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Case report

Rituximab as an alternative for patients with severe systemic vasculitis refractory to conventional therapy: report of seven cases and literature review

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ABSTRACT

The greater understanding of pathophysiology and behavior of systemic vasculitis, together with the development of therapeutic regimens with increasingly better safety and efficacy profiles, dramatically changed the prognosis of patients diagnosed with these clinical entities. Recently, the use of rituximab in the treatment of patients with ANCA-associated vasculitis in randomized clinical trials showed an important alternative in selected cases, especially patients refractory or intolerant to standard therapy with cyclophosphamide and corticosteroids. This article presents the report of seven cases of systemic vasculitis successfully treated with rituximab.

O rituximabe como uma opção para pacientes com vasculite sistêmica grave refratária à terapia convencional: relato de sete casos e revisão de literatura

Palavras-chave:
Rituximabe
Vasculites sistêmicas

RESUMO

O maior entendimento das bases fisiopatológicas e do comportamento das vasculites sistêmicas, aliado ao desenvolvimento de regimes terapêuticos com perfil de segurança e eficácia cada vezes melhores, modificou drasticamente o prognóstico dos pacientes

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Granulomatose com poliangeíte
Poliangeíte microscópica
Poliarterite nodosa

diagnosticados com essas entidades clínicas. Recentemente, o emprego do rituximabe no tratamento de pacientes com vasculites ANCA associadas em ensaios clínicos randomizados se mostrou uma opção importante em casos selecionados, especialmente pacientes refratários ou intolerantes à terapia-padrão com ciclofosfamida e corticosteroides. O presente artigo traz o relato de sete casos de vasculites sistêmicas com tratamento bem-sucedido com rituximabe.

Introduction

The introduction of glucocorticoids and, later, of cyclophosphamide (CYC) in inducing remission of systemic vasculitis (SV) dramatically changed the prognosis of these patients, resulting in symptomatic improvement, high rates of remission and in increased survival.[1,2] However, a significant portion of patients remains refractory or intolerant to conventional therapies,[3] justifying the growing interest in new safer and more effective therapeutic options. Recent evidence points to a crucial role of B lymphocytes in the development of SV.[4] Rituximab (RTX) is a chimeric anti-CD20+ B cell monoclonal antibody widely used in B cell lymphomas, and more recently has been used for various autoimmune conditions in selected cases.

We report seven cases of patients diagnosed with SV treated successfully with RTX.

Case report

Patient 1

Male, 46, with fever, weight loss, severe pulmonary vasculitis (Fig. 1), pauci-immune glomerulonephritis and neuropathy of lower limbs, with Birmingham Vasculitis Activity Score (BVAS) = 20 and ANCA-negative. Treated under a diagnosis of microscopic polyangiitis (MPA), subjected to pulse therapy with methylprednisolone (MP) followed by cyclophosphamide associated with prednisone 40 mg/day. The patient developed hyperglycemia and liver toxicity; thus, this treatment was suspended, with the introduction of weekly doses of RTX 375 mg/m^2 for 4 weeks. After a year of treatment, the patient achieved complete remission without maintenance therapy.

Patient 2

Female, 31, presenting edema and fixed cyanosis of extremities, polyarthralgia, subcutaneous nodules, limb ischemia and acute respiratory failure (BVAS = 15), with a diagnosis of polyarteritis nodosa (PAN) and HBsAg positive for 6 years. Skin biopsy showed fibrinoid necrosis and medium-caliber vessel infiltration. Subjected to pulse therapy with MP and CYC with poor response. Treatment was started with two fortnightly doses of RTX 1 g, with dramatic improvement. Treated with a maintanance infusion of RTX after 6 months, maintaining complete remission without steroids.

Patient 3

Male, 56, admitted with arthritis, nephritis, retinal vasculitis, pulmonary nodules and peripheral neuropathy (BVAS = 17). With a diagnosis of granulomatosis with polyangiitis (GPA) for 3 years with cANCA 1/40, refractory to 7 pulses of MP and CYC. After rescue therapy with 4 weekly infusions of RTX 375 mg/m^2, the patient showed complete remission of the disease for three years, with maintenance therapy with RTX every 6 months.

Patient 4

Female, 47, with ongoing fever, weight loss, hearing loss, palpable purpura, glomerulonephritis and hemoptysis for the duration of 3 years (BVAS = 38 at admission), with a diagnosis of GPA. A chest CT scan revealed multiple pulmonary cavitations. Ancillary and therapeutic tests negative for tuberculosis, with subsequent weekly RTX infusion for 4 weeks. The patient remains in complete remission after 1 year, without maintenance therapy.

Patient 5

Male, 26, with an early weight loss, arthritis, sinusitis, conjunctivitis and abdominal pain for 5 months (BVAS = 12), pANCA 1/20. After ruling out differential diagnoses, the patient was treated as with GPA, beginning with two biweekly infusions of RTX. A maintenance schedule with half-yearly infusions of RTX was chosen.

