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A Randomized Controlled Trial of Rituximab for the Treatment of Severe Cryoglobulinemic Vasculitis

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Objective. To conduct a long-term, prospective, randomized controlled trial evaluating rituximab (RTX) therapy for severe mixed cryoglobulinemia or cryoglobulinemic vasculitis (CV). Methods. Fifty-nine patients with CV and related skin ulcers, active glomerulonephritis, or refractory peripheral neuropathy were

enrolled. In CV patients who also had hepatitis C virus (HCV) infection, treatment of the HCV infection with antiviral agents had previously failed or was not indicated. Patients were randomized to the non-RTX group (to receive conventional treatment, consisting of 1 of the following 3: glucocorticoids; azathioprine or cyclophosphamide; or plasmapheresis) or the RTX group (to receive 2 infusions of 1 gm each, with a lowering of the glucocorticoid dosage when possible, and with a second course of RTX at relapse). Patients in the non-RTX group who did not respond to treatment could be switched to the RTX group. Study duration was 24 months. Results. Survival of treatment at 12 months (i.e., the proportion of patients who continued taking their initial therapy), the primary end point, was statistically higher in the RTX group (64.3% versus 3.5% [P < 0.0001]), as well as at 3 months (92.9% versus 13.8% [P < 0.0001]), 6 months (71.4% versus 3.5% [P < 0.0001]), and 24 months (60.7% versus 3.5% [P < 0.0001]). The Birmingham Vasculitis Activity Score decreased only after treatment with RTX (from a mean SD of 11.9 5.4 at baseline to 7.1 5.7 at month 2; P < 0.001) up to month 24 (4.4 4.6; P < 0.0001). RTX appeared to be superior therapy for all 3 target organ manifestations, and it was as effective as conventional therapy. The median duration of response to RTX was 18 months. Overall, RTX treatment was well tolerated. Conclusion. RTX monotherapy represents a very good option for severe CV and can be maintained over the long term in most patients.

Mixed cryoglobulinemia, which is also known as cryoglobulinemic syndrome or cryoglobulinemic vasculitis (CV), is a systemic vasculitis that is primarily mediated by immune complexes and is associated with hepatitis C virus (HCV) infection and B cell lymphoproliferation (1–5). HCV infection might be crucial for the induction of CV, although not for its persistence (6–8). Treatment options for HCV-associated CV should therefore be focused on both the viral trigger, when detected, and on the expanded rheumatoid factor (RF)–positive B cell population (8,9). Therapy with antiviral agents is a cornerstone for the management of CV. However, this therapy may also be ineffective, contraindicated, or not tolerated, it may sometimes worsen or induce CV, and it does not allow for rapid improvement in the condition (10–13). Current therapeutic approaches aimed at immune activation downstream of the viral infection, such as treatment with glucocorticoids, plasmapheresis, or cytotoxic drugs, may also prove to be ineffective, contraindicated, or poorly tolerated, or may be associated with serious side effects (14). Rituximab (RTX) therapy has been used successfully in patients with CV, but only in retrospective studies, and limited followup data have been reported (15–23). We therefore initiated this long-term, prospective, randomized controlled trial to provide stronger evidence of the efficacy and safety of RTX monotherapy for the severe manifestations of CV in comparison to the usual approaches to immunosuppression in patients in whom treatment with antiviral agents had failed or was not recommended by the expert clinician.

PATIENTS AND METHODS

This was a multicenter, phase III, randomized controlled trial in patients with CV who had type II cryoglobulins, either HCV-related or -unrelated, classified according to published criteria (24), and had serum cryoglobulins at study entry. The study patients had manifestations of severe active CV, such as skin ulcers, active glomerulonephritis, or worsening or refractory peripheral neuropathy. In patients with HCVrelated CV, study inclusion implied that therapy with antiviral agents with interferon plus ribavirin had failed, had been poorly tolerated, or was considered to be contraindicated (25,26). The study patients were 18–80 years old, negative for antibodies against human immunodeficiency virus and hepatitis B virus core antigen, and negative for hepatitis B surface antigen. The study was approved by the Independent Ethical Committee of the coordinating center and then by the local ethics committees of each center involved. It

