

# Rituximab in Systemic Lupus Erythematosus and lupus nephritis

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## ■ ABSTRACT

Systemic Lupus Erythematosus (SLE) is an autoimmune disease characterised by abnormal expression of B cells, loss of immune tolerance and production of autoantibodies. In this pathogenic context, B cells appear to be a logical goal of SLE therapy.

Rituximab, a chimeric antibody directed against CD20 on B lymphocytes, has emerged as a promising therapy in patients non-responders to classic immunosuppression.

While clinical efficacy and tolerability to Rituximab are documented, controlled trials with greater numbers of patients are needed to confirm the therapeutic potential of Rituximab in SLE.

### Key-Words:

B cells CD 20; Rituximab; Systemic Lupus Erythematosus.

## ■ INTRODUCTION

SLE is an autoimmune disease characterised by modifications in cellular and humoral immunity. It appears to involve innate and acquired immune mechanisms, including complex interactions between B lymphocytes, T lymphocytes and other antigen-presenting cells. Tissue lesions and dysfunction are associated with antibody production, either by direct lesion or by formation of immunocomplexes<sup>1,2</sup>.

B lymphocytes play a crucial role in SLE pathogenesis through the production of antibodies, processing and presentation of autoantigens to T cells, regulation and activation of T cells and dendritic cells, and production of cytokines, such as IL 6, IL10, INF  $\gamma$ . B cells are believed to be an attractive target in the therapeutic approach of SLE patients. Several clinical studies have been published suggesting that B cells depletion may have therapeutic effects in SLE<sup>2-4</sup>.

Rituximab, a new monoclonal anti-lymphocyte antibody (anti-CD20), was initially administered in lymphoproliferative disorders, to be later progressively investigated in conditions with immunologic aetiopathogeny, including the more severe clinical forms of SLE with lupus nephritis<sup>2-4</sup>.

## ■ RITUXIMAB MECHANISM OF ACTION

Rituximab is a chimeric murine/human IgG<sub>1</sub>/K monoclonal antibody directed against B cells surface antigen CD20, a membrane protein that appears at the pre-B stage and disappears during differentiation to plasma cells. While the exact function of CD20 is unknown, it is thought that CD20 is important in the activation and differentiation of B lymphocytes<sup>2,5,6</sup>.

It is not completely clear which mechanism leads to the depletion of lymphoma CD20-positive B cells. *In vitro* studies suggest that Rituximab possibly induces the lysis of these cells through three mechanisms: antibody-dependent cell-mediated cytotoxic-

ity (ADCC), complement-mediated cytotoxicity and apoptosis. Recent studies suggest that lysis of CD20-positive B cells in SLE results from ADCC and apoptosis due to Fc receptor binding to natural killer cells and macrophages<sup>7</sup>.

Through these mechanisms Rituximab can eliminate CD 20-positive B cells, prevent expansion and formation of antibody-producing autoreactive cells and induce repopulation of new B cells, thus creating a new homeostasis. Another important effect attributed to Rituximab is the inhibition of co-stimulating molecules of B and T cells (CD40/CD40L, CD28/CD80-CD86) that appear to be active in SLE patients<sup>8,9</sup>.

## ■ CLINICAL USE OF RITUXIMAB IN SYSTEMIC LUPUS ERYTHEMATOSUS

Rituximab was approved by the FDA (Food and Drug Administration) in 1997 as a first-line therapy and maintenance treatment of non-Hodgkin's B lymphoma, and has been cited in medical literature for its administration in over 500000 patients<sup>2,3</sup>. Its use has also been recently approved for the treatment of rheumatoid arthritis, in combination with methotrexate, in adult patients with inadequate response to standard therapy<sup>10-12</sup>. There are several ongoing clinical trials in patients with SLE, essential mixed cryoglobulinemia, polymyositis, dermatomyositis, idiopathic thrombocytopenic purpura, myasthenia gravis, Wegener's granulomatosis, and in the treatment of chronic graft vs. host disease<sup>5,13-15</sup>.

The first studies on the therapeutic use of Rituximab in SLE were published by Leandro *et al*<sup>1</sup> and Perrota *et al*<sup>16</sup> in 2002. Efficacy was documented in patients with lupus nephritis, arthralgias, arthritis, serositis, cutaneous vasculitis, mucositis, fatigue and neurological symptoms.

Several authors point out the clinical benefits of Rituximab, both in adults and in children, in combined use with corticoids and other immunosuppressive agents<sup>7</sup>.

