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Therapeutic antibodies and infectious diseases

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The Therapeutic Antibodies and Infectious Diseases international congress was held in Tours, France on November 20–22, 2012. The first session was devoted to the development of antibodies directed against bacterial toxins or viruses that could be used in a potential bioterrorist threat situation. The second session dealt with the effector functions of anti-microbial antibodies, while the third was oriented toward anti-viral antibodies, with a special emphasis on antibodies directed against the human immunodeficiency and hepatitis C viruses. After a lecture by a speaker from the US Food and Drug Administration on antibody cocktails, the second day ended with a special session dedicated to discussions regarding the involvement of French biotechnology industries in the field. On the last day, the congress concluded with talks about current antibody treatments for infectious diseases, with a particular focus on their adverse events. Participants enjoyed this very stimulating and convivial meeting, which gathered scientists from various countries who had different scientific research interests.

Introduction

The Therapeutic Antibodies and Infectious Diseases international congress[1] opened on November 20, 2013 at the Vinci International Congress Centre with a welcome message from the organizers. **Philippe Roingeard** (UMR INSERM U966—Université François-Rabelais de Tours, France) recalled the importance of the University in the region Centre, with singular emphasis on its international character. Microbial immunology is particularly well-represented in its faculties of Pharmacy, Medicine and Sciences. Philippe Maupas, former Dean of the Faculty of Pharmacy, discovered the hepatitis B vaccine in Tours in 1976 and the French National HIV Reference Center, directed by Professor Francis Barin, is located in the University Hospital of Tours. **Hervé Watier** (CNRS—UMR 7292, Université François-Rabelais de Tours, France) then discussed the historical aspect of the meeting in connection with the 150th anniversary of the death of Pierre-Fidèle Bretonneau, who first described diphtheria. A satellite symposium to commemorate this event was held on the day before; a report of this symposium is also published in this issue of *mAbs*. He continued with the evocation of anti-diphteric serotherapy developed by Emil von Behring and Shibasaburo Kitasato in Germany, then by Emile Roux, Louis Martin, Auguste Chaillou in France.

Although French scientists played a great role in the development of "polyclonal" antibodies, none of the ~30 monoclonal antibodies (mAbs) currently marketed was developed by French groups. To remedy this situation, a Groupement De Recherche (GDR) "Antibodies and Therapeutic targeting" was created in 2009, with funding from the *Centre National de la Recherche Scientifique* (CNRS). This network gathers a hundred research groups from public research (2/3) and from the biopharmaceutical industry (1/3). Thanks to the French national "Investment for the Future" program (French "Big Loan"), a laboratory of excellence (LabEx) called "MAbImprove" has been launched between Tours and Montpellier.[2] It includes 14 teams and approximately 200 researchers working on the pharmacology of therapeutic antibodies. **Dominique Buzoni-Gatel** (UMR 1282—ISP, INRA de Nouzilly, France) described the Cluster of Infectious Diseases of the Région Centre, its technical platforms, animal experimentation facilities, as well as microbiological resources mostly located near Tours in the Institut National de la Recherche Agronomique (INRA) campus.[3] This cluster aims at developing partnerships with pharmaceutical companies, helping young researchers, promoting international exchanges. The organization of this congress results from a synergistic initiative of this cluster, of the GDR "Antibodies and Therapeutic targeting" and of the MAbImprove LabEx.

Day 1: Anti-Bacterial Antibodies

The first session about bioterrorism was introduced by the representative of the French Minister of Defense, which provides all the support from the authorities concerning the development of antibodies against bioterrorism weapons. This session, chaired by **Nathalie Heuzé-Vourc'h** (CEPR—EA 6305, Université François-Rabelais de Tours, France) and **Philippe Thullier** (Unité de biotechnologie des anticorps et des toxines—Institut de Recherche Biomédicale des Armées (IRBA), La Tronche, France), started with a talk from **Thibaut Pelat** (Unité de biotechnologie des anticorps et des toxines—IRBA, La Tronche, France). He first discussed the history of bioterrorist threats, mentioning in particular the dissemination of anthrax spores in the US in 2001. The pathogenicity of *B. anthracis* mainly depends on its lethal