Patient 6

Male, 24, with manifestations of nephritis and with a biopsy revealing pauci-immune glomerulonephritis, compatible with a diagnosis of MPA, refractory to multiple pulses of MP and CYC over 5 years. A scheme of 4 weekly infusions of RTX was started, with early BVAS = 12, achieving complete remission; as maintenance, half-yearly infusions were scheduled.

Patient 7

Female, 45, with weight loss, arthritis and mononeuritis multiplex over 5 years, with p-ANCA 1/40. The patient received a diagnosis of MPA, and started a weekly RTX infusion schedule for 4 weeks, resulting in complete remission.

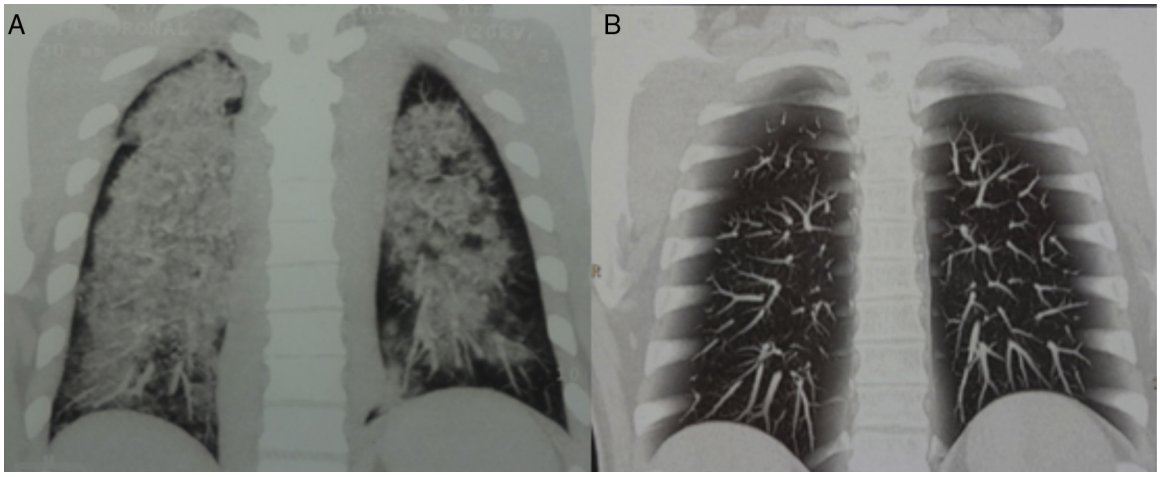

Fig. 1 – Chest CT coronal reconstruction of patient 1. (A) View prior to treatment, showing diffuse opacities compatible with diffuse alveolar hemorrhageand pulmonary capillaritis. (B) View after rituximab therapy, showing regression of lesions.

Discussion

Systemic vasculitides (SV) are a heterogeneous group of conditions whose main landmark is a primary inflammation and damage to blood vessels with subsequent tissue ischemia and/or vascular hemorrhage. Many are the conditions that fit this clinical-pathological profile, affecting vessels of different sizes in different organic systems with variable intensity.[5]

Among the cases described, a diagnosis of MPA for patients 1, 6 and 7 were proposed, and patients 3, 4 and 5 were diagnosed with GPA, while patient 2 was treated under the hypothesis of PAN. Although GPA and MPA are classically referred to as ANCA-associated vasculitides (AAV), patients 1, 4 and 6 had a negative ANCA, a phenotype also referred to as seronegative vasculitis by some authors, with involvement of 10% of cases.[5]

SVs are well recognized for their potential severity, with an often accelerated evolution and resulting in death if not treated properly. Prior to the introduction of effective therapies for SV, the five-year survival rate was around 10%, in contrast to over 80% reported in the literature after the introduction of CYC and corticosteroids.[1,2]

The treatment with CYC, however, is not without serious adverse events, such as myelosuppression (2%), infections (46%), neoplasms (2.8%), and infertility (57%).[6] Furthermore, the 5-year recurrence risk for patients treated appropriately is 38%.[3] The current scenario has motivated a growing interest in new therapeutic agents for SV as drugs of choice or alternative medications in carefully selected cases.

Evidence supports a well-established pathogenic role of B cells in the development of autoimmune diseases. Among the proposed mechanisms, is the fact that B cells are precursors of ANCA-producing plasma cells, besides the production of cytokines critical for the development of T-cell hyperactivity and stimulating proliferation and activation of neutrophils.[4] These factors constituted the premise for experimental studies evaluating the therapeutic response of patients with SV undergoing infusion of RTX.

