB (‘weak’ binder – top 7%), EpiVax (‘strong’ binder – top 1%).

T cells from three Hemophilia A subjects recognized the same HLA-restricted FVIII epitope with a narrow TCR repertoire.
Ettinger RA, Paz P, James EA, Gunasekera D, Aswad F, Thompson AR, Matthews DC, Pratt KP.

3. It is the second paper which shows the absence of immunogenicity of tocilizumab the anti-IL6R mAb, one of the best treatments of RA. And the reason for this remains a mystery

Immunogenicity of tocilizumab in patients with rheumatoid arthritis.
Immunogenicity

*Incidence, characterization, and clinical impact analysis of peginterferon beta1a immunogenicity in patients with multiple sclerosis in the ADVANCE trial.*

*Evaluating Immunogenicity Risk Due to Host Cell Protein Impurities in Antibody-Based Biotherapeutics.*

*Infliximab and CT-P13 immunogenicity assessment in PLANETAS and PLANETRAS main and extension studies: utility of laboratory methods description.*

Methods

*Classification model of amino acid sequences prone to aggregation of therapeutic proteins.*

*Preexisting Antibodies to an F(ab’)2 Antibody Therapeutic and Novel Method for Immunogenicity Assessment.*

*Is an in vitro whole blood cytokine assay useful to detect the potential risk of severe infusion reaction of monoclonal antibody pharmaceuticals?*
Biomarkers

Identification of baseline gene expression signatures predicting therapeutic responses to three biologic agents in rheumatoid arthritis: a retrospective observational study.

Serum tocilizumab trough concentration can be used to monitor systemic IL-6 receptor blockade in patients with rheumatoid arthritis: a prospective observational cohort study.
Kneepkens EL, van den Oever I, Plasencia CH, Pascual-Salcedo D, de Vries A, Hart M, Nurmoohamed MT, Balsa A, Rispens T, Wolbink G.

Biosimilars

Hodgkinson L.

A randomised, single-blind, single-dose, three-arm, parallel-group study in healthy subjects to demonstrate pharmacokinetic equivalence of ABP 501 and adalimumab.
Ann Rheum Dis. 2016 Jul 27

’Lower anti-drug antibodies with etanercept biosimilar: can Ctrough explain the differences?’
Shah CA.

Response to: ’Lower anti-drug antibodies with etanercept biosimilar: Can Ctrough explain the differences’ by Shah.
Animal models

Ingested (oral) rituximab inhibits EAE.
Brod SA.
Cytokine. 2016 Sep;85:177-83.

Recombinant soluble IFN receptor (sIFNAR2) exhibits intrinsic therapeutic efficacy in a murine model of Multiple Sclerosis.

Adjuvants- and vaccines-induced autoimmunity: animal models.
Ruiz JT, Luján L, Blank M, Shoenfeld Y.

In Vivo Expansion of Activated Foxp3+ Regulatory T Cells and Establishment of a Type 2 Immune Response upon IL-33 Treatment Protect against Experimental Arthritis.

Systemic Lupus Erythematosus

1.

Recent advances in the biologic therapy of lupus: the 10 most important areas to look for common pitfalls in clinical trials.
Medina-Rosas J, Al-Rayes H, Moustafa AT, Touma Z.

Therapeutic monitoring of the immuno-modulating drugs in systemic lupus erythematosus.
Mok CC.
Belimumab decreases flare rate and hinders the expected damage progression in patients with active systemic lupus erythematosus.

Post-hoc analysis of the Phase II/III APRIL-SLE study: Association between response to atacicept and serum biomarkers including BLyS and APRIL.
Gordon C, Wofsy D, Wax S, Li Y, Pena Rossi C, Isenberg D.

Arthritis

Room for more IL-6 blockade? Sarilumab for the treatment of rheumatoid arthritis.
June RR, Olsen NJ.

BAFF inhibition does not significantly impair immunization responses in patients with rheumatoid arthritis.
Bingham CO 3rd, Winthrop KL, Yang L, Lee C, Komocsar WJ.
Arthritis Res Ther. 2015 Nov 30;17:347..

Understanding inflammation in juvenile idiopathic arthritis: How immune biomarkers guide clinical strategies in the systemic onset subtype.
Swart JF, de Roock S, Prakken BJ.

Secukinumab for rheumatology: development and its potential place in therapy.
Koenders MI, van den Berg WB.

Drug survival of adalimumab in patients with rheumatoid arthritis over 10 years in the real-world settings: high rate remission together with normal function ability.
Effectiveness and safety of tocilizumab in achieving clinical and functional remission, and sustaining efficacy in biologics-naive patients with rheumatoid arthritis: The FIRST Bio study.
Mod Rheumatol. 2016 Jul 14:1-10

Pharmacokinetics, Pharmacodynamics, Safety, and Tolerability of ASP2408, a Potent Selective T-Cell Costimulation Modulator After Single and Multiple Ascending Doses in Healthy Volunteers and RA Patients.

