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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 December 12 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 highlight a consensus statement made by a team of international RA experts on the effects of IL-6 blocking in rheumatoid arthritis and other inflammatory diseases, published both as concise (Schoels et al.) and extended (Smolen et al.) reports in Annals of the Rheumatic Diseases, the EULAR journal.

In addition, you will find in this issue some EMA regulatory news and an EFPIA announcement.

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 articles

Consensus statement on blocking the effects of interleukin-6 and in particular by interleukin-6 receptor inhibition in rheumatoid arthritis and other inflammatory conditions.
Smolen JS, Schoels MM, Nishimoto N, Breedveld FC, Burmester GR, Dougados M, Emery P, Ferraccioli G, Gabay C, Gibofsky A, Gomez-Reino JJ, Jones G, Kvien TK, Murakami M, Betteridge N, Bingham C 3rd, Bykerk V, Choy EH, Combe B, Cutolo M, Graninger W, Lanas A, Martin-Mola E, Montecucco C, Ostergaard M, Pavelka K, Rubbert-Roth A, Sattar N, Scholte-Voshaar M, Tanaka Y, Trauner M, Valentini G, Winthrop KL, de Wit M, van der Heijde D.
Ann Rheum Dis. 2012 Nov 21

Blocking the effects of interleukin-6 in rheumatoid arthritis and other inflammatory rheumatic diseases: systematic literature review and meta-analysis informing a consensus statement.
Schoels MM, van der Heijde D, Breedveld FC, Burmester GR, Dougados M, Emery P, Ferraccioli G, Gabay C, Gibofsky A, Gomez-Reino JJ, Jones G, Kvien TK, Murikama MM, Nishimoto N, Smolen JS.
Ann Rheum Dis. 2012 Nov 10

Persistent IL-6 overproduction has been implicated in the pathogenesis of many diseases, including several inflammatory disorders such as rheumatoid arthritis (RA), systemic juvenile idiopathic arthritis (JIA) or Crohn's disease. Monoclonal antibodies directed to IL-6 receptor or to the cytokine itself have been developed and numerous clinical trials have investigated their efficacy in ameliorating the above conditions and others among which systemic lupus erythematosus, ankylosing spondylitis and Castelman's disease.

In the present publications by Shoels *et al*. (Concise Report) and Smolen *et al*. (Extended Report), a team of international RA treatment experts have come together to conduct meta-analyses of currently available data on safety and efficacy of IL-6 inhibitors in inflammatory diseases. Data were collected by means of a systematic literature review, searching Medline and Cochrane databases up to January 2012, and abstract archives of EULAR (2010-2012) and ACR (2010-2011) conferences. NIH database on on-going clinical trials was also explored.

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Albeit touching on other IL-6 inhibitors efficacy, the study mainly focused on Tocilizumab in RA. Tocilizumab, a humanized monoclonal antibody targeting the α chain of the IL-6 receptor, is indeed the only IL-6 targeting biotherapeutic agent currently licensed to treat RA and JIA in Europe. Of note, it is also licensed in Japan and India for Castleman's disease.

Meta-analyses of comparable randomised controlled trials data lead to a consensus statement by the committee on the 'Points to consider for the treatment of adult RA with Tocilizumab' (see Box 1, Extended Report), encompassing issues such as indication, contraindications, pre-treatment screening, dose, co-medication and adverse events.

Beside those recommendations, the team also established a comprehensive list of points that they felt should be addressed in future research conducted with Tocilizumab or other IL-6 inhibitors. This 'Research Agenda' can be found on page 7 of the Extend Report, and comprises over 30 pending questions on topics such as doses and concomitant therapies, efficacy, safety other indications.

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Immunogenicity

Antidrug antibodies (ADAb) to tumour necrosis factor (TNF)-specific neutralising agents in chronic inflammatory diseases: a real issue, a clinical perspective.
Vincent FB, Morand EF, Murphy K, Mackay F, Mariette X, Marcelli C.
Ann Rheum Dis. 2012 Nov 24.

Methotrexate polyglutamation in relation to infliximab pharmacokinetics in rheumatoid arthritis.
Dervieux T, Weinblatt ME, Kivitz A, Kremer JM.
Ann Rheum Dis. 2012 Nov 17

Development of factor VIII inhibitors in two patients with moderate haemophilia A.
Paschal RD, Meeks SL, Neff AT.
Haemophilia. 2012 Nov 22.