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toxin (LT), which is quickly secreted after infection. Antibodies neutralizing LT have been demonstrated to synergize with antibiotics to increase the therapeutic window. To develop highly neutralizing antibodies targeting the protective antigen (PA), a subunit of LT, a macaque was hyperimmunized and an immune library was created after PCR amplification of variable heavy (VH) and variable light (VL) coding genes. By phage display, a high-affinity Fab was isolated, Fab $35PA_{83}$, which neutralizes LT by competing directly for its cell receptor.[4] Once expressed as a human immunoglobulin (Ig) G1k, $35PA_{83}$ efficiently protected experimentally infected mice and rabbits, suggesting that the use of IgG $35PA_{83}$ could be envisioned to improve the pre-exposure and post-exposure treatment of anthrax. In parallel, the antigen-binding fragment (Fab) $35PA_{83}$ has been engineered to improve its affinity for PA through random mutations of its complementarity-determining regions (CDRs) and a new variant, 6.20, with a 19-fold enhanced affinity was isolated.[5] The clinical development of this variant, under the name of "ATHENA project," has now started. The IgG derived from 6.20 has the best affinity among all anti-PA IgGs now under clinical development, and an excellent protective capacity is expected. A single-chin variable fragment (scFv), 2LF, neutralizing LT, but directed against its LF subunit, has also been isolated using the same strategy, in addition to a scFv (43RCA) that neutralizes ricin. Currently, Thibaut Pelat's unit coordinates the AntiBotABE European project (FP7), which aims at isolating IgGs neutralizing botulinum toxins.

Thereafter, **Dubravka Drabek** explained how scientists in her Department of Cell Biology at Erasmus Medical Center, Rotterdam, Netherlands, were able to generate transgenic mice containing hybrid llama/human antibody loci (containing two llama variable regions, all human D and J regions and the human Cγ2 and Cγ3 constant regions with or without Cμ).[6] Thus, antigen-specific heavy-chain-only antibodies (HCAbs) of appropriate classes were produced in mice at high levels upon any immunization. A novel method of producing specific human chimeric heavy-chain-only antibodies providing a full antibody repertoire was described. Professor Drabek then focused her talk on the virulence of staphylococcal Panton-Valentine leukocidin (PVL), which creates pores in cells, inducing their osmotic lysis.[7] As HCAbs have many advantages (e.g., stable, soluble and easy to produce), her group decided to generate leukocidin neutralizing HCAbs that bind to bi-component toxin, preventing its action. Initial in vitro and in vivo experimental results appeared promising.

Starting with the example of neutralizing antibodies against diphtheria or tetanus toxins, **Bradley G. Stiles** (Biology Department of Wilson College, Chambersburg, USA) demonstrated the potential benefits of developing mAbs with high affinity for toxins. The 25 staphylococcal enterotoxins responsible for foodborne illness are all possible weapons of bioterrorism. Ten human recombinant monoclonal Fabs were obtained by immunization of human volunteers with attenuated enterotoxin B.[8] In vitro assays with peripheral blood mononuclear cells and in vivo assays in mice demonstrated an interesting cross-reaction with staphylococcal enterotoxin SEC1/SEC2 and with exotoxin (Spe)C of *Streptococcus pyogenes*. Four of these Fabs were further selected and then expressed as full-length IgGs. Among them, two antibodies exhibited a particularly high specificity and neutralizing activity. They could be also useful in the struggle against staphylococcal and streptococcal infections, in addition to conventional antibiotic therapy.

