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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 **February 2014** 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 Koudriavtseva et al. on the long term follow up of peripheral blood lymphocyte subsets in multiple sclerosis patients treated with natalizumab.

In addition, you will find in this issue some news form the biopharmaceutical regulation field.

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

Natalizumab is among the most effective treatments currently available for remitting relapsing multiple sclerosis (RRMS) patients. This humanized monoclonal antibody directed against the α4ß1-integrin molecule (VLA-4) on mononuclear white blood cells prevents adhesion to the vascular endothelium VCAM-1 molecule, hence significantly reducing extravasation of lymphocytes and other inflammatory immune cells across the blood-brain barrier, a mechanism thought to highly contribute to natalizumab efficacy in ameliorating RRMS patients.

In previous short term studies, natalizumab was recurrently found to increase the number of circulating lymphocytes in RRMS patients. Here, Koudriavtseva *et al.* sought to evaluate the impact of natalizumab treatment on the peripheral blood lymphocyte compartment in a longitudinal retrospective observational cohort of 23 RRMS patients, treated for at least 24 (medium term) to 48 (long term) months. Healthy matched subjects were included and non-availability of lymphocyte counts data at baseline was one exclusion criteria. Of note, there were no significant difference in baseline values between patients previously treated with Interferon β or glatiramer acetate. As well, no patients experienced relapse or showed new lesion on RMI over the study period suggestive of natalizumab efficacy.

As the level of expression of α4ß1-integrin varies amongst the lymphocyte population with B cells exhibiting higher level of integrins than T cells for instance, the authors followed not only total lymphocytes but also B, CD4 T, CD8 T and NK cells numbers over time. In fact, as previously observed, the number of lymphocytes increased over time. Within this population, B cells experienced the higher increase. CD4 and CD8 T cells numbers augmented in such manner that the CD4/CD8 ratio did not significantly differed from baseline over time, and a significant increase from baseline was also observed for peripheral NK cells. However It was difficult to solely relate those increases to natalizumab-induced diminished extravasation since natalizumab has also been shown to mobilize haematopoietic precursor cells from the bone marrow.

Long term follow up of peripheral lymphocyte subsets in a cohort of multiple sclerosis patients treated with natalizumab.
Koudriavtseva T, Sbardella E, Trento E, Bordignon V, D'Agosto G, Cordiali-Fei P.
Clin Exp Immunol. 2014 Jan 6.

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Immunogenicity

Aggregation of human recombinant monoclonal antibodies influences the capacity of dendritic cells to stimulate adaptive T-cell responses in vitro.

Rombach-Riegraf V, **Karle AC**, Wolf B, Sordé L, Koepke S, Gottlieb S, Krieg J, Djidja MC, Baban A, **Spindeldreher S,** Koulov AV, Kiessling A.
PLoS One. 2014 Jan 21;9(1):e86322

Identification of oxidation sites and covalent cross-links in metal catalyzed oxidized interferon Beta-1a: potential implications for protein aggregation and immunogenicity.

Torosantucci R, Sharov VS, van Beers M, Brinks V, Schöneich C, Jiskoot W.
Mol Pharm. 2013 Jun 3;10(6):2311-22

Clinical significance of immunogenicity in biologic therapy.

Rivera R, Herranz P, Vanaclocha F.
Actas Dermosifiliogr. 2014 Jan-Feb;105(1):1-4.

Autoimmune thyroid disorders during anti-TNF alpha therapy: Coincidence, paradoxical event or marker of immunogenicity?

Pascart T, Ducoulombier V, Roquette D, Perimenis P, Coquerelle P, Maury F, Baudens G, Morel G, Deprez X, Flipo RM, Houvenagel E.
Joint Bone Spine. 2013 Dec 30. pii: S1297-319X(13)00280-7.

Influence of aggregation and route of injection on the biodistribution of mouse serum albumin.

Kijanka G, Prokopowicz M, Schellekens H, Brinks V.
PLoS One. 2014 Jan 22;9(1):e85281.

Bioanalytical challenges of biosimilars.
Islam R.
Bioanalysis. 2014 Feb;6(3):349-56.

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Methods

Development of at-line assay to monitor charge variants of MAbs during production.

St Amand MM, Ogunnaike BA, Robinson AS.