Immunogenicity and autoimmunity during anti-TNF therapy.
Atzeni F, Talotta R, Benucci M, Salaffi F, Cassinotti A, Varisco V, Battellino M, Ardizzone S, Pace F, Sarzi-Puttini P.
Autoimmun Rev. 2012 Nov 30

Biologics-induced autoimmune diseases.
Perez-Alvarez R, Pérez-de-Lis M, Ramos-Casals M; on behalf of the BIOGEAS study group.
Curr Opin Rheumatol. 2013 Jan;25(1):56-64.

Identification and elimination of an immunodominant T-cell epitope in recombinant immunotoxins based on Pseudomonas exotoxin A.
Mazor R, Vassall AN, Eberle JA, Beers R, Weldon JE, Venzon DJ, Tsang KY, Benhar I, Pastan I.
Proc Natl Acad Sci. 2012 Dec 18;109(51):E3597-603.

Methods

Neutralizing antibodies in multiple sclerosis patients on weekly intramuscular Avonex and biosimilar interferon beta-1a (CinnoVex): Comparing results of measurements in two different laboratories.
Shahkarami MA, Vaziri B, Salami S, Harandi AA, Oger J.
J Immunol Methods. 2012 Dec 6

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Development and optimization of neutralizing antibody assays to monitor clinical immunogenicity.
Civoli F, Kroenke MA, Reynhardt K, Zhuang Y, Kaliyaperumal A, Gupta S.
Bioanalysis. 2012 Nov;4(22):2725-35.

A quantitative flow cytometric assay for determining binding characteristics of chimeric, humanized and human antibodies in whole blood: proof of principle with rituximab and ofatumumab.
Engelberts PJ, Badoil C, Beurskens FJ, Boulay-Moine D, Grivel K, Parren PW, Moulard M.
J Immunol Methods. 2012 Nov 23.

The pharmacology study of a new recombinant TNF receptor-hyFc fusion protein.
Lee JH, Cho JH, Yeo J, Lee SH, Yang SH, Sung YC, Kang JH, Park CS.
Biologicals. 2012 Nov 26.

In Vitro Generation of Long-lived Human Plasma Cells.
Cocco M, Stephenson S, Care MA, Newton D, Barnes NA, Davison A, Rawstron A, Westhead DR, Doody GM, Tooze RM.
J Immunol. 2012 Nov 16.

Biomarkers

Serum levels of IL-17A in patients with relapsing-remitting multiple sclerosis treated with interferon-β
Balasa R, Bajko Z, Hutanu A.
Mult Scler. 2012 Dec 3.

Allelic combinations of immune-response genes as possible composite markers of IFN-β efficacy in multiple sclerosis patients.
Kulakova OG, Tsareva EY, Boyko AN, Shchur SG, Gusev EI, Lvovs D, Favorov AV, Vandenbroeck K, Favorova OO.
Pharmacogenomics. 2012 Nov;13(15):1689-700

Impact of a Multi-Biomarker Disease Activity Test on Rheumatoid Arthritis Treatment Decisions and Therapy Use.
Li W, Sasso EH, Emerling D, Cavet G, Ford K.
Curr Med Res Opin. 2012 Nov 23.

Biospecimens, biomarkers, and burgeoning data: the imperative for more rigorous research standards.
Poste G.
Trends Mol Med. 2012 Nov 1

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Systemic Lupus Erythematosus

Safety profile of belimumab: pooled data from placebo-controlled phase 2 and 3 studies in patients with systemic lupus erythematosus.
Wallace D, Navarra S, Petri M, Gallacher A, Thomas M, Furie R, Levy R, van Vollenhoven R, Cooper S, Zhong Z, Freimuth W, Cervera R; for the BLISS-52 and -76, and LBSL02 Study Groups.
Lupus. 2012 Dec 4

Anti-IFN-α/β Receptor Antibody Treatment Ameliorates Disease in Lupus-Predisposed Mice.
Baccala R, Gonzalez-Quintial R, Schreiber RD, Lawson BR, Kono DH, Theofilopoulos AN.
J Immunol. 2012 Nov 21.

Cytokine inhibition as a strategy for treating systemic lupus erythematosus.
Clark DN, Markham JL, Sloan CS, Poole BD.
Clin Immunol. 2012 Nov 12

Rheumatoid Arthritis

Head-to-head comparison of subcutaneous abatacept versus adalimumab for Rheumatoid Arthritis.
Weinblatt ME, Schiff M, Valente R, van der Heijde D, Citera G, Zhao C, Maldonado M, Fleischmann R.
Arthritis Rheum. 2012 Nov 20

Clinical outcome in patients with rheumatoid arthritis switched to tocilizumab after etanercept or infliximab failure.
Wakabayashi H, Hasegawa M, Nishioka Y, Minami Y, Nishioka K, Sudo A.
Clin Rheumatol. 2012 Nov 21.

