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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.

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WELCOME

Dear Reader,

We would like to welcome you to the first issue of the **ABIRISK Scientific Newsletter**. The Scientific Newsletter will give you a monthly update on the most relevant literature related to ABIRISK areas of research published around the globe, both inside and outside ABIRISK consortium.

Active links to PubMed will lead you to papers' abstracts on various subjects, such as new findings on pathogenesis and treatment of hemophilia A, multiple sclerosis, rheumatoid arthritis and inflammatory bowel diseases, biomarkers, biopharmaceuticals immunogenicity, anti-drug antibodies detection methods, and some basic immunology reports. In the section 'This month's selected paper', we will provide a brief summary of context and findings of one particular paper we chose to highlight.

In addition, in some issues you will also find updates on international regulation on the production and use of biopharmaceuticals as well as alerts/reminders about forthcoming scientific events of interest.

We hope you will enjoy this monthly literature round-up and look forward to your visit on **ABIRISK** website for more information and updates on the program.

Best wishes

The ABIRISK management team

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LITERATURE

This month's selected article

Comparing the long-term clinical outcome of etanercept and adalimumab treatment with respect to immunogenicity.
Krieckaert CL, Jamnitski A, Nurmohamed MT, Kostense PJ, Boers M, Wolbink G.
Arthritis Rheum. 2012 Aug 29.

In this paper, Krieckaert and colleagues continue the analysis of the set of data collected from two prospective long term follow-up RA patient cohorts run between 2004 and 2010 at the Rheumatology department of the Jan van Breemen Research Institute, Reade, Amsterdam, in which 292 patients were treated with etarnercept and 272 patients were treated with adalimumab.
Previous analysis of the adalimumab cohort data revealed that the development of antidrug antibodies was associated with lower adalimumab concentration and lower likelihood of minimal disease activity or clinical remission (Bartelds, JAMA 2011). In parallel, analysis of the etarnecept cohort showed a significant association between clinical response and serum etanercept levels. Of note, no antibodies to etarnercept could be detected in the serum of treated patients (Jamnitski, Ann Rheum Dis.,2012).

In the present study, the authors sought to compare the efficacy of etarnecept and adalimumab and to relate it to the development of anti-adalimumab antibodies (AAA). Achievement of clinical outcome was defined as the occurrence of sustained (at least 12 consecutive months) low disease activity (sLDA; DAS28 <3.2), minimal disease activity (sMDA; DAS28 <2.6) or ACR/EULAR remission (sSDAI).
Overall, etanercept and adalimumab treatment appeared similar in inducing a good long-term clinical outcome (3 year follow-up). However, in the case of adalimumab this was strongly dependent on the presence or absence of AAA, as previously observed. Differences were most apparent in the sSDAI and sMDA categories. For example, 40% of AAA (-) , 23% of etanercept and 4% of AAA (+) patients achieved at least sMDA.

The authors state in the discussion that *'instead of just taking clinical parameters into account, it is necessary to identify pharmacokinetic factors of the drug, in order to come to a more personalized medicine approach in the treatment with these costly therapeutics. In addition, identifying patients at high risk for the development of AAA and investigating ways of dealing with immunogenicity are needed to optimize treatment*'.

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Immunogenicity

Antibody Response Against Betaferon® in Immune Tolerant Mice: Involvement of Marginal Zone B-cells and CD4+ T-cells and Apparent Lack of Immunological Memory.
Sauerborn M, van Beers MM, Jiskoot W, Kijanka GM, Boon L, Schellekens H, Brinks V.
J Clin Immunol. 2012 Sep 4.

A major determinant of the immunogenicity of factor VIII in a murine model is independent of its procoagulant function.
Meeks SL, Cox CL, Healey JF, Parker ET, Doshi BS, Gangadharan B, Barrow RT, Lollar P.
Blood. 2012 Jul 31

Antibodies against polyethylene glycol in healthy subjects and in patients treated with PEG-conjugated agents.
Garay RP, El-Gewely R, Armstrong JK, Garratty G, Richette P.
Expert Opin Drug Deliv. 2012 Aug 30.

Immunogenicity of different stressed IgG monoclonal antibody formulations in immune tolerant transgenic mice.
Filipe V, Jiskoot W, Basmeleh AH, Halim A, Schellekens H, Filipe V.
MAbs. 2012 Sep 5;4(6)

Anti-drug antibodies
Clemens Warnke, Christina Hermanrud, Malin Lundkvist, Anna Fogdell-Hahn
Drugs and Therapy Studies. Vol 2, No 1 (2012)

Source and purity of factor VIII products as risk factors for inhibitor development in patients with hemophilia A.
Mancuso ME, Mannucci PM, Rocino A, Garagiola I, Tagliaferri A, Santagostino E.
J Thromb Haemost. 2012 May;10(5):781-90

F8 gene mutation type and inhibitor development in patients with severe hemophilia A: systematic review and meta-analysis.
Gouw SC, van den Berg HM, Oldenburg J, Astermark J, de Groot PG, Margaglione M, Thompson AR, van Heerde W, Boekhorst J, Miller CH, le Cessie S, van der Bom JG.
Blood. 2012 Mar 22;119(12):2922-34.