was conducted in full conformity with the Declaration of Helsinki and with the Guidelines for Good Clinical Practice. A Scientific Committee and Data Safety Monitoring Board monitored the study. This was a nonprofit, unsponsored, unfunded study. Roche (Basel, Switzerland) provided the study medication (rituximab; MabThera). Roche had no role in the study design or in the collection, analysis, or interpretation of the data, the writing of the manuscript, or the decision to submit the manuscript for publication. Publication of this article was not contingent upon approval by Roche. Study design. Consecutive, unselected patients with CV and type II mixed cryoglobulins were asked to participate in the study. If the patients met the criteria for study entry, they signed informed consent forms and were then randomized at a ratio of 1:1 to the non-RTX group or the RTX group. The non-RTX group received 1 of the following 3 conventional treatments, which was chosen by the expert clinician for that individual patient: glucocorticoids; azathioprine or cyclophosphamide; or plasmapheresis. Glucocorticoids were given at a maximum initial dosage of 1 mg/kg/day of prednisone or equivalent, with or without preceding 6 pulse doses of methylprednisolone (500–1,000 mg/day for 3 consecutive days), and with subsequent reduction of the glucocorticoid dosage during the following months. Azathioprine or cyclophosphamide was given orally at a dosage of 1–2 mg/kg/ day, with or without glucocorticoids (as above). If a response was observed, the azathioprine or cyclophosphamide might be suspended after the end of month 6 following randomization and then reintroduced if clinical relapse occurred (current clinical practice). Plasmapheresis, with or without glucocorticoids (as above) was given, and if a response was observed, therapy could be suspended at the end of month 6 after randomization. If clinical relapse occurred, plasmapheresis could be reintroduced (current clinical practice). At least 2 plasmapheresis procedures per week were required during the first month after randomization, with subsequent reductions according to the observed response as well as local protocols. The RTX group received a 1-gm intravenous infusion of RTX on days 0 and 14. Premedication with 100 mg of intravenous methylprednisolone, 1,000 mg of oral acetaminophen, and 10 mg of intravenous chlorpheniramine maleate was administered before each infusion. Only glucocorticoids were allowed as concomitant treatment. Patients who were taking glucocorticoids before randomization continued this therapy, taking the same or a lower dosage. If glucocorticoid treatment was introduced with the RTX, only low doses (0.1 mg/kg/day of prednisone or equivalent) were allowed. In case of relapse of clinical disease in this group, another course of RTX given under the same schedule was permitted if there had been a previous response to the drug. Patients in the non-RTX group in whom treatment failed could be switched to RTX in an open-label extension (RTX-switch group), as stated in the informed consent materials. Patients who were randomized to treatment were stratified for the following 3 disease manifestations: skin ulcers, active glomerulonephritis (assessed by renal biopsy), or peripheral neuropathy (assessed by electromyography), either sensory (evolving or with severe pain that was unresponsive to, or insufficiently managed with, analgesics and gabapentin or pregabalin) or motor (any type and duration) in nature. Patients with the simultaneous presence of 2 or 3 of these clinical manifestations were randomized to the group in which patient accrual was lower. Exclusion criteria, response criteria, and treatment failure criteria are defined as described in the Supplementary Methods document, which is available on the Arthritis & Rheumatism web site at http://onlinelibrary.wiley.com/journal/ 10.1002/(ISSN)1529-0131. A routine laboratory evaluation was performed monthly. Additional serologic tests included rheumatoid factor (RF) testing by nephelometry (positive 20 IU/ml), quantification of serum C3 and C4 levels, protein electrophoresis, and levels of IgG, IgA, and IgM, as determined by published criteria. According to the protocol, RF levels, rather than serum cryoglobulin levels, were monitored at fixed intervals. Flow cytometry analyses were required to assess B cell depletion. This was performed at baseline and at 1, 6, 12, and 24 months, when possible. Study end points. Primary end point. The primary end point of the study was the proportion of patients who continued to take the treatment to which they were randomized at the end of month 12 after