Canakinumab for the treatment of active systemic juvenile idiopathic arthritis.
Orrock JE, Ilowite NT.

Inflammatory Bowel Disease

Ustekinumab for the treatment of Crohn's disease.
Hansen T, Targownik LE.

CT-P13 (Inflectra™, Remsima™) monitoring in patients with inflammatory bowel disease.
Biologicals. 2016 Jul 16.

Bek S, Nielsen JV, Bojesen AB, Franke A, Bank S, Vogel U, Andersen V.

Advances in the development of new biologics in inflammatory bowel disease.
Ungar B, Kopylov U.
Safety of Long-Term Treatment With Certolizumab Pegol in Patients with Crohn's Disease, Based on a Pooled Analysis of Data From Clinical Trials.

Pharmacokinetics and Exposure-Response Relationship of Golimumab in Patients with Moderately-to-Severely Active Ulcerative Colitis: Results from Phase 2/3 PURSUIT Induction and Maintenance Studies.

Next-Generation Therapeutics for Inflammatory Bowel Disease.
Dulai PS, Sandborn WJ.

Current approaches for optimizing the benefit of biologic therapy in ulcerative colitis.
Sofia MA, Rubin DT.

Multiple Sclerosis

van Pesch V, Sindic CJ, Fernández O.

Safety and efficacy of daclizumab in relapsing-remitting multiple sclerosis: 3-year results from the SELECTED open-label extension study.

Role of IL-17-producing lymphocytes in severity of multiple sclerosis upon natalizumab treatment.
Design of TRUST, a non-interventional, multicenter, 3-year prospective study investigating an integrated patient management approach in patients with relapsing-remitting multiple sclerosis treated with natalizumab.

Use of natalizumab in multiple sclerosis: current perspectives.

Hemophilia

Comparative pharmacokinetics of rVIII-SingleChain and octocog alfa (Advate®) in patients with severe haemophilia A.

Innovating immune tolerance induction for haemophilia.
Batsuli G, Meeks SL, Herzog RW, Lacroix-Desmazes S.

Rituximab for eradicating inhibitors in people with acquired haemophilia A.
Zeng Y, Zhou R, Duan X, Long D.

Potential role of a new PEGylated recombinant factor VIII for hemophilia A.
Wynn TT, Gumuscu B.
Basic immunology

Down-Regulation of Surface CD28 under Belatacept Treatment: An Escape Mechanism for Antigen-Reactive T-Cells.
de Graov GN, Hesselink DA, Dieterich M, Kraaijeveld R, Weimar W, Baan CC.
PLoS One. 2016 Feb 26;11(2):e0148604

Opinions/Commentaries/ Across diseases reviews

New Alternatives for Autoimmune Disease Treatments: Physicochemical and Clinical Comparability of Biosimilar Etanercept.

Pharmacokinetics interactions of monoclonal antibodies.
Ferri N, Bellosta S, Baldessin L, Bocca D, Racagni G, Corsini A.
Pharmacol Res. 2016 Jul 18;111:592-599.

Etanercept (SB4): A Review in Autoimmune Inflammatory Diseases.
Burness CB, Duggan ST.
BioDrugs. 2016 Jul 25
Scientific guideline: Draft review and update of EMA guidelines to implement best practice with regard to 3Rs (replacement, reduction and refinement) in regulatory testing of medicinal products – report on actions taken
Draft: consultation open

Scientific guideline: Draft guideline on the qualification and reporting of physiologically based pharmacokinetic (PBPK) modelling and simulation
Draft: consultation open

Human medicines European public assessment report (EPAR): Orencia, abatacept
Revision: 22, Authorised

Human medicines European public assessment report (EPAR): Humira, adalimumab
Revision: 48, Authorised

Human medicines European public assessment report (EPAR): Remicade, infliximab
Revision: 46, Authorised

Human medicines European public assessment report (EPAR): Flixabi, infliximab
Revision: 1, Authorised

Referral: Article 31 referrals, Factor VIII

Scientific guideline: Concept paper on the revision of the 'Guideline on strategies to identify and mitigate risks for first-in-human clinical trials with investigational medicinal products'
Draft: consultation open
Workshop on immunogenicity assessment of biotechnology-derived therapeutic proteins - Workshop summary:

Draft: consultation open

The research leading to these results has received support from the Innovative Medicines Initiative Joint Undertaking under grant agreement n° [115303], resources of which are composed of financial contribution from the European Union’s Seventh Framework Programme (FP7/2007-2013) and EFPIA companies’ in kind contribution.