Reumatol Clin. 2009;5(4):147–152

Reumatología Clínica

www.reumatologiaclinica.org

Original

Treating severe systemic lupus erythematosus with rituximab. An open study

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INFORMACIÓN DEL ARTÍCULO

Historia del artículo:
Recibido el 16 de junio de 2008
Aceptado el 25 de septiembre de 2008
Available online 6 de mayo de 2009

Keywords:
Systemic lupus erythematosus
Anti-CD20
Lupus nephritis
Neuropsychiatric involvement
Transverse myelitis
Massive pulmonary hemorrhage
Immunosuppressive therapy

A B S T R A C T

Systemic lupus erythematosus (SLE) is an autoimmune disease that may be associated to high morbidity and mortality. Disease course is variable and unpredictable and although the prognosis and survival of these patients has dramatically improved, treatment of severe multiorganic organic affection in this condition remains a therapeutic challenge. Since B lymphocytes have an important role in the pathogenesis of SLE, it is expected that the targeting of these cells exerts a significant therapeutic effect in SLE patients with severe multiorganic manifestations. In an open clinical trial, we have explored the therapeutic potential of Rituximab (an anti-CD20 monoclonal antibody) administration in SLE patients with severe nephritis (n = 22) or neuropsychiatric manifestations (n = 6) or massive pulmonary hemorrhage (n = 3). In most cases, we observed significant improvement in both clinical and laboratory parameters, with good tolerance and few side effects. Thus, patients with severe lupus nephritis showed improvement in disease activity (MEX-SLEDAI index) with a significant reduction ($p < 0.05$), as well as proteinuria in most of them (from 3.710 g/L to 1.786 g/L, $p < 0.05$); patients with serious neurologic involvement had complete remission of their manifestations; but those with pulmonary massive hemorrhage did not have any response. Rituximab could have an important therapeutic potential in severe SLE, and that it is necessary to carry out a controlled blinded clinical trial to further support this point.

Tratamiento del Lupus Eritematoso Severo con Rituximab. Un estudio abierto

Palabras clave:
Lupus eritematoso sistémico
Anticuerpo monoclonal
Nefropatía lúpica
Manifestaciones neuropsiquiátricas
Mielítis transversa
Hemorragia pulmonar masiva
Terapia inmunosupresora

R E S U M E N

El lupus eritematoso sistémico es un padecimiento con bases autoinmunes que puede asociarse a elevada morbilidad y mortalidad. El curso es variable e impredecible, y aunque el pronóstico y la supervivencia de los pacientes han mejorado importantemente, la afección multiorgánica puede representar un reto terapéutico. Dado que los linfocitos B tienen un papel protagónico en esta enfermedad, es esperable que como blanco del tratamiento, pueda resultar en un efecto terapéutico significativo en el lupus eritematoso. En este estudio clínico abierto, exploramos el potencial terapéutico de la administración de rituximab (un anticuerpo monoclonal) en pacientes con lupus grave: nefropatía (n = 22), manifestaciones neuropsiquiátricas (n = 6) o hemorragia pulmonar masiva (n = 3). En la mayoría de los pacientes, observamos mejoría significativa, tanto en los parámetros clínicos como de laboratorio y gabinete, con buena tolerancia y pocos eventos adversos. De tal manera que los pacientes con nefropatía lúpica grave mostraron disminución significativa de la actividad de la enfermedad (MEX-SLEDAI) ($p < 0{,}05$), también en los niveles de proteinuria (de 3.710 g/L a 1.786 g/L, $p < 0{,}05$); los pacientes con afección neurológica grave tuvieron remisión completa de sus manifestaciones, aunque en aquellos con hemorragia pulmonar masiva no observamos respuesta alguna. Rituximab pudiera tener un importante potencial terapéutico en los pacientes con lupus grave; es necesario el realizar un estudio clínico doble ciego controlado a largo plazo que ratifique nuestros hallazgos.

Introduction

Systemic lupus erythematosus (SLE) is a multiorganic autoimmune disease with heterogeneous clinical manifestations and unpredictable disease course.[1] Although the prognosis and survival of SLE patients have dramatically improved, the treatment of severe multiorganic affectation remains as a therapeutic

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doi:10.1016/j.reuma.2008.09.008

challenge.[1,2] Severe nephritis, transverse myelitis and massive pulmonary hemorrhage are three of the most serious manifestations of SLE. These conditions are associated with high morbidity and mortality, including those events that are consequence of the immunosuppressive therapy.[1–4]

Different abnormalities of T and B lymphocytes are involved in the pathogenesis of SLE.[5–9] B lymphocytes synthesize several cytokines involved in the pathogenesis of SLE (including IL-10), have an important role as antigen presenting cells, and are the source of the different auto-antibodies detected in these patients.[10,11] Therefore, B lymphocytes have been considered as a good therapeutic target in SLE.[12,13] Rituximab is a chimeric monoclonal antibody, with human IgG1 and kappa light chain constant domains, and mouse variable regions from a mouse hybridoma producing an anti-human CD20 antibody.[14,15] CD20 is expressed by immature and mature B lymphocytes, but not by early B cell precursors or plasma cells. This biological agent causes B-cell depletion *in vivo*, inducing complement and antibody dependent cellular toxicity as well as antibody mediated apoptosis.[16] Interestingly, administration of Rituximab does not seem to have a significant effect on serum immunoglobulin levels, but its administration could be associated with diminution of autoantibody levels.[17,18]

