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Review

Efficacy of low-dose rituximab for the treatment of mixed cryoglobulinemia vasculitis: Phase II clinical trial and systematic review

Marcella Visentini [a,*], Carmine Tinelli [b], Stefania Colantuono [a], Monica Monti [c], Serena Ludovisi [d], Laura Gragnani [c], Milica Mitrevski [a], Jessica Ranieri [c], Elisa Fognani [c], Alessia Piluso [c], Massimo Granata [a], Annalisa De Silvestri [b], Valeria Scotti [b], Mario U. Mondelli [d], Anna Linda Zignego [c], Massimo Fiorilli [a], Milvia Casato [a]

[a] Department of Clinical Medicine, Sapienza University of Rome, Rome, Italy
[b] Clinical Epidemiology and Biometric Unit, IRCCS Policlinico S. Matteo Foundation, Pavia, Italy
[c] Research Center for Systemic Manifestations of Hepatitis Viruses, Department of Internal Medicine, University of Firenze, Firenze, Italy
[d] Infectious Diseases Research Laboratories, IRCCS Policlinico S. Matteo Foundation, Pavia, Italy

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ABSTRACT

Objective: To evaluate whether rituximab at a low dose of 250 mg/m^2 × 2 may be as effective as at higher dosages, most commonly 375 mg/m^2 × 4, used in previous studies on the treatment of patients with refractory mixed cryoglobulinemia (MC) vasculitis associated with hepatitis C virus (HCV) infection.
Methods: We conducted a phase 2, single-arm two-stage trial (EUDRACT n. 2008-000086-38) of low-dose rituximab in 52 patients with HCV-associated MC who were ineligible/intolerant or non-responder to antiviral therapy. The primary outcomes were response of vasculitis evaluated by the Birmingham Vasculitis Activity Score (BVAS) at months 3, 6 and 12, rate of relapses and time to relapse, and rate of adverse events. Our data were compared with those reported in 19 published studies selected among 291 reviewed in a literature search.
Results: The cumulative response rate (complete and partial) at month 3 was 81% in our patients, and 86% in 208 patients from studies using high-dose rituximab. The relapse rate and median time to relapse were, respectively, 41% and 6 months in our study, and 32% and 7 months in high-dose studies. Treatment-related adverse events were 11.5% in our study and 19.9% in high-dose studies. None of these differences was statistically significant.
Conclusion: Rituximab at a low dosage of 250 mg/m^2 × 2 is as effective as at higher dosages for treating MC vasculitis. This low-dose regimen may improve the cost/benefit profile of rituximab therapy for MC.

Contents

Abbreviations: MC, mixed cryoglobulinemia; HCV, hepatitis C virus; SMZL, splenic marginal zone lymphoma; SVR, sustained virological response; PEG-IFN, pegylated interferon alpha; DAA, direct-acting antiviral; BVAS, Birmingham Vasculitis Activity Score; CR, complete response; PR, partial response.

* Corresponding author at: Department of Clinical Medicine, Sapienza University of Rome, Viale dell'Universittà 37, 00185 Rome, Italy. Tel.: +39 06 49972036; fax: +39 06 4440806.
E-mail address: marcella.visentini@uniroma1.it (M. Visentini).

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1. Introduction

Type II mixed cryoglobulinemia (MC) is a systemic vasculitis caused by immune complexes formed by monoclonal IgM rheumatoid factor and polyclonal IgG, which precipitate at t° less than 37° and cause small vessel vasculitis [1]. It is currently considered a rare disease, although the prevalence of the vasculitis presents geographical differences, in relation to HCV infection prevalence [2]. Indeed in more than 90% of cases MC is secondary to hepatitis C virus (HCV) infection, which determines chronic stimulation and benign monoclonal expansion of B-cells producing a natural poly (auto)-reactive IgM antibody. These B cells proliferate very poorly [3], and this may explain why immunosuppressive and cytotoxic drugs are scarcely effective in MC. Over time, chronic stimulation of B-cells by HCV may give rise to genetic changes and evolution to overt lymphoma, typically splenic marginal zone lymphoma (SMZL) [4], that may regress after eradication of HCV with antiviral therapy [5,6].

The most frequent manifestations of MC are cutaneous leucocytoclastic vasculitis leading to purpura and skin ulceration, peripheral neuropathy, glomerulonephritis [1] and central nervous system vascular lesions that may underlie cognitive impairment [7]. In some patients, MC has an acute onset and presents a life-threatening course with skin ulcers, renal involvement and abdominal vasculitis [8].