Highly aggregated antibody therapeutics can enhance the in vitro innate and late-stage T-cell immune responses.
Joubert MK, Hokom M, Eakin C, Zhou L, Deshpande M, Baker MP, Goletz TJ, Kerwin BA, Chirmule N, Narhi LO, Jawa V.
J Biol Chem. 2012 Jul 20;287(30):25266-79

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Methods

Detection of infliximab levels and anti-infliximab antibodies: a comparison of three different assays.
Casteele NV, Buurman DJ, Sturkenboom MG, Kleibeuker JH, Vermeire S, Rispens T, van der Kleij D, Gils A, Dijkstra G.
Aliment Pharmacol Ther. 2012 Aug 28.

Universal Immunoassay Applied During Early Development of Large Molecules to Understand Impact of Immunogenicity on Biotherapeutic Exposure
Bautista AC, Salimi-Moosavi H, Jawa V.
AAPS J. 2012 Sep 1.

The assay design used for measurement of therapeutic antibody concentrations can affect pharmacokinetic parameters: Case studies.
Fischer SK, Yang J, Anand B, Cowan K, Hendricks R, Li J, Nakamura G, Song A.
MAbs. 2012 Sep 1;4(5)

On silico peptide microarrays for high-resolution mapping of antibody epitopes and diverse protein-protein interactions.
Price JV, Tangsombatvisit S, Xu G, Yu J, Levy D, Baechler EC, Gozani O, Varma M, Utz PJ, Liu CL.
Nat Med. 2012 Aug 19.

Biomarkers

Serum IL-17F does not predict poor response to IM IFNβ-1a in relapsing-remitting MS
Bushnell SE, Zhao Z, Stebbins CC, Cadavid D, Buko AM, Whalley ET, Davis JA, Versage EM, Richert JR, Axtell RC, Steinman L, Medori R.
Neurology. 2012 Aug 7;79(6):531-7

Influence of polymorphisms and TNF and IL1β serum concentration on the infliximab response in Crohn's disease and ulcerative colitis.
Lacruz-Guzmán D, Torres-Moreno D, Pedrero F, Romero-Cara P, García-Tercero I, Trujillo-Santos J, Conesa-Zamora P.
Eur J Clin Pharmacol. 2012 Sep 8.

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Changes in proliferation kinetics of T cells: a new predictive cellular biomarkers for early rheumatoid arthritis?
Pawłowska J, Smoleńska Z, Zdrojewski Z, Witkowski JM, Bryl E.
J Clin Immunol. 2012 Oct;32(5):991-9.

Rheumatoid Arthritis

Rituximab is more effective than second anti-TNF therapy in rheumatoid arthritis patients and previous TNFα blocker failure.
Kekow J, Mueller-Ladner U, Schulze-Koops H.
Biologics. 2012;6:191-9

Simultaneous targeting of TNF and Ang2 with a novel bispecific antibody enhances efficacy in an in vivo model of arthritis.
Kanakaraj P, Puffer BA, Yao XT, Kankanala S, Boyd E, Shah RR, Wang G, Patel D, Krishnamurthy R, Kaithamana S, Smith RG, Lafleur DW, Hilbert DM, Kiener PA, Roschke VV.
MAbs. 2012 Sep 1;4(5).

Adalimumab in the treatment of rheumatoid arthritis.
Voulgari PV, Kaltsonoudis E, Papagoras C, Drosos AA.
Expert Opin Biol Ther. 2012 Sep 6.

Multiple Sclerosis

Clinical relevance of serum natalizumab concentration and anti-natalizumab antibodies in multiple sclerosis.
Vennegoor A, Rispens T, Strijbis EM, Seewann A, Uitdehaag BM, Balk LJ, Barkhof F, Polman CH, Wolbink G, Killestein J.
Mult Scler. 2012 Sep 19

Hemophilia

PEGylated therapeutic proteins for haemophilia treatment: a review for haemophilia caregivers.
Ivens IA, Baumann A, McDonald TA, Humphries TJ, Michaels LA, Mathew P.
Haemophilia. 2012 Aug 23. doi: 10.1111/j.1365-2516.2012.02931.x.

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Basic immunology

Endogenous antigen tunes the responsiveness of naive B cells but not T cells.
Zikherman J, Parameswaran R, Weiss A.
Nature. 2012 Aug 19

Opinions/Commentaries

Alemtuzumab more effective than interferon β-1a at 5-year follow-up of CAMMS223 clinical trial
Deisenhammer F, Hegen H.
Neurology. 2012 Sep 4;79(10):1071-2

(Meta)analyze this: Systematic reviews might lose credibility
Peter Humaidan & Nikolaos P Polyzos
Nature Medicine 18,1321,(2012)

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