Infections associated with monoclonal antibody and fusion protein therapy in humans

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Monoclonal antibodies (mAbs), especially those that interact with immune or hematologic leukocyte membrane targets, have changed the outcome of numerous diseases. However, mAbs can block or reduce immune cells and cytokines, and can lead to increased risk of infection. Some of these risks are predictable and can be explained by their mechanisms of action. Others have been observed only after the mAbs were licensed and used extensively in patients. In this review, we focus on infectious complications that occur upon treatment with mAbs or Fc-containing fusion proteins targeting leukocyte membrane proteins, including CD52, CD20, tumor necrosis factor, VLA4, CD11a and CTLA4. We report their known infectious risks and the recommendations for their use. Although most of these drugs are clinically safe when the indications are respected, we emphasize the need for regular updating of pharmacovigilance data.

Introduction

Monoclonal antibodies (mAbs) have substantially changed the outcome of severe diseases such as rheumatoid arthritis and lymphoma in recent years. These molecules are now frequently used, and some of them have several indications for use in various disorders. The notable feature of mAbs is the specific interaction with an antigen, most of the time an immune or hematologic target. The consequences can be blockade or reduction of effector cell function, depletion of B or T lymphocytes, or inhibition of key intercellular or cytokine interactions; all these mechanisms influence the risk of infection. In some cases, a high risk of infection is expected when the immune target is important for an infectious response, e.g., tumor necrosis factor (TNF). In other cases, the risk of infection was realized after mAbs were licensed and extensively used in patients. Pharmacovigilance is therefore essential for the management of these new drugs. Nevertheless, there have been few reports or recommendations for the uses of therapeutic mAbs.

We review here the known infectious risks and the recommendations for use of the following mAbs and Fc fusion proteins that have been particularly associated with infectious complications in humans in terms of frequency and severity: anti-CD20 alemtuzumab; anti-CD20 rituximab; the TNF-targeting agents infliximab, adalimumab and etanercept; anti-VLA4 natalizumab; anti-CD11a efalizumab; and the CTLA4-Ig fusion proteins abatacept and belatacept.

Anti-CD52 Monoclonal Antibody: Alemtuzumab

Alemtuzumab is a humanized mAb (IgG1kappa) distributed with the trade names of CAMPATH® in the US and MABCAMPATH® in Europe. This antibody is specific to CD52, which is a 21–28 kDa glycoprotein expressed mainly on normal or pathologic B and T peripheral blood lymphocytes. The antigen is also expressed on monocytes, thymocytes, natural killer (NK) cells and macrophages, but not on erythrocytes or platelets. Alemtuzumab targets normal or pathologic mononuclear cells to destroy them, without affecting stem or progenitor cells. This pathway explains the use of alemtuzumab in chronic lymphoid disease and Hodgkin lymphoma, and also in transplantation and graft versus host disease and multiple sclerosis. The drug can also increase regulatory cells in the immune reconstitution phase, induce regulatory T-cell differentiation and inhibit of T-cell transmigration. (1) Different doses are required for different indications, e.g., for hematologic diseases, doses are much higher to obtain effective malignant cell depletion; for transplantation, alemtuzumab was tested as induction therapy to reduce the use of steroid and other conventional immunosuppressive drugs.

Its action appears to be related to antibody-dependent cell-mediated cytotoxicity (ADCC), complement cytotoxicity and apoptosis induction, which leads to neutropenia and reduction in CD4+ and CD8+ T cells, as well as B and NK cells. The cell depletion develops early in treatment, persists for up to a year after therapy is discontinued, and explains opportunistic and non-opportunistic infections. Infectious risk is directly linked to different doses of alemtuzumab administered for different indications.

Several authors reported opportunistic infections and also septicemia and pulmonary infections in refractory chronic lymphocytic leukemia patients treated with alemtuzumab. Such infections led to recommendations regarding pneumocystis and herpes infections, resulting in reduction in the rates of opportunistic infections as reported in the Keating et al. multicenter study.

Martin et al. published a retrospective study in 2006 involving 27 refractory chronic lymphocytic leukemia patients, with
nine patients treated with alemtuzumab combined with prophylactic treatment against pneumocystosis and herpes virus.\textsuperscript{7} Fifteen patients (56\%) developed opportunistic infections and 22 patients (82\%) developed non-opportunistic infections; ten patients died, seven from infections. However, although cytomegalovirus (CMV) viremia significantly increased, survival was greater in the alemtuzumab-treated group.\textsuperscript{7}

In 2007, Peleg et al. reported a retrospective study involving 547 transplant patients who received alemtuzumab.\textsuperscript{5} Fifty-six patients (10\%) developed opportunistic infections, mainly due to CMV, BK virus and Candida; 12 patients died, seven from infections. Patients who received alemtuzumab for induction therapy were significantly less likely to develop opportunistic infections compared with patients who received alemtuzumab for rejection therapy (4.5\% vs. 21\%; \textit{p} < 0.001).

