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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,

Welcome to the March 2013 issue of **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 selected a publication by Paolicelli et al. reporting on the impact of neutralizing antibodies on interferon β efficacy in Multiple Sclerosis patients.

In addition, you will find in this issue some news on biopharmaceuticals regulation and a list of ABIRISK topics-related scientific meetings taking place in April-July 2013.

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

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LITERATURE

This month's selected article

The impact of neutralizing antibodies on the risk of disease worsening in interferon β-treated relapsing multiple sclerosis: a 5 year post-marketing study.
Paolicelli D, D'Onghia M, Pellegrini F, Direnzo V, Iaffaldano P, Lavolpe V, Trojano M.
J Neurol. 2013 Feb 17.

A high percentage of Multiple Sclerosis (MS) patients will develop antibodies to IFNβ during biotherapy. Depending on the method used to detect them, these antibodies will be classified either as Binding (BAbs) or Neutralizing (NAbs) Antibodies. The impact of the latter on treatment efficacy remains unclear, as dissimilar outcomes have been observed in randomised controlled trials. Here, Paolicelli et al. report on a prospective, longitudinal, observational study in MS patients intended to specifically evaluate the risk of disease worsening linked to the development of NAbs to IFNβ.

The study was conducted on 567 Relapsing-Remitting MS (RRMS) patients treated with either Betaseron®, Avonex® , Rebif 22® or Rebif 44®. All patients had been treated for at least 2 years without IFNβ type switch at the time of enrolment. Sera were collected every 6-12 months for up to 5 years and evaluated for the presence of anti-IFNβ NAbs using a cytopathic effect assay. Of note, the authors assumed that NAbs to IFNβ1a would not differ from NAbs to IFNβ1b in their clinical effect.

A multivariate Poisson regression model accounting for overdispersion was used to assess incidence of relapses during the treatment period, and multivariate Cox proportional hazards regression was used to model the time to reach the 1srt relapse and an Expanded Disability Status Scale (EDSS) score of 4. NAb status was regarded as a time-dependent covariate.

Analysis of the data showed that the incidence of relapses was significantly higher in NAb+ versus NAbs- patients. Moreover, NAb+ patients exhibited a significantly shorter time to 1rst relapse compared to NAb- patients.

Further analysis carried out on a subset of NAb+ patients matched to NAb- patients with a Propensity Score matching algorithm confirmed these findings and further revealed that the risk of reaching an EDSS of 4 was 3 times greater in NAb+ patients.

Taken together, the results of this long-term post-marketing study support that the occurrence of NAbs significantly affects the risk of disease worsening in IFNβ-treated RRMS patients.

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Immunogenicity

Effect of Treatment Regimen on the Immunogenicity of Human Interferon Beta in Immune Tolerant Mice.
Kijanka G, Jiskoot W, Schellekens H, Brinks V.
Pharm Res. 2013 Jan 30

Assessing immunogenicity of biosimilar therapeutic monoclonal antibodies: regulatory and bioanalytical considerations.
Chamberlain P.
Bioanalysis. 2013 Mar;5(5):561-74

Methods

Evaluation of dried blood spots for the quantification of therapeutic monoclonal antibodies and detection of anti-drug antibodies.
Kaendler K, Warren A, Lloyd P, Sims J, Sickert D.
Bioanalysis. 2013 Mar;5(5):613-22.

Animal models

Novel genetically-humanized mouse model established to evaluate efficacy of therapeutic agents to human interleukin-6 receptor.
Ueda O, Tateishi H, Higuchi Y, Fujii E, Kato A, Kawase Y, Wada NA, Tachibe T, Kakefuda M, Goto C, Kawaharada M, Shimaoka S, Hattori K, Jishage K.
Sci Rep. 2013;3:1196

Antagonizing the α4β1 Integrin, but Not α4β7, Inhibits Leukocytic Infiltration of the Central Nervous System in Rhesus Monkey Experimental Autoimmune Encephalomyelitis.
Haanstra KG, Hofman SO, Lopes Estêvão DM, Blezer EL, Bauer J, Yang LL, Wyant T, Csizmadia V, 't Hart BA, Fedyk ER.
J Immunol. 2013 Jan 30.

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Biomarkers

Changes in chemokines and their receptors in blood during treatment with the TNF inhibitor infliximab in patients with rheumatoid arthritis.
Eriksson C, Rantapää-Dahlqvist S, Sundqvist K.
Scand J Rheumatol. 2013 Feb 5.

Effects of natalizumab treatment on the CSF proteome of multiple sclerosis patients.
Stoop MP, Singh V, Stingl C, Martin R, Khademi M, Olsson T, Hintzen R, Luider TM.
J Proteome Res. 2013 Jan 22

Free light chain monomer - dimer patterns in the diagnosis of multiple sclerosis.
Kaplan B, Golderman S, Yahalom G, Yeskaraev R, Ziv T, Aizenbud BM, Sela BA, Livneh A.
J Immunol Methods. 2013 Jan 31.

