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The research leading to these results has received support from the Innovative Medicines Initiative Joint Undertaking under grant agreement n° [115303], resources of which are composed of financial contribution from the European Union's Seventh Framework Programme (FP7/2007-2013) and EFPIA companies' in kind contribution.'
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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.

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WELCOME

Dear Reader,

We would like to welcome you to the September 2015 **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

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LITERATURE

This month's selected articles

1. A well documented review, which gives an overview of the many aspects of anti-biopharmaceutical immunogenicity :

   Immunogenicity of biologic agents in rheumatoid arthritis patients: lessons for clinical practice.
   Schaeverbeke T, Truchetet ME, Kostine M, Barnetche T, Bannwarth B, Richez C.
   Rheumatology (Oxford). 2015 Aug 12.

2. This paper clearly underlines the clinical significance of ADA, and does give further support to monitoring all patients. Many clinical centers around the world are still not monitoring ADA and drug levels, and this paper could add value to the optimization of using expensive biologics :

   Clinical utility of random anti-tumour necrosis factor drug testing and measurement of anti-drug antibodies on long-term treatment response in rheumatoid arthritis.
   Jani M, Chinoy H, Warren RB, Griffiths CE, Plant D, Morgan AW, Wilson AG, Hyrich KL, Isaacs J, Barton A.
   Lancet. 2015 Feb 26;385 Suppl 1:S48.

3. The authors developed a novel approach effective in reducing or eliminating the drug interference issues in ADA assays. The method was applied to three therapeutic monoclonal antibodies : a humanized IgG1, a fully human IgG4 and a humanized IgG4.

   A breakthrough novel method to resolve the drug and target interference problem in immunogenicity assays.
   Zoghbi J, Xu Y, Grabert R, Theobald V, Richards S.
   J Immunol Methods. 2015 Aug 6.

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Immunogenicity

Predicting Hemagglutinin MHC-II Ligand Analogues in Anti-TNFα Biologics: Implications for Immunogenicity of Pharmaceutical Proteins.
Andrick BJ, Schwab AI, Cauley B, O'Donnell LA, Meng WS.
PLoS One. 2015 Aug 13;10(8):e0135451.

ANNALS EXPRESS: Serum trough infliximab and anti-infliximab antibodies in a cohort of gastroenterology and rheumatology patients Short title: Infliximab therapeutic drug monitoring.
Barlow NL, Mohammed P, Berg JD.
Ann Clin Biochem. 2015 Aug 19.

Development of interferon beta-neutralising antibodies in multiple sclerosis-a systematic review and meta-analysis.
Govindappa K, Sathish J, Park K, Kirkham J, Pirmohamed M.
Eur J Clin Pharmacol. 2015 Aug 14

Comparative Immunogenicity of TNF Inhibitors: Impact on Clinical Efficacy and Tolerability in the Management of Autoimmune Diseases. A Systematic Review and Meta-Analysis.
Thomas SS, Borazan N, Barroso N, Duan L, Taroumian S, Kretzmann B, Bardales R, Elashoff D, Vangala S, Furst DE.
BioDrugs. 2015 Aug 18.

Methods

An Optimized Anti-infliximab Bridging Enzyme-linked Immunosorbent Assay for Harmonization of Anti-infliximab Antibody Titers in Patients with Inflammatory Bowel Diseases.
Van Stappen T, Billiet T, Vande Casteele N, Compernolle G, Brouwers E, Vermeire S, Gils A.
Inflamm Bowel Dis. 2015 Sep;21(9):2172-7.

Agreement in assessment of infliximab and adalimumab levels in rheumatoid arthritis: interlaboratory and interassay comparison.
Valor L, Hernández-Flórez D, de la Torre I, Llinares F, Rosas J, Yagüe J, Garrido J, Naredo E.
Clin Exp Rheumatol. 2015 Aug 27.

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The Detection of Anti-adalimumab Antibodies in a Series of Inflammatory Polyarthritis: Three ELISA Methods Compared.
Fabris M, Pistis C, Zabotti A, Picco L, Curcio F, Tonutti E, De Vita S.
Drug Metab Lett. 2015 Aug 6.

Animal models

Role of coagulation-associated processes on factor VIII immunogenicity in a mouse model of severe hemophilia A.
Gangadharan B, Delignat S, Ollivier V, Gupta N, Mackman N, Kaveri SV, Lacroix-Desmazes S.
J Thromb Haemost. 2014 Dec;12(12):2065-9.

A Humanized Monoclonal Antibody against Heat Shock Protein 60 Suppresses Murine Arthritis and Colitis and Skews the Cytokine Balance toward an Anti-Inflammatory Response.
Ulmansky R, Landstein D, Moallem E, Loeb V, Levin A, Meyuhas R, Katzavian G, Yair S, Naparstek Y.
J Immunol. 2015 Jun 1;194(11):5103-9.