RTX is a chimeric anti-CD20+ B-cell monoclonal antibody, which selectively induces depletion of B cells through direct stimulation of apoptosis, antibody-dependent cytotoxicity and complement-dependent cytotoxicity.[7] The first report on the use of RTX in inducing remission of SV was published in 2001 by Speck et al.[8] Since then, multiple case reports and studies were published, including two large, controlled trials (RITUXVAS and RAVE) that demonstrated non-inferiority of induction therapy with RTX compared to conventional therapy with CYC.[9,10] The RITUXVAS study was published in 2010 by Jones et al., including 44 patients with newly diagnosed AAV with renal involvement without prior treatment; these patients were randomized into two groups, CYC and RTX.[9] The results of the RAVE study were recently published by Specks et al. and included 197 patients in a multicenter, randomized, double-blind non-inferiority study that compared RTX with daily oral CYC for induction of remission of AAV.[10] The authors concluded for non-inferiority of RTX versus CYC for induction of remission,[9,10] and RTX appears to be more effective in cases of relapse.[10] However, contrary to what was anticipated, there were no significant differences in serious adverse event rates between these two groups.[10]

Recommendations about indication time for RTX as an inducer of SV remission vary. The main recommendations refer to AAV; thus, it is still uncertain whether these can be extrapolated to ANCA-disease negative phenotypes in patients with GEPA, GPA and MPA or other forms of SV. There are no comparative data on cost-effectiveness between RTX and CYC. In general, RTX is indicated as first choice when the treatment aim is trying to avoid the adverse events related to CYC, especially in young patients with reproductive aspirations.[3,11] This matter was decisive for the definition of conduct for patient 5, a 25-year old childless male, who

was initially treated with RTX. Other situations in which CYC must be avoided include a high cumulative dose, hypersensitivity and high risk of malignancy.[3,11] Another consistent indication of RTX is for rescue therapy in patients refractory to conventional therapy due to intolerance or unsatisfactory response; this occurs in 13–30% of cases,[11] including patients 1, 2, 3 and 7 described in this paper, with the first of them due to pharmacological scheme intolerance and the other due to poor responses. patient 4 received her initial treatment with a two-week corticoid pulse and an empirical regimen for tuberculosis, with severe evolution; thus, this patient was subjected to an induction with RTX. Apparently RTX shows better results in patients with relapsing disease and can be recommended as first choice in these cases.[11]

Patients 1, 3, 4, 6 and 7 were subjected to four infusions of RTX, 375 mg/m^2 per dose, at 1-week intervals, while patients 2 and 5 received two biweekly infusions of 1 g. Different infusion schemes may be used for induction of remission in patients with SV. The main evidence refers to lymphoma protocol, 375 mg/m^2/week for 4 weeks, used by most studies, including RITUXVAS and RAVE.[9,10] A minority of authors opted by the scheme commonly used in rheumatoid arthritis, with an infusion of two doses of 1 g intravenously at an interval of 15 days. The protocols used for lymphoma and rheumatoid arthritis appear to be equally effective in AAV, being non-inferior to conventional therapy.[11] A retrospective multicenter study of 65 patients conducted by Jones et al. showed no significant difference between the remission rates for both schemes (81% with lymphoma protocol versus 75% with rheumatoid arthritis protocol).[11]

Although there is convincing evidence that RTX is an effective alternative for induction and maintenance of remission of AAV, its role in patients with ANCA-negative SV is still uncertain. The fact that even patients 1, 4 and 6 described in this paper, besides previous reports,[12,13] all with ANCA-negative subjects, have shown satisfactory responses during induction therapy suggests that RTX may play a role even in the absence of such antibodies, acting through other pathogenic mechanisms related to B cells, for instance, a possible influence on the process of antigen presentation and co-stimulation of B-cell dependent T cells.[7]

Less significant evidence has been presented as to the role of RTX in the treatment of patients with PAN. Studies suggest that in most cases the pathogenesis of PAN are associated with circulating immune complex deposition and/or vascular formation in situ, comprised by HBe antigen and specific antibodies. These factors then induce the complement cascade activation and monocyte and neutrophil recruitment.[5] Thus, the introduction of RTX as a possible therapeutic agent for patients with PAN is based on the depletion of antibody-producing B-cells.[7] There is no information available in the literature on randomized trials comparing standard induction therapy versus RTX in patients with PAN, although isolated reports point to satisfactory results in selected cases,[14,15] such as with patient 2, who reached complete remission despite the severe activity of a disease refractory to conventional therapy, requiring her intensive care unit admission for ventilatory and hemodynamic support.

Current knowledge involving therapies for SV remission induction points to a constant need to develop increasingly effective and safe therapeutic regimens. With the introduction of RTX as an alternative to CYC in refractory cases, or in those patients whom conventional therapy should be avoided, there was a significant increase in published rates of successful induction of remission. However, short and long term adverse events associated with available schemes continue causing a major concern. The cases described in this paper corroborate the data in the literature, and RTX is a good alternative for induction of remission in refractory patients or in those with a contraindication to CYC scheme. Randomized trials with representative samples are needed to confirm assumptions about the efficacy and safety of RTX in patients with PAN or GPA and ANCA-negative MPA.

Conflicts of interest

The authors declare no conflicts of interest.

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