randomization (i.e., survival of treatment at 12 months), that is, after a followup period considered to be sufficient for assessing both the efficacy and the safety of the treatment. Efficacy and safety issues were in fact considered to be equally relevant over the long term, and a single end point integrating both of them was then chosen. The end point was met if survival of treatment was statistically higher in the RTX group as compared to the non-RTX group (conventional treatment). Secondary end points. One of the secondary end points was the proportion of patients continuing to take their randomized treatment (i.e., survival of treatment) at the end of month 24, which evaluates the long-term efficacy and safety of treatment. We also assessed the proportion of patients continuing to take their randomized treatment at the end of month 6 (evaluating the short-term efficacy and safety of treatment) and at the end of month 3 (evaluating the very early efficacy and safety of treatment). Other secondary end points were the superiority of RTX treatment in decreasing global disease activity, as defined by the Birmingham Vasculitis Activity Score (BVAS) (27), the superiority of RTX treatment in decreasing the single CV manifestations considered in the randomization scheme, the efficacy of RTX treatment in patients in whom conventional treatment had failed, the duration of response to RTX and the efficacy of re-treatment, and assessment of the side effects profile of RTX, both over the short term and the long term. Serious adverse events were defined as described in the Supplementary Methods document, which is available on the Arthritis & Rheumatism web site at http://onlinelibrary.wiley.com/journal/10.1002/(ISSN)1529- 0131. Statistical analysis. The study was designed to have 80% probability of detecting an absolute difference of 25% in the 12-month rate for survival of treatment between the RTX group and the non-RTX (conventional treatment) group (i.e., from 50% among patients in the non-RTX group to 75% among those in the RTX group). The sample size necessary for evaluating efficacy was 124 (5% dropout rate included). The rules and the time points for stopping the study that were established prior to study implementation, the way in which comparisons between treatment arms were performed, and the statistical analyses performed are defined as described in the Supplementary Methods document, which is available on the Arthritis & Rheumatism web site at http:// onlinelibrary.wiley.com/journal/10.1002/(ISSN)1529-0131.

RESULTS

Accrual and clinical characteristics. Although the study was designed to enroll 124 patients, superiority of treatment in the RTX group versus the non-RTX group (63.2% versus 4.4%, difference of 58.8% [95% confidence interval (95% CI) 35.6–82.0]; P 0.0001) was statistically evident during the first 12-month interim analysis in 42 randomized patients (33% of the entire sample), and for this reason, enrollment was stopped, as recommended by the Scientific Committee and Data Safety Monitoring Board. A total of 57 patients (29 in the non-RTX group and 28 in the RTX group) were available for data analysis and represented the intent-to-treat population; 2 additional patients could not be assessed after randomization (1 in the RTX and 1 in the non-RTX group) (Figure 1). All of the patients who are still living meet the more recent classification criteria for CV (data not shown) (28). The study population consisted of 46 women and 11 men, with a median age of 65 years (range 37–79 years). Fifty-three patients were HCV positive (93%; all with anti-HCV antibodies and with serum HCV RNA) (Table 1). There were no differences in age, sex, and HCV positivity between the 2 randomized groups. In 25 of the 53 patients (47.2%), previous therapy with antiviral agents had been ineffective or poorly tolerated. In 28 of the 53 patients (52.8%), therapy with antiviral agents was considered to be contraindicated (Table 1). Treatments chosen for the 29 patients in the non-RTX group were glucocorticoids in 17 (58.6%), plasmapheresis in 5 (17.2%), cyclophosphamide in 4 (13.8%), and azathioprine in 3 (10.3%). Patients receiving RTX therapy were given a significantly lower glucocorticoid dose at baseline (i.e., when starting RTX) than patients receiving non-RTX therapy (7.0 6.0 mg/day of prednisone or equivalent versus 19.5 16.3 mg/day; P 0.005), as expected, since the study protocol indicated that the glucocorticoid dosage would be minimized in the RTX treatment group when