Deletion or inhibition of Fc gamma receptor 2B (CD32) prevents FVIII-specific activation of memory B cells in vitro.
Werwitzke S, Vollack N, von Hornung M, Kalippke K, Kutzschbach J, Trummer A, Ganser A, Tiede A.
Thromb Haemost. 2015 Aug 6;114(6).

Abatacept decreases disease activity in a absence of CD4(+) T cells in a collagen-induced arthritis model.
Jansen DT, El Bannoudi H, Arens R, Habets KL, Hameetman M, Huizinga TW, Stoop JN, Toes RE.
Arthritis Res Ther. 2015 Aug 20;17(1):220.

Biomarkers

Polymorphisms within the HLA-E gene and their associations with susceptibility to rheumatoid arthritis as well as clinical outcome of anti-TNF therapy.
Iwaszko M, Świerkot J, Kolossa K, Jeka S, Wiland P, Bogunia-Kubik K.
Clin Exp Immunol. 2015 Aug 26.

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Predictive factors for induction of remission in patients with active rheumatoid arthritis treated with tocilizumab in clinical practice.
Narváez J, Magallares B, Díaz Torné C, Hernández MV, Reina D, Corominas H, Sanmartí R, LLobet JM, Rodriguez de la Serna A, Nolla JM.
Semin Arthritis Rheum. 2015 Jul 6.

In vitro response pattern of monocytes after tmTNF reverse signaling predicts response to anti-TNF therapy in rheumatoid arthritis.
Meusch U, Krasselt M, Rossol M, Baerwald C, Klingner M, Wagner U.
J Transl Med. 2015 Aug 7;13:256.

Investigating the link between disease activity and infliximab serum levels in rheumatoid arthritis patients.
Valor L, Hernández-Flórez D, de la Torre I, Del Río T, Nieto JC, González C, López-Longo FJ, Monteagudo I, Llinares F, Rosas J, Garrido J, Naredo E, Carreño L.
Clin Exp Rheumatol. 2015 Aug 27.

Natalizumab treatment reduces L-selectin (CD62L) in CD4+ T cells.
Spadaro M, Caldano M, Marnetto F, Lugaresi A, Bertolotto A.
J Neuroinflammation. 2015 Aug 12;12:146.

An Increased Serum N-Terminal Telopeptide of Type I Collagen, a Biochemical Marker of Increased Bone Resorption, Is Associated with Infliximab Therapy in Patients with Crohn's Disease.
Sugimoto K, Ikeya K, Iida T, Kawasaki S, Arai O, Umehara K, Watanabe F, Tani S, Oishi S, Osawa S, Yamamoto T, Hanai H.
Dig Dis Sci. 2015 Aug 8.

Predictors of disease activity in 857 patients with MS treated with interferon beta-1b.
Hartung HP, Kappos L, Goodin DS, O'Connor P, Filippi M, Arnason B, Comi G, Cook S, Jeffery D, Petkau J, White R, Bogumil T, Beckmann K, Stemper B, Suarez G, Sandbrink R, Pohl C.
J Neurol. 2015 Aug 5.

Systemic Lupus Erythematosus

Long-term safety and efficacy of epratuzumab in the treatment of moderate-to-severe systemic lupus erythematosus: results from an open-label extension study.
Wallace DJ, Hobbs K, Clowse ME, Petri M, Strand V, Pike M, Merrill JT, Leszczynski P, Neuwelt CM, Jeka S, Houssiau F, Keiserman M, Ordi-Ros J, Bongardt S, Kilgallen B, Galateanu C, Kalunian K, Furie R, Gordon C.
Arthritis Care Res (Hoboken). 2015 Aug 28.

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One year in review 2015: systemic lupus erythematosus.
Mirabelli G, Cannarile F, Bruni C, Vagelli R, De Luca R, Carli L.
Clin Exp Rheumatol. 2015 May-Jun;33(3):414-25.

Efficacy and safety of subcutaneous tabalumab, a monoclonal antibody to B-cell activating factor, in patients with systemic lupus erythematosus: results from ILLUMINATE-2, a 52-week, phase III, multicentre, randomised, double-blind, placebo-controlled study.
Merrill JT, van Vollenhoven RF, Buyon JP, Furie RA, Stohl W, Morgan-Cox M, Dickson C, Anderson PW, Lee C, Berclaz PY, Dörner T.
Ann Rheum Dis. 2015 Aug 20.