Biotechnol Prog. 2013 Dec 19

Anti-Interferon Beta Antibody Titers Strongly Correlate Between Two Bioassays and In Vivo Biomarker Expression, and Indicates That a Titer of 150 TRU/mL Is a Biologically Functional Cut-Point.

Hermanrud C, **Ryner ML**, Engdahl E, **Fogdell-Hahn A.**

J Interferon Cytokine Res. 2014 Jan 20.

Animal models

IL-33 Neutralization Suppresses Lupus Disease in Lupus-Prone Mice.

Li P, Lin W, Zheng X.

Inflammation. 2014 Jan 8.

Of mice and men: how animal models advance our understanding of T-cell function in RA.

Kobezda T, Ghassemi-Nejad S, Mikecz K, Glant TT, Szekanecz Z.

Nat Rev Rheumatol. 2014 Jan 7.

Anti-CD20 as the B-Cell Targeting Agent in a Combined Therapy to Modulate Anti-Factor VIII Immune Responses in Hemophilia a Inhibitor Mice.

Liu CL, Ye P, Lin J, Butts CL, Miao CH.

Front Immunol. 2014 Jan 6;4:502.

Anti-CD79 Antibody Induces B Cell Anergy That Protects against Autoimmunity.

Hardy IR, Anceriz N, Rousseau F, Seefeldt MB, Hatterer E, Irla M, Buatois V, Chatel LE, Getahun A, Fletcher A, Cons L, Pontini G, Hertzberg NA, Magistrelli G, Malinge P, Smith MJ, Reith W, Kosco-Vilbois MH, Ferlin WG, Cambier JC.

J Immunol. 2014 Jan 17

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Biomarkers

Biomarkers of treatment response in multiple sclerosis.
Buck D, **Hemmer B.**
Expert Rev Neurother. 2014 Feb;14(2):165-72.

Neurofilament light antibodies in serum reflect response to natalizumab treatment in multiple sclerosis.
Amor S, van der Star BJ, Bosca I, Raffel J, Gnanapavan S, Watchorn J, Kuhle J, Giovannoni G, Baker D, Malaspina A, Puentes F.
Mult Scler. 2014 Feb 10.

Serum microRNA Levels in Patients with Crohn's Disease during Induction Therapy by Infliximab.
Fujioka S, Nakamichi I, Esaki M, Asano K, Matsumoto T, Kitazono T.
J Gastroenterol Hepatol. 2014 Jan 22.

Predictors of response to Infliximab in children with luminal Crohn's disease.
Grover Z, Biron R, Carman N, Lewindon P.
J Crohns Colitis. 2014 Jan 17. pii: S1873-9946(13)00450-9

Reduction of peripheral blood T cells producing IFN-γ and IL-17 after therapy with abatacept for rheumatoid arthritis.
Scarsi M, Zanotti C, Chiarini M, Imberti L, Piantoni S, Frassi M, Tincani A, Airo' P.
Clin Exp Rheumatol. 2014 Jan 14.

Systemic Lupus Erythematosus

Recent developments in the treatment of patients with systemic lupus erythematosus: focusing on biologic therapies.
Fattah Z, Isenberg DA.
Expert Opin Biol Ther. 2014 Jan 6.

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Successful application of belimumab in two patients with systemic lupus erythematosus experiencing a flare during tocilizumab treatment.

Jüptner M, Zeuner R, Schreiber S, Laudes M, Schröder J.

Lupus. 2014 Jan 30.

Which B-cell subset should we target in lupus?

Ferraccioli G, Houssiau FA.

Ann Rheum Dis. 2013 Dec;72(12):1891-2.

Rheumatoid Arthritis

Genetics of rheumatoid arthritis contributes to biology and drug discovery.

The RACI consortium (95 collaborators)

Nature. 2013 Dec 25.

Safety and effectiveness of adalimumab in patients with rheumatoid arthritis over 5 years of therapy in a phase 3b and subsequent postmarketing observational study.

Burmester GR, Matucci-Cerinic M, **Mariette X,** Navarro-Blasco F, Kary S, Unnebrink K, Kupper H.

Arthritis Res Ther. 2014 Jan 27;16(1):R24.