Anti-Viral Antibodies (I)

An urgent need exists for biopharmaceutical countermeasures to emerging viral infections that could be exploited in bioterrorism, as was discussed in this session chaired by **Isabelle Dimier-Poisson** (ISP Eq. 9—Université François-Rabelais de Tours, France) and **Denys Brand** (UMR INSERM U966—Université François-Rabelais de Tours, France). **Dimiter S. Dimitrov** (National Cancer Institute—National Institutes of Health, Frederick, USA) presented data for m102.4, a human antibody improved by affinity maturation that cross-targets glycoproteins of Nipah and Hendra viruses, mimicking the ephrin-B2 ligand. Testing in ferret and monkey models led to particularly convincing results, even when the mAb was used three days after virus challenge.[9,10] m102.4 demonstrated an excellent safety profile when administered to four humans exposed to Hendra virus in Australia, and it is currently under development by the US National Institute for Allergy and Infectious Diseases and by the Australian government as a prophylactic and therapeutic agent.

Jeffrey W. Froude (United States Army Medical Research and Material Command, Fort Detrick, USA) gave two presentations about the development and use of therapeutic antibodies in Filovirius infections, Marburg and Ebola hemorrhagic fever viruses. For his first presentation, he spoke as a substitute for John M. Dye (US Army Medical Research Institute for Infectious Diseases). Prior studies utilizing antibody therapeutics were unsuccessful in protecting animals from filovirus infection. In novel experiments, Dye et al. reported that macaques were iteratively treated with polyclonal antibodies from convalescent species-matched animals demonstrating complete protection when initiated 48 h post-exposure.[11] Additionally, sustainable immunity was obtained due to protection achieved upon rechallenge with the same virus; thus, the utility of post-exposure antibody administration was clearly demonstrated. Based on these results, collaboration between USAMRIID and IRBA-CRSSA to isolate recombinant antibodies by phage display technology was initiated.[12] This topic was discussed in Captain Froude's second presentation. In two studies, immune libraries were obtained from macaques immunized with virus-like particles expressing the envelope glycoprotein of Marburg and Sudan virus. Of several scFvs obtained and characterized, R4A1 appears as the most active in neutralizing the Marburg virus, while X10B1 appears effective against Sudan virus.

Day 2: Anti-Microbial Antibodies and Effector Functions

Chaired by **Dominique Buzoni-Gatel** (UMR 1282 ISP—INRA de Nouzilly, France) and **Gilles Thibault** (UMR—CNRS 7292, Université François-Rabelais de Tours, France) Wednesday's first

session was devoted to anti-microbial antibodies effector functions. **Antonio Perez** (Kenta Biotech AG, Zürich-Schlieren, Switzerland) initiated his talk with an overview of *Pseudomonas aeruginosa* strains, which are classified according to their lipopolysaccharides (LPS) serotype, a structure also involved in its pathogenesis. Panobacumab, a human IgM mAb, showed its efficacy against *Pseudomonas aeruginosa* infection in rodents,[13] and its tolerance profile was good in humans. A Phase 2 study demonstrated an overall survival rate of 100% in 13 patients receiving panobacumab,[14] with only two relapses vs. 79% in a retrospective cohort, with a clinical resolution rate of 85% vs. 57%, respectively, and the resolution time was shorter with panobacumab (8 vs. 18.5 d). This antibody could therefore become a good adjuvant to antibiotic therapy.

The audience was particularly enthusiastic after **Pierre Bruhns** (Immunology Department, Pasteur Institute of Paris) discussed redefining the concept of activating and inhibiting properties of Fc receptors (FcR). In the INSERM U760, his group did extensive research on the specificity and affinity of human and mouse IgG subclasses for the different FcRs of both species.[15] Substantial differences exist between human and mouse FcRs, particularly in terms of expression pattern on hematopoietic cell subsets.[16] Working with mice expressing human FcRs, he presented recent data on the involvement of human FcγRI (CD64) in the therapeutic effect of anti-cancer mAbs and of both human FcγRI (CD64) and human FcγRIIA (CD32A) in the pathologic effect of antibodies in arthritis and anaphylaxis.[17,18]