possible. Specifically, 1 patient in the RTX group was given 25 mg/day of prednisone or equivalent at baseline, 1 was given 15 mg/day, 19 were given 5–12.5 mg/day, and 7 were not given glucocorticoids. In the non-RTX group, patients receiving glucocorticoid monotherapy as the chosen option were given a mean SD dosage of 28.5 14.1 mg/day of prednisone or equivalent at baseline (range 15–60 mg/day), while patients treated with azathioprine, cyclophosphamide, or plasmapheresis received a mean of 6.7 9.1 mg/day of prednisone or equivalent at baseline (range 0–25 mg/day). At the end of the first month, a between-group difference in the daily dose of glucocorticoids was still evident, with those in the RTX group receiving a mean SD of 6.8 5.9 mg/day of prednisone or equivalent and those in the non-RTX group receiving 13.8 11.6 mg/day (P 0.05). Primary end point. Survival of treatment at month 12 after randomization was the primary end point of this clinical trial. Survival of treatment in the RTX group versus the non-RTX group was 64.3% versus 3.5% (difference of 60.8% [95% CI 43.5–63.9]; P 0.0001) at month 12. Secondary end points. Survival of treatment at month 24 after randomization. Survival of treatment in the RTX group versus the non-RTX group was 60.7% versus 3.5% (difference of 57.3% [95% CI 38.1–76.5]; P 0.0001 by chi-square test) at month 24. Comparison of the distribution of the survival of treatment rates between the 2 groups showed a significant difference (P 0.0001 by log-rank test) (Figure 2). The treatment group into which the patient was randomized was the only variable that was significantly associated with survival of treatment at month 24 (hazard ratio 7.9 [95% CI 3.6–17.2]; P 0.0001) (Table 2). Reasons for treatment failure up to month 24 in patients in the non-RTX group were a lack of response or worsening of target organ manifestations in 25 of the 29 patients (86.2%) and side effects in 3 of the 29 patients (10.3%). Reasons for treatment failure during the same period in patients in the RTX group were a lack of response or worsening of target organ manifestations in 4 of the 28 patients (14.3%) and side effects in 4 of the 28 patients (14.3%). In addition, 3 of the 28 patients in the RTX group, all of whom had responded to RTX therapy, were lost to followup from month 12 of the study. Survival of treatment at month 6 after randomization. Survival of treatment in the RTX group at month 6 was 71.4%, as compared to 3.5% in the non-RTX group (difference of 67.9% [95% CI 50.1–86.1]; P 0.0001 by chi-square test). Survival of treatment at month 3 after randomization. In the earlier phases of treatment of CV, it is crucial to decide whether to maintain the initial therapy, suspend it, or switch to another approach. Both side effects and a lack of even an initial response (any grade of response or disease worsening) were considered causes of treatment failure during the first 3 months after randomization. Survival of treatment in the RTX group was 92.9% at month 3, as compared to 13.8% in the non-RTX group (difference of 79.1% [95% CI 63.3– 94.8]; P 0.0001 by chi-square test). With regard to months 1 and 2, Table 3 shows the course of the target organ manifestations during this interval, as well as the fraction of patients showing an improvement of any grade. Overall, very early improvement was noticed in the majority of patients in the RTX group, which was not generally seen in the non-RTX group. Global disease activity. No difference in the BVAS score was observed between the 2 treatment groups at baseline (mean SD 9.6 3.6 in the non-RTX group versus 11.9 5.4 in the RTX group; P 0.06) or at 2 months (9.6 4.5 in the non-RTX group versus 7.1 5.7 in the RTX group; P 0.076). While no significant improvement in the non-RTX group was observed for the BVAS at baseline versus 2 months (P 0.715), a significant reduction in the BVAS at 2 months was seen in the RTX group (P 0.001), and this difference persisted at 6 months (6.9 6.8; P 0.001), 12 months (5.4 6.2; P 0.0001), and 24 months (4.4 4.6; P 0.0001). Efficacy of study therapy for single-organ manifestations. No target organ manifestation that was randomized was found to influence as a single variable the survival of treatment (Table 2). In addition, the number of target organ manifestations in the same patient, when 2 or 3 were simultaneously present, did not influence the survival of treatment (data not shown). Since there were only 4 cases of CV unrelated to HCV infection (with a response in 1 of the 3 who received RTX, but not in the 1 who received non-RTX therapy), no statistical analysis or assessment of the response of the different target organ manifestations could be performed in this subset. Skin ulcers. In the RTX group, 4 of the 5 complete

responses that occurred during the study and 1 of the 5 major responses were observed at 6 months. The type of response remained unchanged at months 12 and 24. Thus, the response of skin ulcers persisted in RTXtreated patients, and a second course of RTX was not needed. One CV patient in whom there was complete healing of skin ulcers remained in the study in non-RTX group at months 6, 12, and 24. Glomerulonephritis. Among the 7 patients in the RTX group who had glomerulonephritis, 2 showed a complete response, 2 showed a partial response, and 3 showed treatment failure at 6 months. The patients who showed a response at 6 months continued to respond at 12 months (response type unchanged) and at 24 months (3 of 4 with complete response and 1 of 4 with partial response). One of the responders needed a second course of RTX. Peripheral neuropathy. Among the RTX-treated patients with peripheral neuropathy, 11 of 16 responses were observed at 6 months (2 complete, 3 major, and 6 minor responses). At 12 months, 7 of the 16 responses were seen (1 complete, 5 major, and 1 minor response), and 8 of the 16 responses were seen at 24 months (1 complete, 4 major, and 3 minor). Thus, a possible loss of response to RTX after month 6 was noted, and a second course of treatment with RTX was given to 6 of the 11 responders according to the protocol.