In 2010, Reddy et al. compared alemtuzumab induction to rabbit antithymocyte globulin induction in simultaneous kidney and pancreas transplantation.\textsuperscript{8} There was no difference in the rates of CMV infection or BK nephropathy between the two groups.

Because symptomatic CMV infections are probably the most frequently occurring infections with alemtuzumab therapy (estimated at 10–25\%), different management guidelines, especially in chronic lymphocytic leukemia, recommend monitoring of CMV reactivation by weekly-PCR analysis.\textsuperscript{10,11} When CMV reactivation becomes symptomatic or viremia increases, alemtuzumab therapy should be discontinued and anti-CMV therapy started.

Alemtuzumab induces profound T- and B-cell depletion and is used in refractory LLC and organ transplant induction treatment. The risk of opportunistic infection is high, but seems to depend on the dose that is used regarding the different indications. Its use should be evaluated for each patient according to the risk/benefit ratio (Table 1).

\begin{table}[h]
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\caption{\textbf{Anti-CD20 Monoclonal Antibody: Rituximab}}
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\textbf{Rituximab} (RITUXAN\textsuperscript{\textregistered}, MABTHERA\textsuperscript{\textregistered}) & is a chimeric IgG1 that targets CD20, an antigen expressed on both normal and abnormal B cells. Rituximab thus destroys healthy and normal CD20-expressing B without any effect on progenitor stem cells, T cells, myeloid cells or plasma cells. Rituximab is mainly used in oncology for B-cell lymphoma. However, rituximab is increasingly used in B-cell dysfunction, such as auto-immune diseases and rheumatoid arthritis, and also in organ transplantation. As with alemtuzumab, doses and frequency of rituximab administration vary according to the indications, which could explain the differences in infectious complications.
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As with alemtuzumab, the mechanisms of action of rituximab depend on ADCC, complement cytolysis and apoptosis. Rituximab induces profound B-cell lymphopenia without hypogammaglobulinemia or T-cell lymphopenia. However, some cases of hypogammaglobulinemia have been reported after prolonged treatment due to the loss of plasma cells after recurrent doses of rituximab.

The risks of infection with rituximab are relatively low, except for HIV-infected patients and those receiving other immunosuppressive agents. In 2007, Schult et al. published a meta-analysis on six randomized studies involving B lymphoma or Hodgkin disease patients treated with CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone) with or without rituximab. No significant difference was observed in five studies,\textsuperscript{15} and a significantly increased rate of infection was reported only in one study in which all the patients were HIV-positive.\textsuperscript{13} Boué et al. confirmed the low risk for HIV patients treated with rituximab if the number of CD4+ T cells is over 50/\textmu L.\textsuperscript{14}

Apart from the meta-analysis, some reported cases involved related CMV, herpes, parvovirus, BK, JC or enterovirus infections.\textsuperscript{15-17} In 2009, Carson et al. reported 57 cases of JC virus infections in HIV-negative patients treated with rituximab.\textsuperscript{18} However, rituximab was used with other immune suppressive treatments, making any conclusion impossible. Reactivation of hepatitis B virus (HBV) infection has also been reported with rituximab, with increased risk of mortality.\textsuperscript{19-23} In a few cases, bacterial infections with hypogammaglobulinemia were observed, leading to immunoglobulin supplementation. Similarly, Kamar et al. recently reported an increased infection rate after rituximab therapy in a retrospective study involving kidney transplant recipients;\textsuperscript{24} however, the infections reported may also have been due to the combination with other immunosuppressive agents.

Brinkman et al. reported ten studies on the use of rituximab in rheumatoid arthritis. Infections and serious infections were reported in 10–65\% and 0–5.4\% of patients, respectively, with incidence rates of 0.8–1.55\% and 0.038–0.08 events per year.\textsuperscript{25} The published data showed neither increased nor serious infections compared to control groups (placebo or other DMARDs). Two open-label extension studies showed a higher level of serious infection after four or five courses, but in a small number of patients.\textsuperscript{26,27}

Although the risk of infection seems relatively low with rituximab, some authors have suggested prophylactic treatment with lamivudine because of reported HBV reactivation. Prophylactic treatment of pneumocystosis can also be discussed in cases of corticosteroid-associated treatment or T lymphopenia. In addition, the JC virus infections reported must be seen in relation to the large number of patients already treated. Nevertheless, a patient register has been opened to follow this risk towards natalizumab history (Table 1).

