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Review Article

# Rituximab in the Treatment of Eosinophilic Granulomatosis With Polyangiitis☆

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ABSTRACT

*Background:* The general consensus is that for patients with EGPA with poor prognosis, intensive therapy with both GC and CF is indicated. The maintenance of remission is made with GC and AZA. A considerable number of patients with EGPA are refractory to first line therapy, experience dose-limiting side effects or relapse. In clinical trials, RTX was effective for the treatment of ANCA-associated vasculitis. However, patients with a diagnosis of EGPA were not included.
*Objective:* To review and analyze the published literature regarding the use of RTX in the treatment of EGPA.
*Methods:* The literature search was performed in MEDLINE and LILACS from 1965 and 1986 respectively until February 2014.
*Results:* 27 patients were included. RTX treatment was due to refractory disease (n = 20), relapse (n = 5) and with new diagnosis (n = 2). The affected organs were the lungs, peripheral nervous system, kidney and the eyes. Sixteen patients had clinical remission and 8 patients had clinical response.
*Conclusions:* RTX was effective and well tolerated for the treatment of EGPA.


## Rituximab en el tratamiento de la granulomatosis eosinofílica con poliangitis

*Palabras clave:*
Rituximab
Granulomatosis eosinofílica con poliangitis
Vasculitis asociadas a anticuerpos anticitoplasma de neutrófilo

RESUMEN

*Antecedentes:* Algunos pacientes con granulomatosis eosinofílica con poliangitis (EGPA) y factores de mal pronóstico son refractarios o presentan efectos adversos al tratamiento de inducción (glucocorticoides [GC] y ciclofosfamida [CF]), o recaen durante el mantenimiento (GC y azatioprina), haciendo necesaria la búsqueda de alternativas terapéuticas. En ensayos clínicos, el RTX demostró ser eficaz para el tratamiento de las vasculitis asociadas al ANCA; sin embargo, los pacientes con EGPA no fueron incluidos.
*Objetivo:* Revisar y analizar la bibliografía sobre la uso de RTX para el tratamiento de la EGPA.
*Métodos:* La búsqueda se realizó en MEDLINE y LILACS (1965 y 1986, respectivamente, hasta febrero del 2014).
*Resultados:* Se incluyó a 27 pacientes. La indicación de RTX fue por enfermedad refractaria (n = 20), recaída (n = 5) y nuevo diagnóstico (n = 2). Los órganos afectados fueron los pulmones, el sistema nervioso periférico, el riñón y los ojos. Se observó remisión en 16 y respuesta en 8 pacientes.
*Conclusiones:* El RTX fue eficaz y bien tolerado para el tratamiento de la EGPA.


## Introduction

EGPA is a necrotizing vasculitis that primarily affects small and medium caliber blood vessels, and is defined as a granulomatous inflammatory and necrotizing disease rich in eosinophils that often affects the airway and is characterized by the presence of asthma and eosinophilia. Along with granulomatosis

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with polyangiitis (Wegener's granulomatosis [GPA]) and microscopic polyangiitis (MPA), they are part of the antineutrophil cytoplasm antibodies (ANCA) associated vasculitis (AAV).[1]

The general consensus is to treat severe forms of EGPA, defined as those with a score on the 5 factor score (FFS) equal to or greater than 1, with glucocorticoids (GC) and cyclophosphamide (CYP) to achieve clinical remission. Maintaining remission is achieved using GC and AZA. Mild forms (FFA of 0) are treated with GC alone. However, the high rate of adverse events, lack of response to induction treatment or frequent relapses with first line treatments require the study of therapeutic alternatives.[2–4]

Rituximab (RTX) is a chimeric monoclonal antibody that specifically binds the CD20 antigen, a non-glycosilated transmembrane phosphoprotein expressed on pre-B and B lymphocytes. The reasonable use of this drug in EGPA is mainly based on its good results in case reports and small series of patients who have been refractory to first line treatment and, in addition is supported by its proven efficacy in clinical trials for AAV patients (GPA and MPA).[5–8] As patients with EGPA were not included in these trials, RTX approval was not extended to EGPA.

The purpose of this study is to review and analyze the studies published in the literature on the use of RTX in the treatment of EGPA.

## Materials and Methods

*Literature search strategy*: we consulted the databases of the Medical Literature Analysis and Retrieval System on Line (MEDLINE)/National Library of Medicine (NLM)-Library of Medicine of the United States and the Latin American and Caribbean Literature in Health Sciences (LILACS) library, since 1965 and 1986 respectively, until February 2014. Search terms in English and Spanish were Churg-Strauss (síndrome de Churg-Strauss) syndrome, eosinophilic granulomatosis with polyangiitis (granulomatosis eosinofílica conpoliangitis), allergic granulomatous angiitis (angeí-tis granulomatosa alérgica), RXT and monoclonal anti-CD20 (anti-CD20 monoclonal antibody).

The following data were analyzed: age, sex, affected organs/systems when RTX was indicated, clinical disease state (defined as relapse, treatment resistant or new diagnosis), ANCA determination, eosinophil and B lymphocyte counts in peripheral blood, number of immunosuppressive used before and after treatment with RTX, clinical patient progression and adverse events.