Efficacy of RTX in patients in whom conventional treatment failed. Twenty-three of the 28 patients in non-RTX group whose disease did not respond to conventional therapy (82.1%) agreed to undergo therapy with RTX (the RTX-switch group). Treatment failure occurred during the first month after randomization in 60.8% of these 23 patients, during the second month after randomization in 21.8%, and after the second month in the remaining patients (17.4%), and RTX was started within 1–2 months in all of them. Globally, a response to RTX was noted within 6 months in 14 of these 23 patients (60.9%). Manifestations of active CV despite the previous conventional treatment consisted of skin ulcers in 2 patients (with subsequent complete response in both of them), active glomerulonephritis in 8 (with subsequent complete response in 2 and partial response in 4), and refractory peripheral neuropathy in 13 (with subsequent major response in 2 and minor response in 4). Duration of response to RTX and efficacy of a second course of treatment. The median duration of clinical response to RTX was 18 months in the group randomized to RTX and 12 months in the RTX-switch group. A significantly higher risk of clinical relapse was observed in the RTX-switch group than in the RTX group (hazard ratio 3.36 [95% CI 1.21–9.32]; P 0.02). A second course of RTX therapy was administered to 15 patients and was again effective in 11 of them (73.3%). Efficacy was similar in the group randomized to RTX (5 of 7 patients) and in the RTX-switch group (6 of 8 patients). Clinical outcomes for the single-organ manifestations are reported in detail in the Supplementary Methods document, which is available on the Arthritis & Rheumatism web site at http://onlinelibrary.wiley.com/ journal/10.1002/(ISSN)1529-0131. Safety. Fourteen serious adverse events occurred in 12 patients (Table 4). No statistically significant differences in the number of serious adverse events were noted between groups (non-RTX group versus RTX group and RTX group versus RTX-switch group). The number of serious adverse events per drug exposure was greater in the non-RTX group. Death occurred in 6 patients (1 in the non-RTX group, 2 in the RTX group, and 3 in the RTX-switch group). Three patients died of an acute cardiovascular event, 2 died of systemic complications in the presence of decompensated cirrhosis of the liver, and 1 died of pneumonia complicated by hemorrhagic alveolitis (Table 4). Serious infections occurred in 4 patients, with 2 pneumonias (1 in the non-RTX group and 1 in the RTX-switch group) and 2 complicated urinary tract infections (1 in the RTX group and 1 in the RTX-switch group). Three of these patients had previously received intensive treatment with glucocorticoids. In 1 patient with pneumonia who had received intensive therapy with glucocorticoids and immunosuppressors (RTX-switch group), hemorrhagic alveolitis complicated the infection, and the patient died. Six cardiovascular events were documented, 1 in the non-RTX group, 3 in the RTX group, and 2 in the RTX-switch group. One event was related to the RTX infusion (arterial hypotension followed by angina pectoris), and the other events occurred at least 30 days

following the last RTX infusion. No serum sickness reactions were reported. No significant increase in liver enzyme levels over the upper limit of normal was recorded in patients receiving RTX therapy at 6, 12, or 24 months as compared to baseline (P 0.868 for the RTX group; P 0.538 for the non-RTX group). Changes in the viral load of HCV RNA were not evaluated. No significant changes in serum IgG levels were observed in patients who received RTX at 6, 12, or 24 months versus baseline, both in the group randomized to RTX and in the RTX-switch group. However, 1 patient who had received high-dose glucocorticoids and different immunosuppressors before study entry developed hypogammaglobulinemia after RTX therapy. In contrast, a decrease in the serum IgG level was noted in the non-RTX group at 2 months (mean SD 721.65 74.71 mg/dl at baseline, as compared to 659.00 72.62 mg/dl at 2 months; P 0.043), but no patient developed hypogammaglobulinemia. Laboratory data. A decrease in the B cell population to 1% of total blood lymphocytes was seen at 1 month in all 51 patients who were treated with RTX (both those randomized to RTX and those in the RTX-switch group). This decrease persisted up to the end of month 6 in 43 of the 51 patients (84.3%). RF levels showed a significant decrease at the end of month 6 after RTX treatment (mean SD 286.14 67.81 IU/ml at baseline versus 122.31 43.03 IU/ ml; P 0.0003), with no differences between the randomized RTX group and the RTX-switch group (data not shown). Serum C4 levels were increased at 6 months after RTX treatment (mean SD 5.93 1.45 versus 11.58 1.80 mg/dl; P 0.0001), with a significant increase starting from month 2 (5.93 1.45 versus 10.02 1.55; P 0.0001). No statistically significant difference between patients who experienced a relapse and those who did not was noted with regard to possible changes in the RF or C4 values at the time of relapse.