\begin{table}[h]
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\caption{\textbf{Anti-TNF: Infliximab, Adalimumab, Etanercept}}
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\textbf{Anti-TNF: Infliximab, Adalimumab, Etanercept} & Two different types of molecules that neutralize TNF are now marketed. Infliximab and adalimumab (distributed as REMICADE\textsuperscript{\textregistered} and HUMIRA\textsuperscript{\textregistered}, respectively), are mAbs; etanercept (ENBREL\textsuperscript{\textregistered}) is a fusion protein constructed with the human IgG1 Fc fragment and an extracellular portion of the TNFα receptor. TNF produced by macrophages plays a major role in the defense against intracellular organisms, the maintenance and formation of granulomata, and in leukocyte trafficking and immune complex clearance.\textsuperscript{28} Infliximab, adalimumab and etanercept neutralize soluble TNFα, but the mAbs can induce death of activated T cells and macrophages.\textsuperscript{29} There seems to be a relationship between FcγRIII receptor polymorphism and
to recommendations such as clinical examination, chest radiography, and tuberculin test or INF-ELISPOT test before the use of anti-TNF treatment. The systematic detection of tuberculosis before beginning treatment has considerably decreased the risk to 0.02–0.16 cases per 100 treated patients per year.31,32

The British Society for Rheumatology Biologics register has reported several infectious agents (typical and atypical mycobacteria, listeria, nocardia, coccidiosis, streptococci) with infections occurring in 2–6 patients per 100 patients treated with anti-TNF therapy per year, and a 4-fold increased risk of tuberculosis.33 A few cases of fungal infections have also been described with anti-TNF treatment. The updated results of 2011 emphasize the increased risk of serious infection in patients with RA, especially

infliximab biological responses via an ADCC mechanism. The three drugs have several indications in human inflammatory diseases, such as inflammatory bowel disease, rheumatoid arthritis and chronic juvenile arthritis. Their different modes of action explain why etanercept cannot be used for Crohn disease and the infectious risk varies with the drug used. As for rituximab, the use of anti-TNF therapy has markedly increased in the last five years.

Preliminary studies with anti-TNF agents in polyarthritis disease reported tuberculosis infection that was confirmed by post-marketing studies conducted between 1998 and 2001, with 24.4 infections per 100,000 treated patients compared to 6.4 infections in the control group.30 The risk of tuberculosis led

Table 1. Synthetic wee of target molecule, infections, recommendations and references

| Target Molecule | International non-proprietary name | Trade name | Structure | Functions | Indication | Type of immune suppression | Overall safety signals | Recommendations | References |
|----------------|----------------------------------|------------|-----------|-----------|------------|---------------------------|------------------------|----------------|-----------|
| CD52           | Alemtuzumab                       | Campath or Mabcampath | Humanized IgG | ADCC, complement cytotoxicity, apoptosis induction, normal or pathologic mononuclear cells | Approved indication: Chronic lymphoid disease Transplantation and GVH disease Clinical Lymphomas, Autimmune diseases | Persistent neutropenia and decreased T, CD4/8+ B and NK cells | Opportunistic infectious disease | Recommendations for pneumocystis, Herpes and CMV infections | 6, 8 |
| CD20           | Rituximab                         | Mabthera or Rituxan | Chimeric IgG | ADCC, complement cytotoxicity, apoptosis induction on B cells | B cell lymphoma, auto-immune disease, rheumatoid arthritis, transplantation | Profound B-cell lymphopenia; some cases of hypogammaglobulinemia | Viral infections | Discussion regarding lansuline for HBV reactivation, prophylactic treatment for pneumocystis, registry for IC virus, immunoglobulin supplementation if agammaglobulinemia | 12, 24, 25 |
| TNF            | Infliximab; Adalimumab; Etanercept | Remicade; Humira; Enbrel | Chimeric IgG; Human IgG; Human IgG Fc fused with extracellular portion of TNF α receptor | Neutralization of soluble TNFα, induction of T cells and macrophages, apoptosis by ADCC or CDC | Inflammatory bowel disease, rheumatoid arthritis, chronic juvenile arthritis | T cells and macrophages lymphopenia | Intracellular infection+++ | Screening for tuberculosis Screening for non-tuberculosis mycobacteria infections? HBV prophylaxis if chronic hepatitis | 34 |
| VLA-4          | Natalizumab                       | Tysabri    | Humanized IgG4 | Blocks the binding of VLA-4 on VCAM-1, reduces migration of activated leucocytes through endothelium | Neurological disease, e.g., multiple sclerosis Crohn disease | Reduces tissue inflammation of the intestines and blood brain barrier | Infection with JC virus leading to progressive multifocal leuocencephalopathy | Forbidden in cases of immune deficiency (IHV), leukemia or other immunosuppressive drugs | 42 |
| CD11a          | Efalizumab                         | Rapteva    | Humanized IgG1 | Blocks the binding of CD11a on ICAM-1, reduces migration of activated leucocytes through endothelium | Psoriasis | Reduces tissue inflammation | Infection with JC virus leading to progressive multifocal leuocencephalopathy | Withdrawn from the market in 2009 | 42 |
| CTLA-4-lg      | Abatacept; Belatacept              | Orencia; Amgenive | Fe of IgG1 fused to the extracellular domain of CTLA-4 (abatacept and belatacept differ by 2 amino acids) | Inhibits T cell costimulation | Rheumatoid arthritis, particular juvenile arthritis, graft survival | Blocks T-cell activation | Bacterial or viral infection without opportunistic or tuberculosis infection | 50 |