Rheumatoid Arthritis

A randomised, double-blind, phase III study comparing SB2, an infliximab biosimilar, to the infliximab reference product Remicade in patients with moderate to severe rheumatoid arthritis despite methotrexate therapy.
Choe JY, Prodanovic N, Niebrzydowski J, Staykov I, Dokoupilova E, Baranauskaite A, Yatsyshyn R, Mekic M, Porawska W, Ciferska H, Jedrychowicz-Rosiak K, Zielinska A, Choi J, Rho YH, Smolen JS.
Ann Rheum Dis. 2015 Aug 28.

The molecular mode of action and species specificity of canakinumab, a human monoclonal antibody neutralizing IL-1β.
Rondeau JM, Ramage P, Zurini M, Gram H.
MAbs. 2015 Aug 18:0.

Current understanding of the pathophysiology of systemic juvenile idiopathic arthritis (sJIA) and target-directed therapeutic approaches.
Bruck N, Schnabel A, Hedrich CM.
Clin Immunol. 2015 Jul;159(1):72-83

Association of HLA-DRB1 alleles with clinical responses to the anti-interleukin-17A monoclonal antibody secukinumab in active rheumatoid arthritis.
Burmester GR, Durez P, Shestakova G, Genovese MC, Schulze-Koops H, Li Y, Wang YA, Lewitzky S, Koroleva I, Agarwal Berneis A, Lee DM, Hueber W.
Rheumatology (Oxford). 2015 Aug 12.

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Comparison of the efficacies of abatacept and tocilizumab in patients with rheumatoid arthritis by propensity score matching.
Kubo S, Nakayamada S, Nakano K, Hirata S, Fukuyo S, Miyagawa I, Hanami K, Saito K, Tanaka Y.
Ann Rheum Dis. 2015 Aug 5.

Longterm Safety of Rituximab: Final Report of the Rheumatoid Arthritis Global Clinical Trial Program over 11 Years.
van Vollenhoven RF, Fleischmann RM, Furst DE, Lacey S, Lehane PB.
J Rheumatol. 2015 Aug 15.

Rituximab done: what's next in rheumatoid arthritis? A European observational longitudinal study assessing the effectiveness of biologics after rituximab treatment in rheumatoid arthritis.
Walker UA, Jaeger VK, Chatzidionysiou K, Hetland ML, Hauge EM, Pavelka K, Nordström DC, Canhão H, Tomšič M, van Vollenhoven R, Gabay C.
Rheumatology (Oxford). 2015 Aug 27.

A Randomized Trial Comparing Disease Activity Measures to Assess and Predict Response in Rheumatoid Arthritis Patients Initiating Certolizumab Pegol.
Curtis JR, Churchill M, Kivitz A, Samad A, Gauer L, Gervitz L, Koetse W, Melin J, Yazici Y.
Arthritis Rheumatol. 2015 Aug 28.

Inflammatory Bowel Diseases

Pharmacologic therapy for inflammatory bowel disease refractory to steroids.
Martínez-Montiel MP, Casis-Herce B, Gómez-Gómez GJ, Masedo-González A, Yela-San Bernardino C, Piedracoba C, Castellano-Tortajada G.
Clin Exp Gastroenterol. 2015 Aug 17;8:257-69

Patient considerations in the management of ulcerative colitis - role of vedolizumab.
Kothari M, Mudireddy P, Swaminath A.
Ther Clin Risk Manag. 2015 Aug 19;11:1235-42.

Efficacy of Vedolizumab as Induction Therapy in Refractory IBD Patients: A Multicenter Cohort.
Shelton E, Allegretti JR, Stevens B, Lucci M, Khalili H, Nguyen DD, Sauk J, Giallourakis C, Garber J, Hamilton MJ, Tomczak M, Makrauer F, Burakoff RB, Levine J, de Silva P, Friedman S, Ananthakrishnan A, Korzenik JR, Yajnik V.
Inflamm Bowel Dis. 2015 Aug 17

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Where are we heading to in pharmacological IBD therapy?
Rogler G.
Pharmacol Res. 2015 Aug 12.

The Role of Therapeutic Drug Monitoring of Anti-Tumor Necrosis Factor Alpha Agents in Children and Adolescents with Inflammatory Bowel Disease.
Joosse ME, Samsom JN, van der Woude CJ, Escher JC, van Gelder T.
Inflamm Bowel Dis. 2015 Sep;21(9):2214-21.

Biologics for extraintestinal manifestations of IBD.
Vavricka SR, Scharl M, Gubler M, Rogler G.
Curr Drug Targets. 2014;15(11):1064-73.

