

TABLE OF CONTENTS

INTRODUCTION	2
WELCOME	3
LITERATURE	4
This month's selected articles	4
Immunogenicity	6
Methods	7
Biomarkers	7
Systemic Lupus Erythematosus	8
Rheumatoid Arthritis	8
IBD	9
Multiple Sclerosis	9
Hemophilia	9
Basic immunology	9
Opinions/Commentaries	10
REGULATION	11
EMA	11
FDA	11
CONFERENCES & MEETINGS	12
January 2013	12
February 2013	12
March 2013	12

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 rheumatism (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 third 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.

This month, we chose to draw attention to the results of two phase III clinical trials published by The Lancet in its October issue, which confirmed the efficacy of Alemtuzumab (an anti-CD52 monoclonal antibody) in multiple sclerosis.

In addition, you will find in this issue some regulatory news on biopharmaceuticals and a list of ABIRISK topics-related scientific meetings taking place in the first quarter of 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

LITERATURE

This month's selected articles

[Alemtuzumab versus interferon beta 1a as first-line treatment for patients with relapsing-remitting multiple sclerosis: a randomised controlled phase 3 trial.](#)

Cohen JA, Coles AJ, Arnold DL, Confavreux C, Fox EJ, Hartung HP, Havrdova E, Selmaj KW, Weiner HL, Fisher E, Brinar VV, Giovannoni G, Stojanovic M, Ertik BI, Lake SL, Margolin DH, Panzara MA, Compston DA; for the CARE-MS I investigators.

Lancet. 2012 Oct 31

[Alemtuzumab for patients with relapsing multiple sclerosis after disease-modifying therapy: a randomised controlled phase 3 trial.](#)

Coles AJ, Twyman CL, Arnold DL, Cohen JA, Confavreux C, Fox EJ, Hartung HP, Havrdova E, Selmaj KW, Weiner HL, Miller T, Fisher E, Sandbrink R, Lake SL, Margolin DH, Oyuela P, Panzara MA, Compston DA; for the CARE-MS II investigators.

Lancet. 2012 Oct 31

Alemtuzumab is an anti-CD52 humanised monoclonal antibody provoking long-lasting depletion of B and T cells. Currently licensed to treat leukaemia, its potential as a new therapeutic drug for immune inflammatory diseases has also been subject to extensive investigation. Indeed Alemtuzumab was lately reported in a phase II trial as more effective than interferon beta-1a in decreasing clinical relapse rates in previously untreated patients with relapsing-remitting multiple sclerosis (The CAMMS223 Trials Investigators, *N. Engl. J Med.* 2008).

Here, Cohen and colleagues report on the Comparison of Alemtuzumab and Rebif Efficacy in Multiple Sclerosis (CARE-MS I) study, a phase III clinical trial, replicate of the former CAMMS223 phase II trial. In parallel, Coles *et al.* report on CARE-MS II, in which the efficacy of the same drugs have been evaluated in patients having failed first-line therapy (interferon beta or glatiramer).

Both studies showed significant superior efficacy of Alemtuzumab in reducing relapse rates and brain volume loss rates compared to interferon beta-1a. Moreover, in patients who experienced relapses despite first line therapy (CARE-MS II), Alemtuzumab was also found to further reduce the risk of sustained accumulation of disability.

Interestingly, immunogenicity of both biotherapeutics was investigated in these studies. Presence of anti-Alemtuzumab antibodies before and at 1 month, 3 months, and 12 months after each Alemtuzumab dosing was assessed by ELISA and further confirmed on positive samples by cellular competitive binding assay (Meso Scale Discovery, USA). Neutralizing antibodies to interferon beta-1a were revealed using a cytopathic effect inhibition assay (BioMonitor, Denmark) at baseline and at 24 months.

One month after the second Alemtuzumab administration, 86% (CARE-MS I) and 81% (CARE-MS II) of patients receiving Alemtuzumab exhibited specific Alemtuzumab binding antibodies. However, neither the presence nor the concentration of anti-drug antibodies altered Alemtuzumab-induced lymphocyte depletion, subsequent lymphocyte repopulation, or the efficacy and safety of the drug.

At 24 month, 13% (both studies) of patients receiving interferon beta-1a exhibited interferon beta-1a neutralizing antibodies, compared to 18% at baseline (CARE-MS I only). Noteworthy, additional analysis of data collected in CARE-MS I highlighted that the superior efficacy of Alemtuzumab on relapse rate was independent of interferon beta-1-treated patients developing neutralizing antibodies to interferon beta-1a. In the case of patients previously treated with interferon beta-1a (CARE-MS II), the authors state that 'Previous therapy or the presence of anti-interferon antibodies did not affect the results, although the study was not powered to detect an interaction'

Further commentaries on these studies can be found on *The Lancet* website :

[Alemtuzumab for multiple sclerosis](#)

Editorial

[Alemtuzumab for multiple sclerosis: who and when to treat?](#)

Comment by [T. Sprenger](#) and [L. Kappos](#)

Immunogenicity

[The Göttingen minipig\(®\) as an alternative non-rodent species for immunogenicity testing: A demonstrator study using the IL-1 receptor antagonist anakinra.](#)

van Mierlo GJ, Cnubben NH, Kuper CF, Wolthoorn J, Meeteren-Kreikamp AP, Nagtegaal MM, Doornbos R, Ganderup NC, Penninks AH.