Anton Bauer (Intercell AG, Vienna, Austria) started by discussing the need for new prophylactic or therapeutic agents against influenza. The M2 membrane protein was chosen as a candidate target because of its very conserved consensus sequences and its recognized role in passive immunization.[19] The anti-M2 antibody D005 with affinity in the subnanomolar range was selected on the eMAB® proprietary platform, which combines the advantages of rapid FACS-based selection of antigen specific human B cells with the variability given by recombinant libraries displayed on mammalian cells.[20] D005 conferred full protection in mice when applied prophylactically at concentrations as low as 20 μg, lowering fever and diminishing weight loss; D15-overall survival was 100%. D005 also demonstrated a therapeutic effect until day 2 post-flu challenge. A cross-protection was shown against both Influenza A group 1 and group 2 strains.[19] Because D005 failed to directly neutralize the virus in vitro and FcγRIII appeared involved in mice with the UV-inactivated influenza virus, the mechanism of action appeared to be based on elimination of infected cells by antibody-dependent cell-mediated cytotoxicity (ADCC). Indeed, natural killer cells played a crucial role for M2-mediated protection.[21]

In the absence of Antonio Lanzavecchia who was prevented from attending at the last minute, **Mireia Pelegrin** (Institute of Molecular Genetics of Montpellier, France) concluded the session dedicated to effector functions with a brilliant talk. She first presented her robust and reproducible murine model of FrCasE retrovirus-induced leukemia and the ability of the neutralizing 667 mAb (an anti-gp70 IgG2a) to induce a life-long protective immune response composed of a cytotoxic cellular immune response, as well as a humoral response able to lyse infected cells by ADCC mechanism.[22] Immune complexes formed between the administered mAb and infected cells played a key role in the initiation and in the maintenance of such immune response, given that they enhanced antiviral CTL responses in an Fc-dependent way.[22,23]

Anti-Viral Antibodies (II)

The second session on anti-viral antibodies was chaired by **Francis Barin** (UMR INSERM U966—Université François-Rabelais de Tours, France) and **Stéphane Paul** (INSERM CIE3—Vaccinologie, Groupe Immunité des Muqueuses et Agents Pathogènes, Faculté de Médecine de Saint-Etienne), France and initiated by **Pascal Poignard** (IAVI Neutralizing Antibody Center, The Scripps Research Institute, La Jolla, USA). He began his allocution by pointing out that neutralizing antibodies have been shown to protect against HIV, i.e., they can prevent infection in animal models. Unfortunately, the extreme variability of the virus is a major obstacle, and until 2009 only a handful of antibodies able to neutralize a large proportion of the global HIV isolates, i.e., broadly neutralizing antibodies (bnMAbs), was available. Recently, it was shown that a few patients develop broadly neutralizing antibody responses; such elite neutralizers were selected from a collection of 1,800 blood samples for isolation of bnMAbs in collaboration with Theraclone Sciences Inc.[24,25] The research resulted in the characterization of a number of novel broad and highly potent antibodies targeting in particular glycan-dependent epitopes. One of them (PGT 121) is giving promising preclinical results; a dose of 1 mg/kg provides 100% protection in macaques challenged with the chimeric simian/HIV SHIV SF162P3.[26] A flurry of additional potent bnMAbs has now been isolated by various groups in the field. While Poignard et al. previously found limited effects of anti-HIV antibodies,[27] it has recently been shown that a cocktail of the new highly potent bnMAbs can control viral replication in a mouse model of HIV infection,[28] raising new hopes for the treatment of patients.

Naima Abidi-Azzouz (Biochimie Macromoléculaire, Montpellier, France) then presented results on dromedary nanobodies targeting the active site of HIV reverse transcriptase (RT), a critical enzyme for viral replication of the RNA single-strand.[29] Nanobody NbRT20 is a conformational noncompetitive inhibitor recognizing both RT subunits, blocking its DNA polymerase enzymatic activity and limiting intracellular HIV replication in PBMC when combined with the cell penetrating peptide Pep-1. It stabilizes the inactive form of the RT, preventing consequently the processing of dNTP.