Abbreviations: ADCC, antibody-dependent cell-mediated cytotoxicity; CD, cluster of differentiation; CDC, complement-mediated cytotoxicity; CTLA, cytotoxic T-lymphocyte antigen; Fc, crystallizable fragment; GVH, graft vs. host; HBC, hepatitis B virus; HIV, human immunodeficiency virus; ICAM, intercellular adhesion molecule; Ig, immunoglobulin; NK, natural killer; TNF, tumor necrosis factor; VLA, very late antigen.
in the first six months of treatment. The highest serious infection rate is reported for infliximab (46/1,000), followed by abatacept (43/1,000) and etanercept (38/1,000); however, these differences disappear with adjusted analysis. These data suggest that there is in fact a small but significant overall risk of serious infection with anti-TNF therapy, mostly in the first six months of treatment.

Moreover, a review of the US Food and Drug Administration (FDA) Medwatch database has underlined an increase in nontuberculosis mycobacteria (NTM) infections, with most cases reported since 2005, especially with infliximab-treated patients. It is difficult to say whether the risk is higher with infliximab itself or it is due to the characteristics of patients or the more frequent association with methotrexate. However, it raises the question of the need for screening for NTM infections before initiation of anti-TNF therapy.

Finally, because of increased risk of viral infection, particularly HBV reactivation, with combined infliximab/methotrexate treatment, prophylactic treatments have been recommended with anti-TNF therapy.

All patients should be screened for tuberculosis before receiving any anti-TNF treatment, and should be informed about the risk of infection (Table 1).

**Anti-integrin: Anti-VLA-4 (Natalizumab) and Anti-CD11a (Efalizumab)**

Natalizumab (TYSABRI®) is a humanized IgG4 that targets the α4 chain of the α4β2 integrin (VLA-4). The heterodimeric antigen is expressed on leucocytes and belongs to adhesion molecules involved in leukocyte migration. Natalizumab blocks the binding of VLA-4 to vascular cell adhesion molecule-1 expressed on endothelial cells; it reduces migration of activated leucocytes through the endothelium, and therefore reduces tissue inflammation. Natalizumab is indicated in neurological diseases, particularly in aggressive multiple sclerosis and in Crohn disease.

The most severe infectious complication that occurs with natalizumab treatment is a JC virus infection, responsible for progressive multifocal leukoencephalopathy (PML), a fatal form of encephalopathy. The first cases were described in 2005 in multiple sclerosis and in Crohn disease patients, resulting in temporarily suspension of the license. Other cases of PML were described in 2006 (1 in the US, 6 in Europe), but natalizumab was relicensed for relapsing multiple sclerosis in 2008 because of its efficacy. Moreover, it seems that the risk of PML increases proportionally with the duration of exposure (especially after about two years of treatment), which means that drug monitoring is going to be a major challenge for the use of this drug. However, its prescription is forbidden in cases of immune deficiency (HIV patients) and leucopenia and in combination with immunosuppressive drugs.

Efalizumab (RAPTIVA®) is a humanized mAb that targets the CD11a molecule of heterodimer LFA1 (CD11a/CD18). As with VLA-4, this integrin is involved in transendothelial leukocyte migration. Efalizumab blocks CD11a (LFA1) binding to intracellular adhesion molecule-1 (also known as CD54) expressed on endothelial cells. Efalizumab was prescribed for psoriasis, but the product was withdrawn in 2009 because of reports of PML in 4 patients who had never received immunosuppressive treatment.

Anti-integrin mAbs are associated with a high risk of PML, justifying evaluation of the risk/benefit ratio of these molecules, with specific monitoring and ongoing research on the pathogenesis of this severe disease (Table 1).

