

Cytomegalovirus Colitis and Hypo-IgG After Rituximab Therapy for Rheumatoid Arthritis

To the Editor:

Rituximab (RTX) is an anti-CD20 antibody used in patients with rheumatoid arthritis (RA) after failure of anti-tumor necrosis factor (anti-TNF) therapy. Side effects are mainly infectious, probably related to B cell lymphopenia. However, opportunistic infections are not frequent with use of RTX. We describe a case of cytomegalovirus (CMV) colitis in a patient with RA with hypo-IgG after 2 cycles of RTX.

A 66-year-old woman was followed for 18 years for RA with positive anticitrullinated protein antibodies and structural erosions. She was successively treated with methotrexate (MTX) alone for 17 years and then in combination with anti-TNF- α for 9 months (adalimumab, then etanercept), without success. She improved after a first course of RTX (1 gram twice) in 2007 associated with low-dose corticosteroid therapy (prednisone 10 mg daily) and MTX 10 mg. In July 2008, the serum IgG level was found to be low: 5.25 g/l; IgG level was not monitored before starting RTX. In April 2009, because of a new episode of RA, she received a second course of RTX, with good efficacy. In September 2009, she was hospitalized because of mucous diarrhea with more than 20 stools per day, progressing for 3 months. Bacteriologic and parasitologic stool cultures and investigation for *Clostridium difficile* were negative. An abdominal computed tomography scan revealed a slight infiltration of the mesocolon, confirmed by the rectosigmoidoscopy, with superficial ulcerations of variable size. Blood polymerase chain reaction investigations and colonic biopsies were positive for CMV (295 copies). Serum IgG level was 2.77 g/l, the rate of blood B lymphocytes was zero, and the T lymphocyte count was normal (1.964 g/l). She was treated with ganciclovir for 7 days, then valganciclovir for 15 days. She also received an infusion of 25 g human immunoglobulin. By the end of the first week there was almost complete disappearance of diarrhea.

We describe the first case of CMV colitis associated with hypo-IgG in a patient with RA who had received 2 cycles of RTX. One case of ulcerative colitis of noninfectious origin was described¹ after 2 courses of RTX, 375 mg/m², given in a patient with Graves' disease. Two other patients experienced worsening of preexisting Crohn's diseases or ulcerative colitis after RTX^{2,3}.

Humoral immunity is necessary for defence against CMV: a recent study showed that antibodies control either primary dissemination or local viral spreading of CMV infection in mice⁴. In humans, IgG deficiency may be a risk factor for CMV infection according to some reports. A few cases of disseminated CMV infection have been described in patients with common variable immunodeficiency (CVID), mainly with a gastrointestinal presentation^{5,6,7}. An associated T cell defect might favor CMV infection in patients with hypo-IgG. Thus, a study reported 5 cases of post-cardiac-transplant patients who had severe CMV infections⁸. All of them presented with hypo-IgG (3.23 \pm 0.18 g/l) compared to 15 other post-transplant patients without CMV infection (IgG = 6.39 \pm 0.63 g/l). A German study⁹ described a 55-year-old woman treated with azathioprine and corticosteroids after resection of a thymoma, who developed CMV colitis associated with hypogammaglobulinemia (1.8 g/l). In our patient, the T cell defect induced by cotreatment with steroids, even at low dose (10 mg/day), could have played a role in association with hypo-IgG in the occurrence of this severe CMV infection.

A peculiarity of recent literature about RTX is that patients in clinical trials had an increased frequency of hypo-IgG after repeated treatments with RTX (1.7% of patients at baseline and 4.7% after 4 cycles); there were reports of a nonsignificant increase of severe infections in these patients with hypo-IgG after repeated cycles of RTX^{10,11}. Single case reports with dramatic post-RTX hypo-IgG have also been described: e.g., a patient treated with RTX for idiopathic thrombocytopenic purpura and autoimmune neutropenia in whom serum IgG dropped from 13 g/l before treatment to 1.75 g/l after 5 courses of RTX over 7 years, without infectious complications¹². Finally, in RA patients treated with RTX, hypo-IgG may

be present before the start of RTX (i.e., up to 5% of patients in the AutoImmunity and Rituximab registry) and this presents a risk factor for severe infections¹³.

Unpredictable opportunistic infections are possible in patients treated with RTX, and some of them could be favored by hypo-IgG and steroid-associated treatment. We recommend IgG monitoring before start of RTX treatment and at regular intervals afterward in patients with RA. Before starting RTX, it could be useful to look for other underlying immunodeficiency states such as CD4 deficiency.

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