Anti-Viral Antibodies (III)

Philippe Roingeard (UMR INSERM U966—Université François-Rabelais de Tours, France) and **Valérie Gouilleux-Gruart** (GICC—UMR CNRS 6239, Université François-Rabelais de Tours, France) chaired the last session on anti-viral antibodies. **Laurent Dacheux** (National Reference Centre for Rabies, Institut Pasteur, Paris, France), first described the

importance of rabies in developing countries, a major but neglected public health issue, with an estimated 55,000 human deaths reported each year. Efficient post-exposure prophylaxis (PEP) requires timely administration of tissue-culture vaccine, in combination with polyclonal rabies immunoglobulins (RIG) of human or equine origin in case of severe exposure. Nearly 60% of severely exposed individuals, however, do not receive any passive immunotherapy due to the high cost and short supply of RIG. The development and massive production of antirabies mAbs and their use as cocktails therefore represent a promising alternative to traditional polyclonal preparations, overcoming the major drawbacks associated to RIG.[30] Nearly ten clinical trials are in progress with candidate drugs that demonstrated activity in vitro or in vivo.[31]

The two next presentations were devoted to hepatitis C virus. **Pierre Lafaye** (Pasteur Institute of Paris, France) generated nanobodies by immunizing alpacas with soluble monomeric hepatitis C virus (HCV) E2-ectodomain of genotype 2BE2e.[32] Among the four VHH candidates isolated by phage display, D03 had the highest in vitro neutralizing potential on virus-like particles and viral cultures, regardless of the HCV genotype tested. Moreover, its activity is preserved on virus with a mutated E2-glycoprotein; VHH D03 is also the only antibody fragment that inhibits HCV cell-to-cell transmission.

Mirjam Zeisel (INSERM, Université de Strasbourg, France) then focused on HCV cellular receptors. The group obtained rat mAbs against two HCV receptors, scavenger-receptor class B type-1 (SRB1)[33,34] and *Claudin-1* (CLDN1)[35,36] following cDNA immunization. In vitro neutralization assays with these mAbs showed that both receptors have a critical role in productive HCV infection.[33,36] Anti-SRB1 mAbs modulate the transmission of HCV from cell-to-cell via a key post-binding function.[34] Because these mAbs are active whatever the HCV genotype, including highly infectious patient-derived escape variants, they appear as promising therapeutic approaches.

Keynote Lecture

A highlight of Wednesday afternoon was a lecture by **Patrick G. Swann** (Division of Monoclonal Antibodies, Food and Drug Administration, Bethesda, USA), who was introduced by the chair of the session, **Hervé Watier** (CNRS—UMR 7292, Université François-Rabelais de Tours, France). Dr Swann detailed the regulatory features concerning the development of mAb cocktails to the audience. Starting in the 1980s, numerous mAbs were developed for infectious disease indications. As of November 2012, however, only 1 such mAb (palivizumab, which targets RSV) has been approved (post-meeting note: FDA approved raxibacumab, which targets anthrax toxin, on December 14, 2012). With respect to investigational products, 52 very diverse mAb-related products are now being evaluated in this field, mainly against HIV, hepatitis viruses and influenza viruses. Among them, 5 are presented as cocktails. The development of antibody cocktails is facilitated by existing knowledge listed in the repositories about plasma derivatives and mAbs, including published methods to assess cocktails.[37]