**CTLA4-Ig: Abatacept, Belatacept**

Abatacept (ORENCIA®) is a fusion protein composed of an immunoglobulin Fc fused to the extracellular domain of CTLA4. It selectively modulates the CD80/CD86 CD28 co-stimulatory signal required for T-cell activation. It is licensed for the treatment of rheumatoid arthritis as a first line of treatment. A new indication is for polyarticular juvenile arthritis. A second-generation fusion protein, belatacept, is currently being tested in Phase 2 clinical trials to provide extended graft survival with limited toxicity.

The safety of abatacept has been reported in several randomized trials. In the first pilot study of abatacept compared with placebo, 90 patients received abatacept; the only infectious event in the double-blind period was a case of septic arthritis 40 days after a steroid infusion. In 2005, Kremer et al. compared 100 patients treated with placebo or CTLA4-Ig at 2 or 10 mg/kg. The serious adverse events were comparable, with an average of 12 patients in each group having upper respiratory tract infections and one case of cellulitis of the foot in the treated group. There was no opportunistic infection in the treated group. Genovese et al. reported serious infection in 2.3% of 258 abatacept-treated patients, comparable with the placebo group. There were no unusual or opportunistic infections, and the infection rate was similar in the abatacept and the placebo groups (37.6 vs. 32.3%, p = 0.3), with cases of nasopharyngitis, sinusitis, upper respiratory tract infection and bronchitis that were mild or minor. The incidence and types of adverse events were consistent with the double-blind period over 18 months of long-term extension treatment for 218 patients. In 2006, 385 methotrexate-resistant patients were treated with abatacept or placebo in a randomized, double-blind controlled trial. There was a higher incidence of serious infections (2.5 vs. 0.9%; difference, 1.6 percentage points). A similar increase in infection rate was reported by Weinblatt et al. in 959 patients (2.9 vs. 1.9%) with serious infections without opportunistic infection or tuberculosis. To date, only one study has combined data from double-blind and open-label phases of all abatacept clinical studies. It included 4,134 patients (8,392 patient-years). The control group comprised patients treated for RA with disease-modifying antirheumatic drugs, age and sex adjusted (137,000 patients). There were 3.05 vs. 2.15 observed incidence rates per 100 patients respectively in the treated and the placebo groups, with no significant difference for infections requiring hospitalization. Three cases of tuberculosis, one of aspergillosis, one of blastomycosis and one of systemic Candida infection were reported in the abatacept group, similar to the DMARD group. This study suggests that in the long term the risk with abatacept in open-label studies is comparable with
the risk for patients receiving non-biological DMARD therapy. The FDA is in the process of evaluating a biologic license application for belatacept: little information regarding risks of infection is available to date, but since belatacept does not selectively target alloreactive T cells, it must be used with other immunosuppressive drugs, which increases the risk of infection.51

**Conclusion**

The therapeutic use of mAbs and fusion proteins has revolutionized the treatment of several severe inflammatory and hematological diseases. However, blockade of key immunologic pathways in both innate and adaptive responses can directly or indirectly induce immune deficiency. Risk of infection increases according to the disease, the immune target, the dose and the other drugs administered concurrently. Pharmacogenetics will probably play a major role in the future, as shown with the importance of the FcγRIII receptor in the use of infliximab. The wide experience accumulated has improved the understanding of the mechanisms involved in these infections and has subsequently improved clinical safety, supported by the respect for indications, weighing of the risk/benefit ratios, identification of patients at risk, detection of latent infections before commencing treatment and careful clinical and biological monitoring. This approach requires regular updating of pharmacovigilance data on mAbs; specific informed patient consent and clear information for medical practitioners.

Nevertheless, there are cases where the relationship between the cell expression pattern of the target antigen and the immunosuppression pattern are not always clear (e.g., agammaglobulinemia and anti-CD20, which do not target plasma cells). More fundamental research is needed to improve understanding of the paradoxical immunosuppression pattern, especially the impact of mAbs on untargeted cells, e.g., neutrophils observed with rituximab.52

We should also be asking ourselves how these new drugs may be made safer. Drug monitoring could be considered, but is still not usual except for certain drugs (infliximab). The hypothesis that rituximab could lead to regulatory B-cell destruction could be an argument to use intermittent B-cell depletion, with regular “resting” periods for the immune system.53 Nevertheless, it has not yet been demonstrated whether the infectious risk is related to the dose or to the mechanism of action: it is quite probable that there is more than one cause that could be associated. Moreover, we should consider the targets that have to be selected for the development of new mAbs. Nevertheless, the use of anti-CD20 and anti-TNFα is associated with infectious risk when these drugs mainly induce depletion. We therefore have to be careful with the second generation of anti-CD20 (ocrelizumab, ofatumumab, veltuzumab), which are more effective in inducing apoptosis than rituximab and could probably lead to a higher risk of infection.54 Finally, we have to bear in mind that the best model for mAb studies is the human body. Registers, fundamental research (based on clinical observations) and genetic studies are necessary to improve the safety of these new drugs and to develop biomarkers that could help us to determine when a patient is going to enter a biological period of infectious risk or which patient is genetically determined to be at high risk of infection.