There are different preliminary studies on the therapy of SLE and other autoimmune diseases with Rituximab.[19–24] In this regard, it has been reported that this biological agent seems to induce clinical improvement and diminution of the abnormalities found in B lymphocytes in patients with this condition.[25–28] In addition, we have previously found that the addition of Rituximab to the immunosuppressive therapy of patients with refractory lupus nephritis resulted in a marked improvement in both, renal function and disease activity.[29] Furthermore, it has been reported that Rituximab therapy of SLE patients is associated with diminution of activation markers of T lymphocytes, including the expression of CD40L, as well as with a significant effect on the levels and function of T regulatory cells, and the induction of T cell apoptosis.[29,30]

In an open clinical trial we have explored the possible therapeutic effect of Rituximab in SLE patients with severe manifestations, specifically with severe nephritis or CNS affectation or massive pulmonary hemorrhage. Our data strongly suggest that Rituximab exerts an important beneficial effect in most of these patients. In our previous report we emphasize that patients with severe nephritis (type IV: 18, type III and type V: 2) had improvement of levels and function of T regulatory cells and induction of T cell apoptosis, immunological facts which could explain the clinical response to diverse dosages of rituximab in spite do not have increased steroids therapy or do not have used steroids. In this paper we show our clinical data of this group of patients, besides two additional groups, one of them with very serious neurological affectation and the other one, three patients with massive pulmonary hemorrhage.

Patients and methods

Thirty-one SLE patients with severe disease, and in most of them refractory to conventional intensive treatment were enrolled in a preliminary open and prospective clinical trial. Patients had severe lupus manifestations, twenty-two with lupus nephritis, six with neuropsychiatry manifestations, and three with massive pulmonary hemorrhage. All patients fulfilled the classification criteria of the American College of Rheumatology for the diagnosis of SLE,[31] and disease activity was scored according to the MEX-SLEDAI index.[32] Most of our patients with lupus nephritis had WHO type IV (18), and less frequent were type II (2) and V (2); all of them under DMARD's therapy and most with variable doses of steroids, with persistent activity, through proteinuria, urinary red or white cells or casts. Following was made with creatinine levels, diary proteinuria and creatinine clearance. Patients received Rituximab 500 to 1000 mg once or twice, at 2 week intervals, and the therapeutic response was evaluated by clinical and laboratory parameters. The rituximab dosage varied because economic limitation; previously we have used low dosage of rituximab in diverse autoimmune diseases (rheumatoid arthritis, dermatomyositis, and systemic lupus erythematosus) with similar results (B cell depletion, immune-regulatory effects, and clinical response) of those reported with conventional approved doses. All patients were pretreated with dexametasone (8 mg i.v.) or prednisone, (40 mg., p.o.), and loratadine (10 mg p.o.). Infusion of Rituximab started slowly (15 drops/min), increasing each 20 min. Because patients with renal involvement were under immunosuppressive therapy (most of them with 2 or more DMARD's) when occurred their renal exacerbation or relapse, we decided that did not necessary to increase steroid dosage and maintain without this drug in 6 of them. We included here, two other patient groups, one with severe central neurologic involvement and the other one with acute massive pulmonary hemorrhage, and all of these patients received high doses of metylprednisolone together. Massive pulmonary hemorrhage was defined characteristically with severe acute respiratory failure with diminution of 3 or more grams of haemoglobin without any other potential responsible causes; so, three patients with massive pulmonary hemorrhage diagnosis were treated with 1 g of rituximab, and additionally received methylprednisolone (at least 1 g/day for 4 days), cyclophosphamide (500 mg/m^2), and azathioprine (150 mg/day) or methotrexate (15 mg), beside diary hemodialysis. When data of an allergic reaction were detected, infusion was stopped, and hydrocortisone was administered (100 mg i.v.). In these cases, after a careful clinical evaluation, Rituximab infusion was re-started, upon the continuous monitoring of these patients.

To evaluate differences from basal and 60 days post-rituximab therapy, we used decriptive statistical analysis and comparison media values with t student.

Results

We have previously reported that the addition of Rituximab to the immunosuppressive therapy of patients with refractory lupus nephritis is associated with significant improvement in different clinical and laboratory parameters.[29] All, except two of them had B cell depletion with 500 to 2 g of rituximab. All patients were under intensive immune-regulatory therapy and we decided that in spite renal activity the dose of glucocorticoids remained unchanged during the study, and in six cases whose did not are with steroid therapy, these drugs were not administered, but the patients continued with their DMARD's therapy.

In the Table 1, we show the demographic characteristics of our patients with SLE and severe glomerulonephritis. As previously reported in these patients, Rituximab therapy induced a significant improvement in different clinical parameters in most of them, in spite the administration of only 1.0 g of this biologic agent. It is worth mentioning that in six of these patients, no glucocorticoids additionally to those associated to rituximab infusion were administered and that in the rest of the group the dose of these anti-inflammatory drugs remained unchanged. In these patients with severe glomerulonephritis, the disease activity (MEX-SLEDAI index) significantly diminished ($p < 0.05$) as well as proteinuria, in most of them (from 3.710 g/L to 1.786 g/L, $p < 0.05$). Diminution of proteinuria occurred as early as at day 8 after the