DISCUSSION

The findings of this multicenter, phase III, randomized controlled trial demonstrate the superiority of RTX monotherapy as compared to conventional therapy with corticosteroids, azathioprine, cyclophosphamide, or plasmapheresis for the treatment of severe HCV-related CV when therapy with antiviral agents failed or were considered by the expert clinician to be contraindicated. This level of evidence was previously lacking, and although this was not a blinded study, the results of our study support the use of RTX in this disease. RTX proved useful over the long term, even with lower doses of glucocorticoids, and was effective in patients who switched from conventional treatment to RTX. Since the study involved experts in different branches of medicine, the risk of specialty-oriented treatment choices for the conventional treatment study arm was probably reduced (26). Very few patients in this study had CV that was unrelated to infection with HCV. Thus, additional investigation in this subset of patients will be required (29). The degree of global disease activity did not differ between the 2 treatment groups at baseline, and patients were stratified according to target organ manifestations. Based on these data, it is unlikely that there were more patients with difficult-to-treat disease in the non-RTX group as compared to the RTX group. Survival of treatment at 12 months after randomization was the primary end point of the study, in order to better evaluate the relevance of treatment after a sufficiently long followup period, integrating both the efficacy data and the safety data. Superiority of RTX therapy over conventional therapy was also observed earlier, within 2–6 months after treatment. On the other hand, in complex diseases such as CV, which are often complicated by comorbid conditions and with an increased risk of infections during treatment, a long followup period is advisable in order to better evaluate the efficacy and safety of any novel treatment. This was recently stressed, for example, in antineutrophil cytoplasmic antibody– associated vasculitis treated with RTX (30). In patients in whom RTX therapy was previously effective, it may be repeated if a disease relapse occurs, and this is a second reason for requiring a long-term study. Thus, the usefulness of RTX over the long term was also investigated in this 24-month study, since the possibility of maintaining RTX therapy over time in patients with CV had not previously been explored in detail. The percentage of patients continuing to take RTX therapy over 2 years was satisfactory (60.7%) when taking into account the severity of disease in the

treated patients. Since the median time to relapse after RTX therapy was

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1.5 years in the RTX group, a regimen of retreatment at the time of clinical relapse, rather than a maintenance regimen, is supported in general by the results of the present study. Maintenance treatment could, however, be useful in some patients with very severe CV, in whom the risk of relapse should definitely be avoided (19,26). RTX was effective even in patients in whom conventional therapy had failed. The response rate in this subset of patients in the RTX-switch group (60.9%) was slightly lower than that in patients who were initially randomized to the RTX group (71.4%). Furthermore, earlier and more frequent relapses were noted in patients in the RTX-switch group as compared to those randomized to RTX. However, it remains to be determined whether earlier treatment with RTX may also be more convenient for this reason. Patients were usually switched to RTX because of a lack of clinical response or because of worsening of the disease with conventional therapy, rather than because of side effects. In the design of this trial, defining the time to response and the degree of response to either maintain or suspend the different treatment approaches was a major issue. Clinically and ethically acceptable criteria for defining treatment failure were mainly considered. A response to glucocorticoids and to plasmapheresis, which represented the usual treatment options chosen in the non-RTX group (22 of 29 patients [75.9%]), is expected early, while improvement after cyclophosphamide, azathioprine, or RTX may occur later. However, most patients treated with RTX started to respond early, and this represents additional information from our study that may prove important in making treatment decisions. The minimization of the glucocorticoid dosage, which was attempted at randomization into the RTX group according to the study protocol, should also be emphasized. Glucocorticoids may induce important side effects, and this is particularly relevant in elderly patients with concomitant HCV infection, as in the case of most patients with CV (31,32). A role of RTX in reducing the dosage of concomitant glucocorticoids in patients with CV (when possible) is therefore suggested. The biologic effects of RTX observed in this trial reproduced those previously reported in CV. However, a different schedule of RTX administration was used, as has been reported for patients with rheumatoid arthritis (33). Both the clinical and laboratory results are therefore consistent with the efficacy of this regimen. As with other diseases treated with RTX, B cell reconstitution was not related to disease relapse, suggesting a possible immune reset (34–36). Besides B cell depletion, a decrease in RF levels and an increase in C4 levels was noted, which is consistent with the biologic effects of RTX on this RF-positive, immune complex–mediated condition. The profile of side effects in the study reproduced the profile observed previously in patients with CV (15–23) as well as in those with other autoimmune diseases (33,37–39). As compared to conventional therapy, the overall rate of serious adverse events was similar in the RTX-treated patients, the latter remaining under treatment for a longer time, however. Six deaths were recorded in patients treated with RTX. Ferri et al (32) reported a cumulative 10-year survival rate of 53%, which decreased to 33% in CV patients with nephritis. Although the calculation of an expected death rate is inappropriate on statistical grounds (31,32), the number of deaths observed in our study does not appear to be increased. In addition, patients with severe CV were recruited for this study, many of whom had nephritis. Severe infections usually occurred in patients who had previously received intensive therapy with glucocorticoids. Together with hypogammaglobulinemia, intensive glucocorticoid therapy represents a warning for possible infections during treatment with RTX. No case of serum sickness was recorded, and the cardiovascular events reported as serious adverse events occurred more than 1 month after the RTX infusion. Thus far, the occurrence of serum sickness has been reported rarely in patients with CV treated with RTX (15–21,23,40,41). In contrast, one group of investigators observed serum sickness much more frequently (22,42,43). Care should therefore be taken with regard to this potential side effect. Finally, liver toxicity was not observed after RTX therapy in our study patients. The liver safety profile of RTX therapy in CV, despite HCV infection and liver disease (15–23,44), is therefore