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**References**

1. Fontoura P. Monoclonal antibody therapy in multiple sclerosis: Paradigm shifts and emerging challenges. mAbs 2010; 2:670-81.
2. Riechmann L, Clark M, Waldmann H, Winter G. Reshaping human antibodies for therapy. Nature 1988; 332:323-7.
3. Nuckel H, Frey UH, Rohr A, Dühnem U, Siffert W. Alectumab induces enhanced apoptosis in vitro in B-cells from patients with chronic lymphocytic leukaemia by antibody-dependent cellular cytoxicity. Eur J Pharmacol 2005; 514:217-24.
4. Osterborg A, Dyer MJ, Bunjes D, Pangalis GA, Bastion Y, Gattoky D, et al. Phase II multicenter study of human CD52 antibody in previously treated chronic lymphocytic leukemia. European Study Group of CAMPATH-1H Treatment in Chronic Lymphocytic Leukaemia. J Clin Oncol 1997; 15:1567-74.
5. Rai KR, Fereczt CE, Mercier RJ, Cooper MR, Mitchell BA, Stadmauer EA, et al. Alectumab in previously treated chronic lymphocytic leukemia patients who also had received fludarabine. J Clin Oncol 2002; 20:3891-7.
6. Keating MJ, Flinn I, Jain V, Binet JL, Holland E, Byrd J, et al. Therapeutic role of alectumab (CAMPATH-1H) in patients who have failed fludarabine: results of a large international study. Blood 2002; 99:3554-61.
7. Martin SI, Marty FM, Fiumara K, Teon SR, Gribben JG, Baden LR. Infectious complications associated with alectumab use for lymphoproliferative disorders. Clin Infect Dis 2006; 43:16-24.
8. Peleg AY, Husain S, Kwak EJ, Silveira FP, Nidrangu M, Tran J, et al. Opportunistic infections in 547 organ transplant recipients receiving alectumab, a humanized monoclonal CD-52 antibody. Clin Infect Dis 2007; 44:204-12.
9. Reddy KS, Devarapalli Y, Mazur M, Hamawi K, Chakkeria H, Moss A, et al. Alectumab with rapid steroid taper in simultaneous kidney and pancreas transplantation: comparison to induction with antithymocyte globulin. Transplant Proc 2010; 42:2006-8.
10. Osterborg A, Karlsson C, Lundin J, Kühly E, Mellstedt H. Strategies in the management of alectumab-related side effects. Semin Oncol 2006; 33:29-35.
11. Osterborg A, Foa R, Bezares RE, Deardor C, Dyer MJ, Geisler C, et al. Guidelines for the use of alectumab in chronic lymphocytic leukemia. Leukemia 2009; 23:1980-8.
12. Schütz H, Bohtius JF, Trelle S, Soketz N, Reiser M, Kober T, et al. Immunochemotherapy with rituximab and overall survival in patients with indolent or mantle cell lymphoma: a systematic review and meta-analysis. J Natl Cancer Inst 2007; 99:706-14.
13. Kaplan LD, Lee JY, Ambridge RE, Sparrano JA, Cesarman E, Chadburn A, et al. Rituximab does not improve clinical outcome in a randomized phase 3 trial of CHOIP with or without rituximab in patients with HIV-associated non-Hodgkin lymphoma. AIDS Malignancies Consortium Trial 010. Blood 2005; 106:1538-43.
14. Bouf F, Gabarre J, Gisselbrecht C, Reynez J, Cheret A, Bonnet F, et al. Phase II trial of CHOIP plus rituximab in patients with HIV-associated non-Hodgkin's lymphoma. J Clin Oncol 2006; 24:1423-8.
15. Goldberg SL, Ivecoa AL, Alter RS, Kroll MS, Rowley SD, Waintraub SE, et al. Unusual viral infections (progressive multifocal leukencephalopathy and cytomegalovirus disease) after high-dose chemotherapy with autologous blood stem cell rescue and peritransplantation rituximab. Blood 2002; 99:1468-8.
16. Suzan F, Amnor M, Ribrag V. Fatal reactivation of cytomegalovirus infection after use of rituximab for a post-transplantation lymphoproliferative disorder. N Engl J Med 2001; 345:1000.
17. Valler S, Tempescu A, Tran A, Legrand-Quillien MC, Narbonne V, Berthou C. Cytomegalovirus-associated meningoradiculoneuritis after treatment of mantle cell lymphoma with a combination of chemotherapy and rituximab. Ann Hematol 2005; 84:545-7.
18. Carson KR, Raven AM, Richey EA, Habermann TM, Fociosi D, Seymour JF, et al. Progressive multifocal leukencephalopathy after rituximab therapy in HIV-negative patients: a report of 57 cases from the Research on Adverse Drug Events and Reports project. Blood 2009; 113:4834-40.
19. Nicora P, Del Principe MI, Maurillo L, Vendiiri A, Buccisano F, Piccioni D, et al. Fulminant B hepatitis in a surface antigen-negative patient with B-cell chronic lymphocytic leukaemia after rituximab therapy. Leukemia 2005; 19:1840-1.
20. Perea G, Díaz N, Entinas O, Derancourt C, Lévy S, Bernard P, Late lethal hepatitis B virus reactivation after rituximab treatment of low-grade cutaneous B-cell lymphoma. Br J Dermatol 2006; 155:1053-6.
21. Devire J, Hober D, Morel P. Acute hepatitis B in a patient with antibodies to hepatitis B surface antigen who was receiving rituximab. N Engl J Med 2001; 344:68-9.
Society for Rheumatology Biologics Register (BSRBR).