Abatacept Use After Failure of Multiple Biologic Agents in Patients With Severe Rheumatoid Arthritis.
Hazlewood GS, Barnabe C, Barr SG, Martin L.
J Clin Rheumatol. 2012 Nov 26

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Targeting monocytes/macrophages in the treatment of rheumatoid arthritis.
Davignon JL, Hayder M, Baron M, Boyer JF, Constantin A, Apparailly F, Poupot R, Cantagrel A.
Rheumatology. 2012 Nov 30.

Abatacept (CTLA-4Ig) treatment reduces the migratory capacity of monocytes in patients with rheumatoid arthritis (RA).
Bonelli M, Ferner E, Göschl L, Blüml S, Hladik A, Karonitsch T, Kiener H, Byrne R, Niederreiter B, Steiner C, Rath E, Bergmann M, Smolen J, Scheinecker C.
Arthritis Rheum. 2012 Nov 30

IBD

Immunosuppressive and biologic therapy for ulcerative colitis.
Ardizzone S, Cassinotti A, de Franchsi R.
Expert Opin Emerg Drugs. 2012 Nov 19

Infliximab trough levels may predict sustained response to infliximab in patients with Crohn's disease.
Bortlik M, Duricova D, Malickova K, Machkova N, Bouzkova E, Hrdlicka L, Komarek A, Lukas M.
J Crohns Colitis. 2012 Nov 28.

Multiple Sclerosis

Alemtuzumab Therapy for Multiple Sclerosis.
Coles AJ.
Neurotherapeutics. 2012 Nov 27

Humoral-Targeted Immunotherapies in Multiple Sclerosis.
Lulu S, Waubant E.
Neurotherapeutics. 2012 Dec 4

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Opinions/Commentaries

Old drug, new price?*
Yvonne Bordon
Nat. Rev. Immunol., November 12
**Refers to the potential marketing of Alemtuzumab for MS (see November issue of ABIRISK Scientific Newsletter)*

Letter: measurement of anti-TNF-α levels and antibodies against the drug.
Chaparro M, Gisbert JP.
Aliment Pharmacol Ther. 2013 Jan;37(1):163-4

Commentary: detection of infliximab levels and anti-infliximab antibodies.
Seow CH, Panaccione R.
Aliment Pharmacol Ther. 2013 Jan;37(1):153-4

Anti-TNF-α biotherapies: perspectives for evidence-based personalized medicine.
Bendtzen K.
Immunotherapy. 2012 Nov;4(11):1167-79.

Setting the stage for biosimilar monoclonal antibodies
Christian K Schneider, Camille Vleminckx, Iordanis Gravanis, Falk Ehmann, Jean-Hugues Trouvin, Martina Weise & Steffen Thirstrup
*Nature Biotechnol.*30,1179–1185

Interchangeability, immunogenicity and biosimilars
Hans C Ebbers, Stacy A Crow, Arnold G Vulto & Huub Schellekens
Nature Biotechnol. 30,1186–1190(2012)

As Open Access Explodes, How to Tell the Good From the Bad and the Ugly?*
Martin Enserink
Science, November 12
** IMI strongly support publication in open access journals*

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REGULATION

EMA

Humanised monoclonal IgG4 antibody against tissue-factor-pathway inhibitor for the treatment of haemophilia A
Orphan designation
November 2012

Paediatric Investigation Plan (PIP): Tysabri, Natalizumab, Therapeutic area: Neurology
Opinion/decision
November 2012

Paediatric Investigation Plan (PIP): Glycopegylated recombinant coagulation factor VIII, Therapeutic area: Haematology-Hemostaseology
Opinion/decision
November 2012

Human medicines European Public Assessment Report (EPAR): Kogenate Bayer,octocog alfa
Revision: 23, Authorised
November 2012

Recombinant human factor XIII (composed of two A subunits) for the Treatment of hereditary factor-XIII deficiency
Orphan designation/updated
December 2012

Human medicines European Public Assessment Report (EPAR): Enbrel, Etanercept
Revision: 35, Authorised
December 2012

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OTHER NEWS

Announcement

*"The **E**uropean **F**ederation of **P**harmaceutical **I**ndustries and **A**ssociations (Brussels) has announced the designation of **Christopher A. Viehbacher** (right), CEO of Sanofi, as its new president-elect beginning in June 2013 for a two-year term. Viehbacher is also chairman of Genzyme, which Sanofi acquired in February 2011. He was chairman of the Pharmaceutical Research and Manufacturers of America from December 2010 to April 2012 and is currently chairman of the CEO Roundtable on Cancer."*

Nature Biotechnol. 30,1254(2012)

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