We excluded all those publications that did not have detailed data from the final analysis.

*Statistical analysis*: Qualitative variables were presented as percentages, and quantitative variables as means ± standard deviations or median with minimal and maximum values.

## Results

Table 1 shows the general characteristics of 27 patients with a diagnosis of EGPA included for analysis. Fifteen (55.5%) were male and 12 (44.5%) were female. Median follow-up was 15 months (3–60 months). The indication for RTX treatment was refractory

**Table 1**
General Characteristics of the 27 EGPA Patients Treated With RTX Until February 2014.

| Patient/ reference | Age/ gender | Status | Organs affected | **Previous** and concomitant treatments | Time of follow up (Months) | No. of cycles of RTX and indication | Result | Adverse events |
|---|---|---|---|---|---|---|---|---|
| 1[9] | 49/F | Rf | Skin, lung | **PS,** CF, AZA | 3 | 1 | RM | Pneumonia, herpes zoster |
| 2[10] | 37/F | Rl | Lung, PNS, VAS | **PS,** CF, Ig, MFM, Alemtuzumab | 18 | 3 (relapse) | RM | NR |
| 3[10] | 35/F | Rf | Lung, VAS, PNS, articular | **PS,** CF, AZA, MFM, INF Alemtuzumab | 15 | 1 | RM | Respiratory infection |
| 4[11] | 40/M | Rf | Skin, kidney, eye | MP, **PS, CF,** PF | 9 | | RM | NR |
| 5[11] | 66/M | Rf | PNS, heart | MP, **PS,** Ig, CF | 3 | 1 | RM | NR |
| 6[12] | 60/M | Rf | PNS, joints, skin | MP, **PS,** CF, Ig | 12 | 1 | RM | NR |
| 7[13] | 44/F | Rf | PNS, lung | PS, AZA, MTX, CF | – | – | NA | Bronchospasm |
| 8[13] | 33/F | Rl | Joint | PS, CF, MFM, AZA | – | – | NA | Bronchospasm |
| 9[14] | 46/M | Rf | CNS | **PS,** CF, **MFM** | 4 | 1 | RM | NR |
| 10[15] | 50/M | Rf | Lung, ear | **PS,** AZA, **MTX,** CSP, infliximab, anakinra | 19 | 5 (prophylaxis) | RM | NR |
| 11[15] | 35/F | Rl | Lung VAS | **PS, AZA** | 6 | 2 (prophylaxis) | RM | NR |
| 12[16] | 35/M | Rf | Lung, joint | **PS** | 36 | 2 (relapse) | RM | NR |
| 13[17] | 54/M | Rl | PNS, kidney | **PS,** CF | 12 | 2 (relapse) | RM | NR |
| 14[17] | 54/F | ND | PNS, kidney, lung | **PS** | 12 | 1 | RM | NR |
| 15[17] | 64/F | ND | PNS, kidney, muscle | **PS** | 12 | 1 | RM | NR |
| 16[18] | 59/F | Rf | PNS, kidney | **PS, CF,** AZA | 16 | 1 | RM | NR |
| 17[19] | 44/F | Rf | PNS, febrile syndrome | MP, **PS,** Ig, CF | 6 | 1 | RM | NR |
| 18[20] | 70/M | Rf | Lung, kidney | MP, CF, PF | 60 | 1 | RM | NR |
| 19[21] | F | Rf | Lung, eye, ear, heart | **PS, CF, AZA** | 19 | 1 | RP | NR |
| 20[21] | F | Rf | Lung, eye, ear, heart, PNS | **PS, AZA** | 6 | 1 | RP | NR |
| 21[21] | F | Rf | Lung, eye, ear, PNS, SNC | **PS,** MTX, **AZA** | 6 | 1 | RP | NR |
| 22[21] | M | Rf | Lung, eye, ear, heart, CNS, skin | **PS, CF, AZA** | 32 | 2 (prophylaxis) | RP | NR |
| 23[21] | M | Rf | Lung, eye, ear, heart | **PS, CF, AZA** AZA | 34 | 4 (prophylaxis) | RP | Seminoma |
| 24[21] | M | Rf | Lung, eye, ear, PNS, skin, kidney | **PS,** CF, **MFM,** MTX, LF | 36 | 6 (prophylaxis) | RP | NR |
| 25[21] | M | Rf | Lung, eye, ear, heart, skin, PNS, CNS, kidney | **PS, AZA,** CF, MTX | 13 | 1 | RP | NR |
| 26[21] | M | Rf | Lung, PNS, kidney | **PS, CF, AZA** | 6 | 1 | RP | NR |
| 27[21] | M | Rc | Lung, eye, ear, PNS | **PS, MTX** | 6 | 1 | RM | NR |

AZA: azathioprine; CF: cyclophosphamide; CSP: cyclosporin; ND: new diagnosis; F: female; Ig: immunoglobulin; M: male; MFM: mycohenolate mofetil; MP: methylprednisolone; MTX: methotrexate, NA: not applicable; NR: not reported; PF: plasmapheresis; PS: prednisone; Rl: relapse; Rf: refractory; RP: response; RM: remission; CNS: central nervous system; PNS: peripheral nervous system; RTX: rituximab; UA: upper airway.