Others studies document the successful use of Rituximab in patients with severe lupus nephritis refrac-

tory to cyclophosphamide or mofetil mycophenolate, combined with corticoids.

Table I summarises the studies with higher numbers of patients with SLE and lupus nephritis treated with Rituximab. Isolated case reports of lupus nephritis treated with Rituximab have also been published, showing good response to administration of this drug<sup>18-22</sup>.

A review of studies published from 1985 to 2005 on the therapeutic options of proliferative and membranous lupus nephritis resistant to standard immunosuppression therapy concluded that there is no universal consensus for the treatment of resistant lupus nephritis<sup>23</sup>. There are several ongoing clinical trials with new immunosuppressive and immunomodulating agents, such as Rituximab, that show encouraging outcomes and the clinical remission rate in those patients with lupus nephritis under treatment with Rituximab combined with other immunosuppressive agents is high, reaching almost 80%.

Among the patients with SLE treated with Rituximab, in those showing B cells depletion within the first 3 months, a favourable clinical response could be demonstrated. After treatment with Rituximab, B cells depletion can persist for 3-12 months, and often clinical benefit was shown beyond this period<sup>7</sup>.

Anti-chimeric human antibodies are more frequently found in patients who received a single dose of Rituximab, in Afro-American patients, and in those with lower B lymphocytes depletion and low levels of Rituximab two months after infusion<sup>3,6,7</sup>.

For patients responders to this therapy, anti-DNA ds (double strand) and complement do not always return to normal, and should not be used as good clinical response markers<sup>7</sup>.

The most common side effects reported during Rituximab therapy are not severe and include mild to moderate transfusional reactions and hypogammaglobulinemia. The development of opportunistic infections is rare and malignancies or deaths related to Rituximab administration have not been reported.

**Table I**

Studies of patients with SLE and lupus nephritis treated with Rituximad.

Investigator	Patients	Number of patients with lupus nephritis	Therapy	Response
Leandro <i>et al</i> (1)	6	3 Class IV	RIT 500 mg/wk/2wks CYC 750 mg/wk/2wks PRED	1 patient lost to follow-up 5 pts with clinical response
Lonney <i>et al</i> (2)	18	3 Class III 3 Class IV 1 not classified	<b>6 pts – low dose</b> (4 with lupus nephritis) RIT 100 mg/m2 (unique dose) <b>6 pts – intermediate dose</b> (3 with lupus nephritis) RIT 375 mg/m2 (unique dose) <b>6 pts – high dose</b> RIT 375 mg/m2/wk (4 wks) PRED	20% reduction vs. baseline Cr in all pts at 12M
Leandro <i>et al</i> (6)	24	16 Class IV 1 Class V	<b>6 pts</b> RIT 500 mg (d1,d15) CYC 750 mg (d1,d15) PRED <b>18 pts</b> RIT 1000 mg (d1,d15) CYC 750 mg (d1,d15) MPD 250 mg (d1,d15)	21 pts with 23M follow-up: 13 stable pts 7 retreated pts 1 developed anti-RIT antibody
Sfikakis <i>et al</i> (9)	10	4 Class III 6 Class IV	RIT 375 mg/m2/wk/4 wks PRED	8 pts with PR at 2M and of these, 5 pts with CR at 3M and continued in 4 pts at 12M
Perez <i>et al</i> (17)	22	22 Classes III, IV	RIT – 500 mg-1 gr (d1,d15) CYC PRED	77% improved in 1 or 2 measures (Pu < 500 mg/day, inactive sediment)

RIT=Rituximab; PRED=Predisone; CYC=Cyclophosphamide; MPD=Methylprednisolone; CR=Complete Remission; PR=Partial Remission; M=months; W=week; d=day; Cr=creatinine; Pu=proteinuria; pts=patients.

**Complete remission** was defined as normalisation of serum values of creatinine and albumin as well as proteinuria lower than 500mg/day. **Partial remission** corresponded to a decrease higher than 50% compared to baseline.

## CONCLUSION

The near future may see Rituximab as an effective and well-tolerated therapeutic option for patients with moderate to severe SLE, including lupus nephritis refractory to other therapies. The more effective dose, frequency and duration of the treatment are still under analysis, and more clinical trials with a greater number of patients and longer follow-ups are needed to accurately and safely determine Rituximab use in SLE.

**Conflict of interest statement.** None declared.

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