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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.

WELCOME

Dear Reader,

We would like to welcome you to the July 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.

From now on, we will draw your attention to a selection of articles each month 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. This review highlights what is apparent to many in the industry, namely that improvements in assay sensitivity and drug tolerance in recent years is leading to detection of higher incidences of ADA. The paper includes a lengthy section on confirming samples as true positives. The observations for natalizumab, infliximab and adalimumab will be of interest to the ABIRISK audience. The review concludes with the need to understand the impact of the ADA, through further characterizing the ADA positive population:

    Understanding the Supersensitive Anti-Drug Antibody Assay: Unexpected High Anti-Drug Antibody Incidence and Its Clinical Relevance.
    Song S, Yang L, Trepicchio WL, Wyant T.
    J Immunol Res. 2016;2016:3072586

2. It is the first demonstration in a strategy trial that the use in front line therapy of a biologic which is here anti-IL6R tocilizumab could be beneficial in RA vs the classical approach with MTX alone :

    Early rheumatoid arthritis treated with tocilizumab, methotrexate, or their combination (U-Act-Early): a multicentre, randomised, double-blind, double-dummy, strategy trial.
    Bijlsma JW, Welsing PM, Woodworth TG, Middelink LM, Pethö-Schramm A, Bernasconi C, Borm ME, Wortel CH, Ter Borg EJ, Jahangier ZN, van der Laan WH, Bruyn GA, Baudoin P, Wijngaarden S, Vos PA, Bos R, Starmans MJ, Griep EN, Griep-Wentink JR, Allaart CF, Heurkens AH, Teitsma XM, Tekstra J, Marijnissen AC, Lafeber FP, Jacobs JW.
    Lancet. 2016 Jun 7

3. Very interesting paper which shows a difference regarding Treg stimulation between adalaimumab ans etanercept due to a paradoxical stimulation on membrane TNF by Adalimumab which does not exists with etanaecrpt which binds poorly membrane TNF :

    Anti-TNF drives regulatory T cell expansion by paradoxically promoting membrane TNF-TNF-RII binding in rheumatoid arthritis.
    Nguyen DX, Ehrenstein MR.
    J Exp Med. 2016 Jun 27;213(7):1241-53.

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Immunogenicity

The role of neutralizing antibodies to interferon-β as a biomarker of persistent MRI activity in multiple sclerosis: a 7-year observational study.
Paolicelli D, Manni A, Iaffaldano A, Di Lecce V, D'Onghia M, Iaffaldano P, Trojano M.
Eur J Clin Pharmacol. 2016 Jun 1.

Methods

Comparison of originator and biosimilar therapeutic monoclonal antibodies using comprehensive two-dimensional liquid chromatography coupled with time-of-flight mass spectrometry.
Sorensen M, Harmes DC, Stoll DR, Staples GO, Fekete S, Guillarme D, Beck A.
MAbs. 2016 Jun 30:0.

Whole cell-based surface plasmon resonance measurement to assess binding of anti-TNF agents to transmembrane target.
Ogura T, Tanaka Y, Toyoda H.
Anal Biochem. 2016 Jun 24.

Rational Design of Biobetters with Enhanced Stability.
Courtois F, Schneider CP, Agrawal NJ, Trout BL.
J Pharm Sci. 2015 Aug;104(8):2433-40.

Characterisation of Stress-Induced Aggregate Size Distributions and Morphological Changes of a Bi-Specific Antibody Using Orthogonal Techniques.
Hamrang Z, Hussain M, Tingey K, Tracka M, Casas-Finet JR, Uddin S, van der Walle CF, Pluen A.
J Pharm Sci. 2015 Aug;104(8):2473-81.

Animal models

Epratuzumab modulates B-cell signalling without affecting B-cell numbers or B- cell functions in a mouse model with humanised CD22.
Özgör L, Brandl C, Shock A, Nitschke L.
Eur J Immunol. 2016 Jun 29.

Biomarkers

Anti-citrullinated peptide antibodies and their value for predicting responses to biologic agents: a review.
Martin-Mola E, Balsa A, García-Vicuna R, Gómez-Reino J, González-Gay MA, Sanmartí R, Loza E.
Rheumatol Int. 2016 Jun 6.

Assessment of IL-17A, IL-10 and TGF-beta1 serum titers in RRMS patients treated with Avonex, possible biomarkers for treatment response.
Bălaşa R, Maier S, Voidăzan S, Huţanu A, Bajkó Z, Moţăţăianu A, Tilea B, Tiu C.
CNS Neurol Disord Drug Targets. 2016 Jun 15.