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Das S, Vital EM, Horton S, Bryer D, El-Sherbiny Y, Rawstron AC, Ponchel F, Emery P, Buch MH.

Ann Rheum Dis. 2014 Jan 2.

Risk estimation in rheumatoid arthritis-from bench to bedside.

van der Helm-van Mil AH.

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Clinical, radiographic and immunogenic effects after 1 year of tocilizumab-based treatment strategies in rheumatoid arthritis: the ACT-RAY study.

Dougados M, Kissel K, Conaghan PG, Mola EM, Schett G, Gerli R, Hansen MS, Amital H, Xavier RM, Troum O, Bernasconi C, **Huizinga TW.**

Ann Rheum Dis. 2014 Jan 28.

One-year Efficacy and Safety Results of Secukinumab in Patients With Rheumatoid Arthritis: Phase II, Dose-finding, Double-blind, Randomized, Placebo-controlled Study.

Genovese MC, Durez P, Richards HB, Supronik J, Dokoupilova E, Aelion JA, Lee SH, Codding CE, Kellner H, Ikawa T, Hugot S, Ligozio G, Mpofu S.

J Rheumatol. 2014 Jan 15.

Efficacy of biological disease-modifying antirheumatic drugs: a systematic literature review informing the 2013 update of the EULAR recommendations for the management of rheumatoid arthritis.

Nam JL, Ramiro S, Gaujoux-Viala C, Takase K, Leon-Garcia M, Emery P, Gossec L, Landewe R, Smolen JS, Buch MH.

Ann Rheum Dis. 2014 Jan 7.

Safety of synthetic and biological DMARDs: a systematic literature review informing the 2013 update of the EULAR recommendations for management of rheumatoid arthritis.

Ramiro S, Gaujoux-Viala C, Nam JL, Smolen JS, Buch M, Gossec L, van der Heijde D, Winthrop K, Landewé R.

Ann Rheum Dis. 2014 Jan 8.

Efficacy of biologic agents in improving the Health Assessment Questionnaire (HAQ) score in established and early rheumatoid arthritis: a meta-analysis with indirect comparisons.

Barra L, Ha A, Sun L, Fonseca C, Pope J.

Clin Exp Rheumatol. 2014 Jan 24

Theory-based analysis of anti-inflammatory effect of TNF inhibitors on rheumatoid arthritis.

Kimura K, Takayanagi R, Yokoyama H, Yamada Y.

Drug Metab Pharmacokinet. 2014 Jan 14.

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Certolizumab pegol in rheumatoid arthritis patients with low to moderate activity: the CERTAIN double-blind, randomised, placebo-controlled trial.

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Ann Rheum Dis. 2014 Jan 15.

Certolizumab for rheumatoid arthritis.

Markatseli TE, Papagoras C, Nikoli A, Voulgari PV, Drosos AA.

Clin Exp Rheumatol. 2014 Jan 20

Effectiveness of TNF inhibitor switch in RA: results from the national Swedish register.

Chatzidionysiou K, Askling J, Eriksson J, Kristensen LE, van Vollenhoven R; for the ARTIS group.

Ann Rheum Dis. 2014 Jan 15.

Rituximab versus an alternative TNF inhibitor in patients with rheumatoid arthritis who failed to respond to a single previous TNF inhibitor: SWITCH-RA, a global, observational, comparative effectiveness study.

Emery P, Gottenberg JE, Rubbert-Roth A, Sarzi-Puttini P, Choquette D, Martínez Taboada VM, Barile-Fabris L, Moots RJ, Ostor A, Andrianakos A, Gemmen E, Mpofu C, Chung C, Gylvin LH, Finckh A.
Ann Rheum Dis. 2014 Jan 29

Inflammatory Bowel Disease

Review article: anti-adhesion therapies for inflammatory bowel disease.

Lobatón T, **Vermeire S**, Van Assche G, Rutgeerts P.

Aliment Pharmacol Ther. 2014 Jan 30.

Therapeutic Drug Monitoring of Anti-TNF Therapy in Inflammatory Bowel Disease.

Scott FI, Lichtenstein GR.

Curr Treat Options Gastroenterol.

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Biologic therapies in inflammatory bowel disease.

Cohen LE, Nanau RM, Delzor F, Neuman MG.