HCV clearance with sustained virological response (SVR) is the main goal in the treatment of patients with HCV-associated MC, and leads to remission of vasculitis and reduced mortality [8,9]. So far, the best combination for achieving HCV eradication in MC patients is with pegylated interferon alpha (PEG-IFN) and ribavirin [9]. Unfortunately, many patients are ineligible/intolerant, fail to respond or relapse after initial response to this regimen; these patients may have a grim prognosis and bear high health care costs [10].

New direct-acting antiviral (DAA) agents yielding 90–100% SVR rates [11] may change this scenario, and clinical trials with IFN-free regimens for HCV-associated cryoglobulinemia are eagerly awaited [12].

Starting 15 years ago, a number of studies (open studies and case reports) have demonstrated that the anti-CD20 chimeric monoclonal antibody rituximab is highly effective for the treatment of HCV-associated MC, refractory or intolerant to antiviral therapy [13–31]. Only recently, two randomized controlled trials [29,30] showed that rituximab is largely superior to conventional immunosuppressive drugs for treating cryoglobulinemic vasculitis, providing further evidence of its clinical efficacy and safety in this setting. The rituximab dosage used in nearly all published reports was 375 mg/m^2 given four times, the treatment schedule used for B cell NHL [13,14,16–20,22–28,30]. Other studies used the dosage of 1000 mg for two administrations, as for the treatment of rheumatoid arthritis [22,27,29,31] and only few patients were treated with the higher dosage of 375 mg/m^2 for four administrations plus two monthly maintenance dosages [15,18,21,27]. However, the issue of optimal dosing of rituximab for treating MC has not been addressed so far.

Low-dose regimens of rituximab have been shown to be efficacious in different immunological disorders such as rheumatoid arthritis [32–34], systemic lupus erythematosus [35,36], autoimmune haemolytic anemia [37], immune thrombocytopenia [38], pemphigus [39] and myasthenia gravis [40]. Remarkably, a recent meta-analysis [41] demonstrated that low-dose rituximab (500 mg × 2) has similar effectiveness and meets non-inferiority criteria compared to the licensed dose of 1000 mg × 2 for the treatment of rheumatoid arthritis.

Based on a pilot study in 6 patients [42], we designed a phase II, single-arm two-stage multicenter study to evaluate the efficacy of low-dose rituximab (250 mg/m^2 given twice one week apart) in patients with refractory HCV-associated mixed cryoglobulinemia. The mid-term results in 27 of the 52 patients to be enrolled in this study were published in 2011 [43]. Here we report the final results of the study, providing confirmatory evidence of equal efficacy of low-dose compared to high-dose rituximab for the treatment of patients with HCV-associated MC who are ineligible/intolerant or unresponsive to antiviral therapy.

2. Methods

2.1. Study design

This phase 2, single-arm, two-stage multicenter study (EUDRACT n. 2008-000086-38), aimed at assessing the efficacy/safety profile of low-dose rituximab for refractory mixed cryoglobulinemia, was conducted in three university centers (Sapienza University of Rome, University of Florence and University of Pavia). The study was approved by the Internal Review Boards of all participating institutions, and written informed consent was obtained from each patient according to the ethical guidelines of the Declaration of Helsinki.

2.2. Sample size determination and stopping rules

Sample size estimate was performed using the Simon's optimal two-stage procedure. Based on prior data [43], the estimated percentage of patients reaching a 50% reduction of the Birmingham Vasculitis Activity Score (BVAS) and of cryocrit was 40–60% after 10–12 weeks of treatment (primary objective). Fifty-two patients were planned to be treated; for >27/52 responders the conclusion would be that the investigational therapy is effective in these patients. The procedure described above tests the null hypothesis (Ho) that the true response rate is 60% versus the alternative hypothesis (Ha) that the true response rate is at least 40%. The level of significance (i.e., the probability of rejecting the Ho when it is true) is 0.03; the power (i.e., the probability of rejecting the Ha when it is true) is 0.85.

Interim analysis of the results, made by the IDSMB, involved 16 patients entered into the first stage of the study. For <5/16 patients responding to investigational therapy at week 12, the study would be stopped on the basis of the assumption that the drug is not active in this subset of patients. Supplementary Table 1 summarizes the characteristics of the study design.

2.3. Patients

Fifty-two consecutive, unselected patients were enrolled in the study. Requirements for enrolment were: diagnosis of mixed cryoglobulinemia (type II or III) evidenced by at least one of the following manifestations: purpura, skin ulcers, peripheral neuropathy, renal,