confirmed within 2 years of observation. In conclusion, we report herein the results of our long-term, prospective, randomized controlled trial of RTX monotherapy in patients with CV. RTX was found to be superior to standard immunosuppressive therapy for severe CV over the long term, where therapy with antiviral agents is not indicated in the opinion of the expert (26,45). In this setting, RTX monotherapy may represent a first therapeutic option (44,45), associated with lower doses of glucocorticoids when possible.

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AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be published. Dr. De Vita had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Study conception and design. De Vita, Quartuccio. Acquisition of data. De Vita, Quartuccio, Isola, Mazzaro, Scaini, Lenzi, Campanini, Naclerio, Tavoni, Pietrogrande, Ferri, Mascia, Masolini, Zabotti, Maset, Roccatello, Zignego, Pioltelli, Gabrielli, Filippini, Perrella, Migliaresi, Galli, Bombardieri, Monti. Analysis and interpretation of data. De Vita, Quartuccio.

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Figure 1. Flow chart showing the distribution of study patients from randomization, over the subsequent course of the study, and to completion of the study in patients randomized to receive rituximab (RTX) or conventional therapy (non-rituximab [non-RTX]), consisting of glucocorticoids, azathioprine, cyclophosphamide, or plasmapheresis. ITT intent-to-treat.

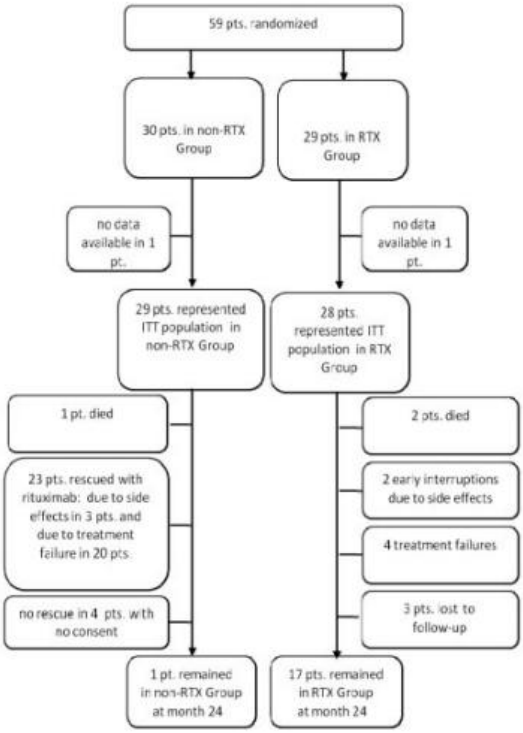

Table 1. Characteristics of the patients who were randomized into the study, by treatment group*