Natalizumab Therapy Modulates miR-155, miR-26a and Proinflammatory Cytokine Expression in MS Patients.
Mameli G, Arru G, Caggiu E, Niegowska M, Leoni S, Madeddu G, Babudieri S, Sechi GP, Sechi LA.
PLoS One. 2016 Jun 16;11(6):e0157153.

Genetic and clinical biomarkers of tocilizumab response in patients with rheumatoid arthritis.
Maldonado-Montoro M, Cañadas-Garre M, González-Utrilla A, Plaza-Plaza JC, Calleja-Hernández MÁ.
Pharmacol Res. 2016 Jun 20.

Biosimilars

Evaluation of the structural, physicochemical, and biological characteristics of SB4, a biosimilar of etanercept.
Cho IH, Lee N, Song D, Jung SY, Bou-Assaf G, Sosic Z, Zhang W, Lyubarskaya Y.
MAbs. 2016 May 31:0.

Comparison of the pharmacokinetics, safety, and immunogenicity of MSB11022, a biosimilar of adalimumab, with Humira® in healthy subjects.
Hyland E, Mant T, Vlachos P, Attkins N, Ullmann M, Roy S, Wagner V.
Br J Clin Pharmacol. 2016 Jun 10.

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Systemic Lupus Erythematosus

Update on clinical trials in systemic lupus erythematosus.
Narain S, Furie R.
Curr Opin Rheumatol. 2016 Jun 16.

Arthritis

Rheumatoid arthritis: U-Act-Early finds tocilizumab favours RA remission.
Barranco C.
Nat Rev Rheumatol. 2016 Jun 23.

Efficacy and safety of an anti-CD20 monoclonal antibody (Reditux™) for the treatment of patients with moderate to severe rheumatoid arthritis following the failure of conventional synthetic disease-modifying anti-rheumatic drugs.
Bhati M, Bandyopadhyay S.
Clin Rheumatol. 2016 Jun 22.

Biologics in Pediatric Rheumatology: Quo Vadis?
Sterba Y, Ilowite N.
Curr Rheumatol Rep. 2016 Jul;18(7):45.

Rheumatoid arthritis: Adalimumab drives Treg cell expansion via membrane TNF.
Onuora S.
Nat Rev Rheumatol. 2016 Jun 23. doi: 10.1038/nrrheum.2016.109.

Safety of Repeated Open-Label Treatment Courses of Intravenous Ofatumumab, a Human Anti-CD20 Monoclonal Antibody, in Rheumatoid Arthritis: Results from Three Clinical Trials.
Quattrocchi E, Østergaard M, Taylor PC, van Vollenhoven RF, Chu M, Mallett S, Perry H, Kurrasch R.
PLoS One. 2016 Jun 23;11(6):e0157961

Inflammatory Bowel Diseases

Predicting Outcomes to Optimize Disease Management in Inflammatory Bowel Diseases.
Torres J, Caprioli F, Katsanos KH, Lobatón T, Micic D, Zerôncio M, Van Assche G, Lee JC, Lindsay JO, Rubin DT, Panaccione R, Colombel JF.
J Crohns Colitis. 2016 Jun 9.

Vedolizumab compared with certolizumab in the therapy of Crohn's disease: a systematic review and indirect comparison.
Kawalec P, Moćko P, Pilc A, Radziwon-Zalewska M, Malinowska-Lipień I.
Pharmacotherapy. 2016 Jun 13.

The Next Wave of Biological Agents for the Treatment of IBD: Evidence from Cochrane Reviews.
Khanna R, Chande N, Vermeire S, Sandborn WJ, Parker CE, Feagan BG.
Inflamm Bowel Dis. 2016 Jul;22(7):1737-43.

Safety profile of biologic drugs in the therapy of ulcerative colitis: a systematic review and network meta-analysis.
Moćko P, Kawalec P, Pilc A.
Pharmacotherapy. 2016 Jun 17.

Considerations, challenges and future of anti-TNF therapy in treating inflammatory bowel disease.
Pouillon L, Bossuyt P, Peyrin-Biroulet L.
Expert Opin Biol Ther. 2016 Jun 22.

Multiple Sclerosis

Interferon-β therapy specifically reduces pathogenic memory B cells in Multiple Sclerosis patients by inducing a FAS-mediated apoptosis.
Rizzo F, Giacomini E, Mechelli R, Buscarinu MC, Salvetti M, Severa M, Coccia EM.
Immunol Cell Biol. 2016 Jun 6.

Population PK-PD Analyses of CD25 Occupancy, CD56bright NK Cell Expansion, and Regulatory T Cell Reduction by Daclizumab HYP in Subjects with Multiple Sclerosis.
Diao L, Hang Y, Othman AA, Mehta D, Amaravadi L, Nestorov I, Tran JQ.
Br J Clin Pharmacol. 2016 Jun 22.