Galloway J, Ustianowski A, et al. Drug-specific risk reactivation of latent infection. Arthritis Rheum 2007; 58:124-31.

Winthrop KL, Chang E, Yamashita S, Iademarco MF, LoBue PA. Nontuberculous mycobacteria infections and anti-tumor necrosis factor-alpha therapy. Emerging Infect Dis 2009; 15:1556-61.

Kim YJ, Bae SC, Sung YK, Kim HJ, Jun JB, Yoo DH, et al. Possible reactivation of potential hepatitis B virus occult infection by tumor necrosis factor-alpha therapy. Emerging Infect Dis 2009; 15:1556-61.

Van Asche G, Van Ranst M, Sciot R, Dubois B, Vermeire S, Noman M, et al. Progressive multifocal leukoencephalopathy after natalizumab therapy for Crohn's disease. N Engl J Med 2005; 353:362-8.

Langer-Gould A, Atlas SW, Green AJ, Bollen AW, Pelletier D. Progressive multifocal leukoencephalopathy in a patient treated with natalizumab. N Engl J Med 2005; 353:375-81.

Clifford DB, De Luca A, DeLuca A, Simpson DM, Arendt G, Giovannini G, et al. Natalizumab-associated progressive multifocal leukoencephalopathy in patients with multiple sclerosis: lessons from 28 cases. Lancet Neurol 2010; 9:438-46.

Gärtner KR, Fooson D, Major EO, Pettrini M, Richey EA, West DJ, et al. Monoclonal antibody-associated progressive multifocal leukoencephalopathy in patients treated with rituximab, natalizumab and efalizumab: a Review from the Research for Adverse Drug Events and Reports (RADARE) Project. Lancet Oncol 2009; 10:816-24.

Berger JR. Progressive multifocal leukoencephalopathy and newer biological agents. Drug Saf 2010; 33:969-83.

Tan P, Aanaesthi C, Hansen JA, Melrose J, Brunvand M, Bradshaw J, et al. Induction of alloantigen-specific hyposensitiveness in human T lymphocytes by blocking interaction of CD28 with its natural ligand B7/BB1. J Exp Med 1999; 187:165-73.

Moreland LW, Alten R, van den Bosch F, Appelboom T, Leon M, Emery P, et al. Costimulatory blockade in patients with rheumatoid arthritis: a pilot, dose-finding, double-blind, placebo-controlled clinical trial evaluating CTLA-4Ig and LEA29Y eighty-five days after the first infusion. Arthritis Rheum 2002; 46:1470-9.

Galloway JB, Hyrich KL, Merzcr LK, Dixon WG, Fu B, Ustianowski AP, et al. Anti-TNF therapy is associated with an increased risk of serious infections in patients with rheumatoid arthritis especially in the first 6 months of treatment: updated results from the British Society for Rheumatology Biologics Register with special emphasis on risks in the elderly. Rheumatology 2011; 50:124-31.

Winthrop KL, Chang E, Yamashita S, Iademarco MF, LoBue PA. Nontuberculous mycobacteria infections and anti-tumor necrosis factor-alpha therapy. Emerging Infect Dis 2009; 15:1556-61.