Involvement of the French Biotech Industry in the Field

The last session of the day was chaired by **Jean-Luc Teillaud** (CRC, Equipe 14 Biotechnologie des anticorps, Paris, France) and **André Pelegrin** (Institut de Recherche en Cancérologie de Montpellier, France). In this session, three speakers from French biotechnology companies discussed mAbs for infectious diseases that are currently in development. A recent outbreak in Germany and France alerted the public to lethality due to hemolytic uremic syndrome (HUS) induced by Shiga toxin-producing *E. coli* (STEC).[38] **Christian K. Behrens** (LFB Biotechnologies, Les Ulis, France) presented the design and results of the Phase 2 SHIGATEC study conducted by its development partner Thallion Pharmaceuticals, Inc., which assessed the safety and efficacy of Shigamabs®. This drug is composed of two chimeric mAbs (cαStx1 and cαStx2), each targeting one of the two secreted toxins, that have demonstrated activity in vitro on different serovars and Shiga toxin (Stx) subtypes. Forty-five children with macroscopic bloody diarrhea for less than 36 h and STEC-positive stools were randomized into three groups receiving either 1 or 3 mg/kg of each antibody or placebo. Three serious adverse events, including two cases of HUS, were reported and all were considered unrelated to study the drug. Adverse events were mostly mild and transient and equally distributed between groups. One patient from the 3 mg/kg group developed an asymptomatic immune response against cαStx2. Shigamabs® thus appeared safe and well-tolerated in STEC-infected children. Given the small sample size, no clear trends in efficacy were observed in this study.

Majid Mehtali (Vivalis, Saint-Herblain, France) brilliantly revealed the Viva/Screen™ technology to the audience. This technology allows the exhaustive detection of specific antibody-secreting B cells from peripheral blood of donors. Each coated well of a microarray chip with 62,500–250,000 wells is conceived to isolate single B cells through immunoadsorption specific of their BCR, producing biologically active antibodies (which represents 1–5% of the total antibodies), even if they are in infinitesimal quantities. B cells of interest are extracted from the considered well, then genes are isolated and antibodies are industrially produced. In collaboration with several pharmaceutical companies, this technique has potential application in the field of anti-infectious biopharmaceuticals.

Laurent Fraisse (Sanofi, Toulouse, France), concluded the session by presenting two of the 20 immunotherapeutic projects currently in development in Sanofi. The humanized IgG1 mAb SAR279356 recognizes the poly-N-acetyl-glucosamine polysaccharide of the bacterial cell wall and displays opsonophagocytic functions.[39] Its protective activity was demonstrated in murine models of *S. aureus* systemic and local infection, pneumococcal pneumonia, *K. pneumoniae* systemic infection and *A. baumannii* tracheo-pulmonar infection. Phase 1 studies showed two cases (from 20) of local skin reactions at infusion site immediately after administration, but no anti-drug antibodies; SAR279356 is currently in a Phase 2 study for the prevention of nosocomial infections in intensive care unit patients on mechanical ventilation. To widen the spectrum of nosocomial infections considered, an

agreement has been concluded between Sanofi and KaloBios to develop KB001-A, a pegylated monoclonal Fab fragment directed against PcrV, a structural protein of Type III secretion system involved in the pathogenesis of *P. aeruginosa*. KB001 protected mice in a model of lung infection.[40] A Phase 2 clinical trial in ventilated patients colonized with *P. aeruginosa* demonstrated a satisfactory general tolerance, with a non-significant trend toward fewer *P. aeruginosa* infections beginning from colonized sites.[41]

Day 3: Therapeutic Antibodies and Infectious Diseases: A Double-Edged Sword?

Thursday morning was dedicated to discussion of approved mAbs that can be used to treat patients with infectious diseases. The session chairs **Yvon Lebranchu** (CDG—E.A. 4245, Université François-Rabelais de Tours, France) and **Théodora Angoulvant** (GICC, Université François-Rabelais de Tours, France) introduced the first speaker, **Christian Combe** (INSERM U1026, Université Bordeaux Segalen, France) who recalled the 2011 French outbreak of HUS due to *E. coli* 0104:H4 shigatoxin.[38] Assuming that eculizumab (Soliris®) blocks the complement C5 fraction activation and hence the formation of the membrane attack complex involved in the pathophysiology of HUS,[42] he related the successful use of this humanized mAb in 9 adult patients in his clinical department. Platelet counts returned to normal levels in 3 d, hemoglobin in 7 d and creatinine and LDH concentrations progressively in ~30 d. No major adverse effects were noticed and all patients survived. These new data have contradicted previous studies that did not exhibit a clear beneficial effect, probably because of concomitant plasma exchanges.[43]