Transl Res. 2014 Jan 7. pii: S1931-5244(14)00003-6.

Systematic review with meta-analysis: malignancies with anti-tumour necrosis factor-α therapy in inflammatory bowel disease.

Williams CJ, Peyrin-Biroulet L, Ford AC.

Aliment Pharmacol Ther. 2014 Jan 20.

Multiple Sclerosis

Multiple sclerosis in 2013: Novel triggers, treatment targets and brain atrophy measures.
Montalban X, Tintoré M.
Nat Rev Neurol. 2014 Feb;10(2):72-3.

Immunology of Relapse and Remission in Multiple Sclerosis.
Steinman L.
Annu Rev Immunol. 2014 Jan 15.

Differential effects of fingolimod on B-cell populations in multiple sclerosis.
Nakamura M, Matsuoka T, Chihara N, Miyake S, Sato W, Araki M, Okamoto T, Lin Y, Ogawa M, Murata M, Aranami T, Yamamura T.
Mult Scler. 2014 Feb 13.

The challenges of measuring disability accumulation in relapsing-remitting multiple sclerosis: evidence from interferon beta treatments.
Kieseier BC.
Expert Rev Neurother. 2014 Jan;14(1):105-20.

The efficacy and safety of daclizumab and its potential role in the treatment of multiple sclerosis.

Milo R.

Ther Adv Neurol Disord. 2014 Jan;7(1):7-21.

Safety and efficacy of ofatumumab in relapsing-remitting multiple sclerosis: A phase 2 study.

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Basic immunology

GILT: Shaping the MHC Class II-Restricted Peptidome and CD4 T Cell-Mediated Immunity.
Hastings KT.
Front Immunol. 2013 Dec 4;4:429

Opinions/Commentaries

Do immunoglobulin levels and CD4 cell count interact during Rituximab treatment?
Mulleman D.
Arthritis Rheumatol. 2014 Jan 27. doi: 10.1002/art.38361.

Direct and indirect rituximab-induced T-cell depletion.
Thibault G, **Mulleman D.**
Arthritis Rheum. 2014 Jan 8.

Putting the value into biosimilar decision making: The judgment value criteria.
Mendes de Abreu M, Strand V, Levy RA, Araujo DV.
Autoimmun Rev. 2014 Jan 15. pii: S1568-9972(14)00063-9.

The BAFF/APRIL system: emerging functions beyond B cell biology and autoimmunity.
Vincent FB, Saulep-Easton D, Figgett WA, Fairfax KA, Mackay F.
Cytokine Growth Factor Rev. 2013 Jun;24(3):203-15.

Interleukin-22: A likely target for treatment of autoimmune diseases.
Yang X, Zheng SG.
Autoimmun Rev. 2014 Jan 10. pii: S1568-9972(14)00010-X

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REGULATION

EMA

Scientific guideline: Guideline for the conduct of efficacy studies for non-steroidal anti-inflammatory drugs
Adopted : January 14
Date for coming into effect : August 14


EMA Guideline.pdf

Orphan designation: Humanised monoclonal modified IgG4 antibody with bispecific structure targeting factors IX, IXa, X and Xa for the treatment of haemophilia A
January 14

Human medicines European public assessment report (EPAR): Benlysta, belimumab
Revision: 8, Authorised
Januray 2014

Human medicines European public assessment report (EPAR): Inflectra, infliximab
Revision: 2, Authorised
January 2014

Orphan designation:Recombinant human monoclonal antibody to human IL-1beta of the IgG1/K class
Updated
January 2014

Human medicines European public assessment report (EPAR): Simponi, golimumab
Revision: 16, Authorised
January 2014

Human medicines European public assessment report (EPAR): ReFacto AF ,moroctocog alfa
Revision: 26, Authorised
January 2014

Opinion/decision on a Paediatric Investigation Plan (PIP): Cimzia, Certolizumab pegol
Therapeutic area: Immunology-Rheumatology-Transplantation
Updated
January 2014

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Human medicines European public assessment report (EPAR): MabThera, rituximab
Revision: 31, Authorised
January 2014

Human medicines European public assessment report (EPAR): Cimzia, certolizumab pegol
Revision: 10, Authorised
January 2014

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