Relevance of the type I interferon signature in multiple sclerosis towards a personalized medicine approach for interferon-beta therapy.
Verweij CL, Vosslamber S.
Discov Med. 2013 Jan;15(80):51-60.

A multi-biomarker score measures rheumatoid arthritis disease activity in the BeSt study.
Hirata S, Dirven L, Shen Y, Centola M, Cavet G, Lems WF, Tanaka Y, **Huizinga TW**, Allaart CF.
Rheumatology. 2013 Feb 7.

Blood Monocyte Chemotactic Protein-1 (MCP-1) and Adapted Disease Activity Score28-MCP-1: Favorable Indicators for Rheumatoid Arthritis Activity.
Liou LB, Tsai WP, Chang CJ, Chao WJ, Chen MH.
PLoS One. 2013;8(1):e55346

Predictors of long-term outcome in multiple sclerosis patients treated with interferon beta.
Bermel RA, You X, Foulds P, Hyde R, Simon JH, Fisher E, Rudick RA.
Ann Neurol. 2013 Jan;73(1):95-103.

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Systemic Lupus Erythematosus

Sifalimumab, a human anti-interferon-a monoclonal antibody, in systemic lupus erythematosus: A phase 1 randomized controlled, dose-escalation study.
Petri M, Wallace DJ, Spindler A, Chindalore V, Kalunian K, Mysler E, Neuwelt CM, Robbie G, White WI, Higgs BW, Yao Y, Wang L, Ethgen D, Greth W.
Arthritis Rheum. 2013 Feb 11.

Membrane-bound complement regulatory proteins as biomarkers and potential therapeutic targets for SLE.
Das N, Biswas B, Khera R.
Adv Exp Med Biol. 2013;735:55-81.

Rheumatoid Arthritis

Phosphorylation of FOXP3 controls regulatory T cell function and is inhibited by TNF-α in rheumatoid arthritis.
Nie H, Zheng Y, Li R, Guo TB, He D, Fang L, Liu X, Xiao L, Chen X, Wan B, Chin YE, Zhang JZ.
Nat Med. 2013 Feb 10

Novel Mechanisms of Action of the Biologicals in Rheumatic Diseases.
Chighizola CB, Favalli EG, Meroni PL.
Clin Rev Allergy Immunol. 2013 Jan 24.

Certolizumab Pegol : A Review of Its Use in the Management of Rheumatoid Arthritis.
Deeks ED.
Drugs. 2013 Jan 22.

A rheumatoid factor paradox: inhibition of rituximab effector function.
Jones JD, Shyu I, Newkirk MM, Rigby WF.
Arthritis Res Ther. 2013 Jan 25;15(1):R20.

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Dendritic cells and the promise of antigen-specific therapy in rheumatoid arthritis.
Thomas R.
Arthritis Res Ther. 2013 Feb 4;15(1):204

Amelioration of arthritis through mobilization of peptide-specific CD8+ regulatory T cells.
Leavenworth JW, Tang X, Kim HJ, Wang X, Cantor H.
J Clin Invest. 2013 Feb 8.

Effect of interleukin-6 receptor blockade on the balance between regulatory T cells and T helper type 17 cells in rheumatoid arthritis patients.
Pesce B, Soto L, Sabugo F, Wurmann P, Cuchacovich M, López MN, Sotelo PH, Molina MC, Aguillón JC, Catalán D.
Clin Exp Immunol. 2013 Mar;171(3):237-42

Genetics and epigenetics of rheumatoid arthritis.
Viatte S, Plant D, Raychaudhuri S.
Nat Rev Rheumatol. 2013 Feb 5

IBD

Adalimumab and Infliximab are Equally Effective for Crohn's disease in Patients not Previously Treated with Anti-Tumor Necrosis Factor-α Agents.
Kestens C, van Oijen MG, Mulder CL, van Bodegraven AA, Dijkstra G, de Jong D, Ponsioen C, van Tuyl SA, Siersema PD, Fidder HH, Oldenburg B; Dutch Initiative on Crohn and Colitis (ICC).
Clin Gastroenterol Hepatol. 2013 Jan 29.

A Test-Based Strategy is More Cost Effective than Empiric Dose-Escalation for Patients with Crohn's Disease Who Lose Responsiveness to Infliximab.
Velayos FS, Kahn JG, Sandborn WJ, Feagan BG.
Clin Gastroenterol Hepatol. 2013 Jan 25

The burden of inflammatory bowel disease in Europe.
Burisch J, Jess T, Martinato M, Lakatos PL; on behalf of ECCO -EpiCom.
J Crohns Colitis. 2013 Feb 7

Vedolizumab for Crohn's disease.
Mosli MH, Feagan BG.
Expert Opin Biol Ther. 2013 Mar;13(3):455-63.

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Multiple Sclerosis

Treatment with interferon-beta does not induce anti-nuclear and anti-neuronal serum autoantibodies in multiple sclerosis patients.
Comabella M, Rentzsch K, Río J, Bustamante MF, Borowski K, Stoecker W, **Montalban X.**
J Neuroimmunol. 2013 Feb 15;255(1-2):102-4

Dendritic cells in multiple sclerosis: key players in the immunopathogenesis, key players for new cellular immunotherapies?
Nuyts A, Lee W, Bashir-Dar R, Berneman Z, Cools N.
Mult Scler. 2013 Jan 31.