J Immunotoxicol. 2012 Nov 7.

[The Utility of Modeling and Simulation Approaches to Evaluate Immunogenicity Effect on the Therapeutic Protein Pharmacokinetics.](#)

Perez Ruixo JJ, Ma P, Chow AT.

AAPSJ. 2012 Nov 10.

[Addition of an Immunomodulator to Infliximab Therapy Eliminates Anti-Drug Antibodies in Serum and Restores Clinical Response of Patients with Inflammatory Bowel Disease.](#)

Ben-Horin S, Waterman M, Kopylov U, Yavzori M, Picard O, Fudim E, Awadie H, Weiss B, Chowers Y.

Clin Gastroenterol Hepatol. 2012 Oct 24

[Immunogenicity, safety and efficacy of abatacept administered subcutaneously with or without background methotrexate in patients with rheumatoid arthritis: Results from accompany, a phase III study.](#)

Nash P, Nayiager S, Genovese MC, Kivitz AJ, Oelke K, Ludivico C, Palmer W, Rodriguez C, Delaet I, Elegbe A, Corbo M.

Arthritis Care Res. 2012 Oct 24.

[Immune tolerance in haemophilia: the long journey to the fork in the road.](#)

Dimichele DM.

Br J Haematol. 2012 Oct;159(2):123-34.

[Dangerous liaisons: how the immune system deals with factor VIII.](#)

Wroblewska A, Reipert BM, Pratt KP, Voorberg J.

J Thromb Haemost. 2012 Nov 12

[Potential of Thrombin Generation in Hemophilia A Plasma by Coagulation Factor VIII and Characterization of Antibody-Specific Inhibition.](#)

Doshi BS, Gangadharan B, Doering CB, Meeks SL.

PLoS One. 2012;7(10):e48172

[Impact of Antibodies to Infliximab on Clinical Outcomes and Serum Infliximab Levels in Patients With Inflammatory Bowel Disease \(IBD\): A Meta-Analysis.](#)

Nanda KS, Cheifetz AS, Moss AC.
Am J Gastroenterol. 2012 Nov 13.

Methods

[Cell-Based Reporter Gene Assay for Therapy-Induced Neutralizing Antibodies to Interferon-Beta in Multiple Sclerosis.](#)

Martins TB, Rose JW, Gardiner GL, Kusakawa N, Husebye D, Hill HR.
J Interferon Cytokine Res. 2012 Nov 15.

[Free and total biotherapeutic evaluation in chromatographic assays: interference from targets and immunogenicity.](#)

White JT, Bonilla LE.
Bioanalysis. 2012 Oct;4(19):2401-11.

[Humanized mice for immune system investigation: progress, promise and challenges.](#)

Shultz LD, Brehm MA, Garcia-Martinez JV, Greiner DL.
Nat Rev Immunol. 2012 Oct 12

[With or Without Sugar? \(A\)glycosylation of Therapeutic Antibodies.](#)

Hristodorov D, Fischer R, Linden L.
Mol Biotechnol. 2012 Oct 25.

Biomarkers

[Serum proteome analysis in patients with rheumatoid arthritis receiving therapy with etanercept, a chimeric tumor necrosis factor-alpha receptor.](#)

Yanagida M, Jung G, Tanaka Y, Sone S, Fujishiro M, Ikeda K, Nozawa K, Kaneko H, Takasaki Y, Ogawa H, Takamori K, Sekigawa I.
Int J Rheum Dis. 2012 Oct;15(5):486-95

[Serological changes in the course of traditional and biological disease modifying therapy of rheumatoid arthritis.](#)

Böhler C, Radner H, Smolen JS, Aletaha D.

Ann Rheum Dis. 2012 Oct 19.

[Monitoring C-reactive protein levels to predict favourable clinical outcomes from tocilizumab treatment in patients with rheumatoid arthritis.](#)

Kojima T, Yabe Y, Kaneko A, Hirano Y, Ishikawa H, Hayashi M, Miyake H, Takagi H, Kato T, Terabe K, Wanatabe T, Tsuchiya H, Kida D, Shioura T, Funahashi K, Kato D, Matsubara H, Takahashi N, Hattori Y, Asai N, Ishiguro N.