Kim YJ, Bae SC, Sung YK, Kim HJ, Jun JB, Yoo DH, et al. Possible reactivation of potential hepatitis B virus occult infection by tumor necrosis factor-alpha therapy. Emerging Infect Dis 2009; 15:1556-61.

Van Asche G, Van Ranst M, Sciot R, Dubois B, Vermeire S, Noman M, et al. Progressive multifocal leukoencephalopathy after natalizumab therapy for Crohn's disease. N Engl J Med 2005; 353:362-8.

Langer-Gould A, Atlas SW, Green AJ, Bollen AW, Pelletier D. Progressive multifocal leukoencephalopathy in a patient treated with natalizumab. N Engl J Med 2005; 353:375-81.

Clifford DB, De Luca A, DeLuca A, Simpson DM, Arendt G, Giovannini G, et al. Natalizumab-associated progressive multifocal leukoencephalopathy in patients with multiple sclerosis: lessons from 28 cases. Lancet Neurol 2010; 9:438-46.

Gärtner KR, Fooson D, Major EO, Pettrini M, Richey EA, West DJ, et al. Monoclonal antibody-associated progressive multifocal leukoencephalopathy in patients treated with rituximab, natalizumab and efalizumab: a Review from the Research for Adverse Drug Events and Reports (RADARE) Project. Lancet Oncol 2009; 10:816-24.

Berger JR. Progressive multifocal leukoencephalopathy and newer biological agents. Drug Saf 2010; 33:969-83.

Tan P, Aanaesthi C, Hansen JA, Melrose J, Brunvand M, Bradshaw J, et al. Induction of alloantigen-specific hyposensitiveness in human T lymphocytes by blocking interaction of CD28 with its natural ligand B7/BB1. J Exp Med 1999; 187:165-73.

Moreland LW, Alten R, van den Bosch F, Appelboom T, Leon M, Emery P, et al. Costimulatory blockade in patients with rheumatoid arthritis: a pilot, dose-finding, double-blind, placebo-controlled clinical trial evaluating CTLA-4Ig and LEA29Y eighty-five days after the first infusion. Arthritis Rheum 2002; 46:1470-9.

Kremer JM, Dougados M, Emery P, Durez P, Sibilia J, Sergy W, et al. Treatment of rheumatoid arthritis with the selective costimulation modulator abatacept: twelve-month results of a phase ib, double-blind, randomized, placebo-controlled trial. Arthritis Rheum 2005; 52:2263-71.

Genovese MC, Becker JC, Schiff M, Luggen M, Sherrer Y, Kremer J, et al. Abatacept for rheumatoid arthritis refractory to tumor necrosis factor alpha inhibition. N Engl J Med 2005; 353:1114-23.

Genovese MC, Schiff M, Luggen M, Becker JC, Aranda R, Teng J, et al. Efficacy and safety of the selective co-stimulation modulator abatacept following 2 years of treatment in patients with rheumatoid arthritis and an inadequate response to anti-tumour necrosis factor therapy. Ann Rheum Dis 2008; 67:547-54.

Kremer JM, Genant HK, Moreland LW, Russell AS, Emery P, Abud-Mendoza C, et al. Effects of abatacept in patients with methotrexate-resistant active rheumatoid arthritis: a randomized trial. Ann Intern Med 2006; 144:809-16.

Weinblatt ME, Combe B, Covacci A, Aranda R, Becker JC, Keystone E. Safety of the selective costimulation modulator abatacept in rheumatoid arthritis patients receiving background biologic and nonbiologic disease-modifying antirheumatic drugs: A one-year randomized, placebo-controlled study. Arthritis Rheum 2006; 54:2807-16.

Simon TA, Akling J, Lancelle D, Franklin J, Wolfe F, Covacci A, et al. Infections requiring hospitalization in the abatacept clinical development program: an epidemiological assessment. Arthritis Res Ther 2010; 12:67.

Stanojlov R, Zuver J, Legendre C. Co-stimulation blockade as a new strategy in kidney transplantation: benefits and limits. Drugs 2010; 70:2121-31.

Tesić D, Ajeganová S, Hägglund H, Sander B, Faddei B, Hafström I, et al. Late-onset neutropenia following rituximab therapy in rheumatic diseases: Association with B-lymphocyte depletion and infections. Arthritis Rheum 2011; Available from: http://www.ncbi.nlm.nih.gov/pubmed/21560117.

Fontoura P. Roles of B lymphocytes in multiple sclerosis: diversifying beyond the antibody response. Immunotherapy 2009; 1:181-5.

Robak T, Robak E. New anti-CD20 monoclonal antibodies for the treatment of B-cell lymphoid malignancies. BioDrugs 2011; 25:13-25.