Multiple sclerosis: Reprogramming the immune repertoire with alemtuzumab in MS.
Wiendl H, Kieseier B.
Nat Rev Neurol. 2013 Jan 29

Multiple sclerosis in 2012: Novel therapeutic options and drug targets in MS.
Methner A, Zipp F.
Nat Rev Neurol. 2013 Feb;9(2):72-3

Cellular immune responses in multiple sclerosis patients treated with interferon-beta.
Bustamante MF, Rio J, Castro Z, Sánchez A, **Montalban X, Comabella M.**
Clin Exp Immunol. 2013 Mar;171(3):243-6

A Web-based tool for personalized prediction of long-term disease course in patients with multiple sclerosis.
Galea I, Lederer C, Neuhaus A, Muraro PA, Scalfari A, Koch-Henriksen N, Heesen C, Koepke S, Stellmann P, Albrecht H, Winkelmann A, Weber F, Bahn E, Hauser M, Edan G, Ebers G, Daumer M.
Eur J Neurol. 2012 Dec 7.

Hemophilia

Cytokine profile and FVIII inhibitors development in haemophilia A.
Oliveira CA, Velloso-Rodrigues C, Machado FC, Carvalho BN, Gentz SH, Martins-Filho OA, Chaves DG.
Haemophilia. 2013 Feb 6.

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Treatment of refractory hemorrhage with factor XIII in a patient with hemophilia A with inhibitor.
Ng C, Silliman CC, Pearl G, Smith W, Manco-Johnson M, Wang M.
Pediatr Blood Cancer. 2013 Feb 4.

Recommendations on the potency labelling of factor VIII and factor IX concentrates.
Hubbard AR, Dodt J, Lee T, Mertens K, **Seitz R**, Srivastava A, Weinstein M; The Factor Viii Factor Ix Subcommittee Of The Scientific Standardisation Committee Of The International Society On Thrombosis Haemostasis.
J Thromb Haemost. 2013 Feb 13.

Enhancing the pharmacokinetic properties of recombinant factor VIII: First-in-man trial of glycoPEGylated recombinant factor VIII in patients with hemophilia A.
Tiede A, Brand B, Fischer R, Kavakli K, Lentz SR, Matsushita T, Rea C, Knobe K, Viuff D.
J Thromb Haemost. 2013 Feb 11.

Basic immunology

Interleukin-2 at the crossroads of effector responses, tolerance, and immunotherapy.
Liao W, Lin JX, Leonard WJ.
Immunity. 2013 Jan 24;38(1):13-25.

Opinions/Commentaries

Biosimilars in rheumatology: the wind of change.
Schneider CK.
Ann Rheum Dis. 2013 Mar;72(3):315-8.

More or less rituximab? Biology and clinic, regulators and researchers.
van Vollenhoven RF.
Arthritis Rheum. 2011 Mar;63(3):594-6

How I manage patients with acquired haemophilia A.
Sborov DW, Rodgers GM.
Br J Haematol. 2013 Feb 4

An end to the myth: there is no drug development pipeline.
Baxter K, Horn E, Gal-Edd N, Zonno K, O'Leary J, Terry PF, Terry SF.
Sci Transl Med. 2013 Feb 6;5(171):171cm1.

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Comment on "the role of naive T cell precursor frequency and recruitment in dictating immune response magnitude".
Maillere B.
J Immunol. 2013 Mar 1;190(5):1895

REGULATION

EMA

Scientific guideline: Reflection paper on GCP compliance in relation to trial master files (paper and/or electronic) for management, audit and inspection of clinical trials,
Draft: consultation open
February 2013

Human medicines European Public Assessment Report (EPAR): Tysabri, natalizumab
Revision: 14, Authorised
February 2013

Human medicines European Public Assessment Report (EPAR): Extavia, interferon beta-1b
Revision: 9, Authorised
February 2013

Scientific guidelines : Guideline on Similar Biological Medicinal Products Containing Interferon Beta
Adopted
March 2013


Guideline on Similar Biological Medicinal Pr

Draft guideline on clinical investigation of medicinal products for the treatment of systemic lupus erythematosus, cutaneous lupus and lupus nephritis,
Drraft: consultation open
March 2013

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OTHER NEWS

Forthcoming international scientific meetings

April	Controversies in Rheumatology & Autoimmunity (CORA)	4-6, Budapest, Hungary
	Keystone S. "Advances in the knowledge and treatment of autoimmunity"	4-9, Whistler, Canada
	PEGS	30-4th May, Boston, Massachusetts, USA
May	Immunology 2013TM	3-7, Honolulu, Hawaii
June	EULAR	12-15, Madrid, Spain
	FOCIS	27-30, Boston, Massachusetts, USA
July	Tumor Necrosis Factor 2013	7-10, Quebec, Canada

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