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Immunological treatment of multiple sclerosis.
Diebold M, Derfuss T.
Semin Hematol. 2016 Apr;53 Suppl 1:S54-7

New insights into the pharmacokinetics and pharmacodynamics of natalizumab treatment for patients with multiple sclerosis, obtained from clinical and in vitro studies.
Sehr T, Proschmann U, Thomas K, Marggraf M, Straube E, Reichmann H, Chan A, Ziemssen T.
J Neuroinflammation. 2016 Jun 27;13(1):164.

Reduced inflammation in relapsing-remitting multiple sclerosis after therapy switch to rituximab.
de Flon P, Gunnarsson M, Laurell K, Söderström L, Birgander R, Lindqvist T, Krauss W, Dring A, Bergman J, Sundström P, Svenningsson A.
Neurology. 2016 Jun 17.

Assessing response to interferon-β in a multicenter dataset of patients with MS.
Sormani MP, Gasperini C, Romeo M, Rio J, Calabrese M, Cocco E, Enzingher C, Fazekas F, Filippi M, Gallo A, Kappos L, Marrosu MG, Martinelli V, Prosperini L, Rocca MA, Rovira A, Sprenger T, Stromillo ML, Tedeschi G, Tintorè M, Tortorella C, Trojano M, Montalban X, Pozzilli C, Comi G, De Stefano N; MAGNIMS study group.
Neurology. 2016 Jun 15.

Hemophilia

Efficacy and safety of BAY 81-8973, a full-length recombinant factor VIII: results from the LEOPOLD I trial.
Saxena K, Lalezari S, Oldenburg J, Tseneklidou-Stoeter D, Beckmann H, Yoon M, Maas Enriquez M.
Haemophilia. 2016 Jun 24.

Efficacy and safety of rVIII-SingleChain: results of a phase I/III multicenter clinical trial in severe hemophilia A.
Mahlangu J, Kuliczkowski K, Abdul Karim F, Stasyshyn O, Kosinova MV, Lepatan LM, Skotnicki A, Boggio LN, Klamroth R, Oldenburg J, Hellman A, Santagostino E, Baker RI, Fischer K, Gill JC, P'Ng S, Chowdary P, Escobar MA, Djambas Khayat C, Rusen L, Bensen-Kennedy D, Blackman N, Limsakun T, Veldman A, St Ledger K, Pabinger I.
Blood. 2016 Jun 21.

The story of a unique molecule in hemophilia A: recombinant single-chain factor VIII.
Pabinger-Fasching I.
Thromb Res. 2016 May;141 Suppl 3:S2-4.

Opinions/Commentaries/Across diseases reviews

An Overview of the Mechanism of Action of the Monoclonal Antibody Vedolizumab.
Wyant T, Fedyk E, Abhyankar B.
J Crohns Colitis. 2016 Jun 1. pii: jjw092. [Epub ahead of print] Review.

Could therapeutic drug monitoring of anti-TNF-α be useful to consider a de-escalation of treatment?
Flamant M, Roblin X.
Expert Opin Biol Ther. 2015;15(11):1657-60.

Optimising B-cell depletion in autoimmune disease: is obinutuzumab the answer?
Reddy V, Dahal LN, Cragg MS, Leandro M.
Drug Discov Today. 2016 Jun 22.

REGULATION

EMA

Multidisciplinary: biosimilar (updated)
June 2016

Orphan designation: Recombinant humanised anti-human interleukin-1 beta monoclonal antibody
for the: Treatment of Behçet's disease (updated)

Pending EC decision: RoActemra, tocilizumab
Opinion date: 23-Jun-2016

Human medicines European public assessment report (EPAR): MabThera, rituximab
Revision: 37, Authorised

Human medicines European public assessment report (EPAR): Humira, adalimumab
Revision: 46, Authorised

Human medicines European public assessment report (EPAR): RoActemra, tocilizumab
Revision: 19, Authorised

Human medicines European public assessment report (EPAR): Flixabi, infliximab
Revision: 0, Authorised

Human medicines European public assessment report (EPAR): Entyvio, vedolizumab
Revision: 6, Authorised

Opinion/decision on a Paediatric investigation plan (PIP): Cimzia, Certolizumab pegol
Therapeutic area: Dermatology

Opinion/decision on a Paediatric investigation plan (PIP): Ixekizumab
Therapeutic area: Immunology-Rheumatology-Transplantation (updated)

Opinion/decision on a Paediatric investigation plan (PIP): Humira, Adalimumab
Therapeutic area: Dermatology/Immunology-Rheumatology-
Transplantation/Ophthalmology/Gastroentology-Hepatology (updated)

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