Mod Rheumatol. 2012 Oct 26

[Infliximab reduces CD147, MMP-3, and MMP-9 expression in peripheral blood monocytes in patients with active rheumatoid arthritis.](#)

Huang JL, Xie BZ, Li QX, Xie XJ, Zhu S, Wang MX, Peng WX, Gu JR.

Eur J Pharmacol. 2012 Nov 9

Systemic Lupus Erythematosus

[Safety and pharmacodynamics of rontalizumab in patients with systemic lupus erythematosus: Results of a phase I, placebo-controlled, double-blind, dose-escalation study.](#)

McBride JM, Jiang J, Abbas AR, Morimoto A, Li J, Maciucă R, Townsend M, Wallace DJ, Kennedy WP, Drappa J.

Arthritis Rheum. 2012 Nov;64(11):3666-76.

Rheumatoid Arthritis

[Mavrilimumab , a human monoclonal GM-CSF receptor- \$\alpha\$ antibody for the management of rheumatoid arthritis: a novel approach to therapy.](#)

Nair JR, Edwards SW, Moots RJ.

Expert Opin Biol Ther. 2012 Oct 25.

IBD

[Ustekinumab induction and maintenance therapy in refractory Crohn's disease.](#)

Sandborn WJ, Gasink C, Gao LL, Blank MA, Johanns J, Guzzo C, Sands BE, Hanauer SB, Targan S, Rutgeerts P, Ghosh S, de Villiers WJ, Panaccione R, Greenberg G, Schreiber S, Lichtiger S, Feagan BG; CERTIFI Study Group.
N Engl J Med. 2012 Oct 18;367(16):1519-28.

[New Drug Therapies on the Horizon for IBD.](#)

Perrier C, Rutgeerts P.
Dig Dis. 2012;30 Suppl 1:100-5.

Multiple Sclerosis

[The discovery of natalizumab, a potent therapeutic for multiple sclerosis.](#)

Steinman L.
J Cell Biol. 2012 Oct 29;199(3):413-6.

Hemophilia

[Development and Characterization of Recombinant Ovine Coagulation Factor VIII.](#)

Zakas PM, Gangadharan B, Almeida-Porada G, Porada CD, Spencer HT, Doering CB.
PLoS One. 2012;7(11):e49481.

Basic immunology

[Elimination of Germinal Center-Derived Self-Reactive B Cells Is Governed by the Location and Concentration of Self-Antigen.](#)

Chan TD, Wood K, Hermes JR, Butt D, Jolly CJ, Basten A, Brink R.
Immunity. 2012 Nov 6

Opinions/Commentaries

[Why the findings of published multiple treatment comparison meta-analyses of biologic treatments for rheumatoid arthritis are different: an overview of recurrent methodological shortcomings.](#)

Thorlund K, Druyts E, Aviña-Zubieta JA, Wu P, Mills EJ.

Ann Rheum Dis. 2012 Oct 20.

[Do we need guidelines to stop as well as to start biological therapies for rheumatoid arthritis?](#)

van den Broek M, Lems WF, Allaart CF.

Clin Exp Rheumatol. 2012 Oct 16

[Evolution of the European guidelines for the clinical development of factor VIII products: little progress towards improved patient management.](#)

Mannucci PM.

Haemophilia. 2012 Oct 23

REGULATION

EMA

[Opinion/decision on a Paediatric Investigation Plan \(PIP\): Cimzia, Certolizumab pegol](#)
October 2012

[Opinion/decision on a Paediatric Investigation Plan \(PIP\): Human-cell-line recombinant human factor VIII \(updated\)](#)
October 2012

[Concept paper on the revision of the guideline on the development of new medicinal products for the treatment of Crohn's disease](#)
Draft: consultation open
November 2012

[Concept paper on the revision of the guideline on the development of medicinal products for the treatment of ulcerative colitis](#)
Draft: consultation open
November 2012

[Human medicines European Public Assessment Report \(EPAR\): RoActemra \(Tocilizumab\)](#)
November 2012

FDA

[Xeljanz \(Tofacitinib\) approved for rheumatoid arthritis](#)
November 12

CONFERENCES & MEETINGS

January 2013

Keystone Symposia 'Multiple sclerosis'	11-16, Big Sky, Montana, USA	http://www.kestonesymposia.org
Keystone Symposia 'Antibodies as drugs'	27-1st Feb, Vancouver, Canada	http://www.kestonesymposia.org

February 2013

EUCRAF Biopharmaceuticals workshop	7-8 Friburg, Germany	http://www.eucraf-workshop2013.com/
EIP Symposium	25-27, Munich, Germany	http://www.e-i-p.eu/eip_symposium.cfm

March 2013

IMMUNO 2013	11-12, Barcelona, Spain	http://www2.kenes.com/immuno
Immunogenicity for Biotherapeutics	18-20, Baltimore, Maryland, USA	http://www.iirusa.com