Inspired by previous observations in a study of rituximab in cryoglobulinemic vasculitis,[44] **Marcella Visentini** (Sapienza University of Rome, Italy) presented the preliminary results of a Phase 2 single-arm study of rituximab (MabThera®) at low dose (250 mg/m^2 twice) for the treatment of mixed cryoglobulinemia associated with HCV infection.[45] In the first 27 enrolled patients, overall response rate was of 79% with a mean time to relapse of 6.5 mo. Overall, 42% of patients relapsed. Side effects were comparable to those seen in patients treated with high-dose rituximab. Increase in HCV viral load, reported in some previous studies, using high-dose rituximab was not observed in patients treated with low-dose rituximab and serum ALT levels did not change significantly.[46] Based on these results, low-dose rituximab may provide a more cost/effective and possibly safer alternative for treating refractory HCV-associated mixed cryoglobulinemia.

Xavier Mariette (Université de Paris-Sud, France) showed the results of the French RATIO network monitoring opportunistic infections occurring under anti-tumor necrosis factor (TNF) therapies. He emphasized that they are much rarer than the common infections, such as bacterial pneumonias. In his cohort collected over three years, 69 patients developed tuberculosis within the first year following the initiation of therapy, even if 66% presented a prior negative tuberculin intradermal test. This risk was multiplied by 12 compared with the general population. In contrast, there was no case emerging during chemoprophylaxis with rifampicin-isoniazid. Like in a British study,[47] the risk of tuberculosis seemed to be higher with mAbs (infliximab, adalimumab and even certolizumab pegol), compared with the fusion protein etanercept. A similar trend was observed for the 43 cases of non-tuberculous opportunistic infections.[48] A stronger binding of mAbs to the membrane TNF and exacerbated apoptosis of activated T cells is a possible explanation.[49]

By targeting the α4 integrin of T cells, natalizumab (Tysabri®) prevents the entry of pathogenic T cells in brain; the product is indicated as a second-line treatment of multiple sclerosis. It also prevents the entry of anti-JC virus (JCV)-specific T cells in brain, rendering patients more susceptible to progressive multifocal leukoencephalopathy (PML).[50] Studying a cohort of 285 patients treated with natalizumab, **Patrick Vermersch** (Université Lille-Nord, France) showed that the relative risk to develop PML was 0.25%. In these patients with PML, lethality rate was 22%, occurring within 2–3 mo and severe sequelae were noticed in survivors.[51] The risk of PML increased with time of exposure to natalizumab, in the presence of anti-JCV antibodies indicating latent past infection,[52] and with the use of other immunosuppressive therapies prior to initiation of natalizumab. In JCV-seronegative subjects, immunological status should be checked every 6 mo to detect possible seroconversion.

Belatacept, a CTLA4-Fc fusion protein that binds with high affinity to CD80/86,[53] is used to prevent graft rejection in kidney transplant recipients. Although the overall-tolerance profile was satisfactory,[54] an increased risk of early (within 18 mo) post-transplantation lymphoproliferative disorder (PTLD) was observed, mainly in the group receiving high doses. The central nervous system is affected in 57% of cases. The cases of PTLD were reported in 5% of patients presenting primary Epstein-Barr virus (EBV) infections and in only 0.5% of former EBV-seropositive patients. These clinical data was presented by **Bernard Charpentier** (Université de Paris-Sud, France) and highlighted the importance of the CD80/CD86 co-stimulatory pathway in controlling primary EBV infection. As a consequence, belatacept is not indicated in EBV-seronegative patients.

At the end of these fascinating scientific talks, all the attendees left Tours in an enthusiastic ambiance. In spite of the very intensive program, the congress attendance did not decline over the three days, highlighting a general undeniable interest in therapeutic antibodies and infectious diseases.

Disclosure of Potential Conflicts of Interest

No potential conflict of interest were disclosed.

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