Biologic agents for IBD: practical insights.
Danese S, Vuitton L, Peyrin-Biroulet L.
Nat Rev Gastroenterol Hepatol. 2015 Aug 18

Multiple Sclerosis

Differential glatiramer acetate treatment persistence in treatment-naive patients compared to patients previously treated with interferon.
Fernández-Fournier M, Tallón-Barranco A, Chamorro B, Martínez-Sánchez P, Puertas I.
BMC Neurol. 2015 Aug 19;15:141

Blockade of the High-Affinity Interleukin-2 Receptors with Daclizumab High-Yield Process: Pharmacokinetic/Pharmacodynamic Analysis of Single- and Multiple-Dose Phase I Trials.
Minocha M, Tran JQ, Sheridan JP, Othman AA.
Clin Pharmacokinet. 2015 Aug 5.

Relapsing multiple sclerosis patients treated with disease modifying therapy exhibit highly variable disease progression: a predictive model.
Scott TF, Hackett CT, Quigley MR, Schramke CJ.
Clin Neurol Neurosurg. 2014 Dec;127:86-92.

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Hemophilia

Novel, human cell line-derived recombinant factor VIII (human-cl rhFVIII; Nuwiq®) in adults with severe haemophilia A: efficacy and safety.
Lissitchkov T, Hampton K, von Depka M, Hay C, Rangarajan S, Tuddenham E, Holstein K, Huth-Kühne A, Pabinger I, Knaub S, Bichler J, Oldenburg J.
Haemophilia. 2015 Aug 28.

The role of previously untreated patient studies in understanding the development of FVIII inhibitors.
Carcao M, Re W, Ewenstein B.
Haemophilia. 2015 Aug 27.

Opinions/Commentaries/Across diseases reviews

Biosimilars in rheumatology: current perspectives and lessons learnt.
Dörner T, Kay J.
Nat Rev Rheumatol. 2015 Aug 18.

The biology of IL-23 and IL-17 and their therapeutic targeting in rheumatic diseases.
Sherlock JP, Taylor PC, Buckley CD.
Curr Opin Rheumatol. 2015 Jan;27(1):71-5.

B-cell survival factors in autoimmune rheumatic disorders.
Morais SA, Vilas-Boas A, Isenberg DA.
Ther Adv Musculoskelet Dis. 2015 Aug;7(4):122-51.

A comparison of rheumatoid arthritis and systemic lupus erythematosus trial design: a commentary on ways to improve the number of positive trials in SLE.
Miles A, Pope JE.
Clin Exp Rheumatol. 2015 Aug 27.

Which patients with rheumatoid arthritis, spondyloarthritis, or juvenile idiopathic arthritis receive TNF-α antagonists in France? The CORPUS cohort study.
Saraux A, Benichou J, Guillevin L, Idbrik L, Job-Deslandre C, Sibilia J, Soudant M, Wendling D, Guillemin F.
Clin Exp Rheumatol. 2015 Aug 27.

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REGULATION

EMA

Human medicines European public assessment report (EPAR): Humira, adalimumab
Revision: 39, Authorised
August 2015

Human medicines European public assessment report (EPAR): NovoEight, turoctocog alfa
Revision: 2, Authorised
August 2015

Human medicines European public assessment report (EPAR): Tysabri, natalizumab
Revision: 19, Authorised
August 2015

Workshop on haemophilia registries
European Medicines Agency, London, UK, From: 01-Jul-2015, To: 02-Jul-2015
Updated
August 2015

Scientific guideline: Guideline for good clinical practice E6(R2) 4 - Step 2b
Draft : **consultation open**
Consultation start date 04/08/2015
Consultation end date 03/02/2016

Scientific guideline: Guideline on good pharmacovigilance practices (GVP) - Module VIII Addendum I – Requirements for transmission of information on non-interventional post-authorisation safety studies (Rev. 2)
Draft : **consultation open**
Consultation start date 11/08/2015
Consultation end date 09/10/2015

List of nationally authorised medicinal products: human coagulation factor VIII (antihemophilic factor A) PSUSA/00001620/201411
August 2015

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Human medicines European public assessment report (EPAR): Simponi, golimumab
Revision: 22, Authorised
August 2015

Human medicines European public assessment report (EPAR): Avonex, interferon beta-1a
Revision: 23, Authorised
August 2015

Human medicines European public assessment report (EPAR): Rebif, interferon beta-1a
Revision: 30, Authorised
August 2015

Human medicines European public assessment report (EPAR): RoActemra, tocilizumab
Revision: 18, Authorised
August 2015

Public summary of the evaluation of a proposed product-specific waiver: Belimumab for treatment of systemic lupus erythematosus
August 2015

Human medicines European public assessment report (EPAR): Inflectra, infliximab
Revision: 8, Authorised
August 2015

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