	All patients (n = 57)	Non-RTX group (n = 29)	RTX group (n = 28)
Age, mean ± SD years	63.27 ± 10.78	63.0 ± 10.6	62.85 ± 11.36
Sex, no. female/male	46/11	22/7	24/4
No. HCV positive/no. tested	53/57	28/29	25/28
Antiviral therapy failure/not indicated	28/25	14/14	14/11
BVAS at baseline, mean ± SD	10.51 ± 4.49	9.55 ± 3.64	11.89 ± 5.42
No. with skin ulcers	7	2	5
No. with nephritis	17	10	7
No. with neuropathy	33	17	16
Rheumatoid factor, mean ± SD IU/ml	528.55 ± 840.12	556.58 ± 784.04	501.38 ± 891.81
C4, mean ± SD mg/dl	6.62 ± 8.05	6.81 ± 7.37	6.27 ± 8.7

* There were no significant differences between the two treatment groups. RTX = rituximab; HCV = hepatitis C virus; BVAS = Birmingham Vasculitis Activity Score.

Figure 2. Survival curves in patients randomized to receive rituximab (RTX) therapy or conventional therapy (non-rituximab [non-RTX]), consisting of glucocorticoids, azathioprine, cyclophosphamide, or plasmapheresis.

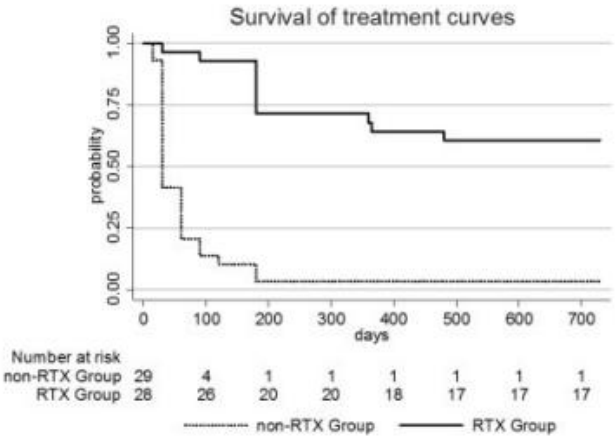

Table 2. Factors associated with survival of treatment*

Factor	HR (95% CI)	*P*
Age, modeled as a continuous variable	0.99 (0.96–1.02)	0.499
Sex		
Female	1	
Male	1.92 (0.93–3.98)	0.077
Target organ involvement		
Skin ulcers	1	
Nephritis	3.60 (0.85–15.27)	0.082
Neuropathy	4.05 (0.91–18.03)	0.066
Baseline BVAS, modeled as a continuous variable	0.99 (0.92–1.05)	0.681
Treatment group		
Non-RTX group	1	
RTX group	8.21 (3.77–17.87)	<0.0001

* HR = hazard ratio; 95% CI = 95% confidence interval; BVAS = Birmingham Vasculitis Activity Score; RTX = rituximab.

Table 3. Improvement during the first two months of the study*

	Non-RTX group			RTX group		
	Baseline	Month 1	Month 2	Baseline	Month 1	Month 2
Skin ulcers						
No. of ulcers	2.5 (1–4)	2.5 (1–4)	4.0 (1–7)	2.0 (1–10)	2.0 (1–5)	0 (0–2)
Diameter, cm	2.5 (1–4)	2.5 (1–4)	2.5 (2–3)	5.0 (2–7)	4.0 (1–6)	0 (0–3)
Glomerulonephritis						
Serum creatinine, mg/dl	1.2 (0.7–2.3)	1.2 (1.0–2.0)	1.5 (0.8–2.4)	1.6 (0.7–2.8)	1.2 (0.8–6.0)	1.6 (0.8–6)
Proteinuria, gm/24 hours	2.0 (0.9–6.8)	2.1 (0.9–7.0)	1.85 (1.0–11.0)	2.0 (0.6–7.9)	0.6 (0.5–7.8)	0.9 (0.5–4.5)
Active urinary sediment	8/10	7/9	9/9	6/7	5/7	3/7†
Peripheral neuropathy‡						
VAS score for pain	88 (30–100)	80 (20–100)	90 (0–100)	70 (10–100)	52 (0–100)†	40 (0–81)§
VAS score for paresthesias	90 (10–100)	70 (10–100)	80.5 (0–100)	89 (30–100)	63 (30–100)	44 (10–100)
Any grade of improvement vs. baseline¶						
Skin ulcers	–	0/2	1/2	–	3/5	5/5
Glomerulonephritis	–	2/9	1/9	–	4/7	5/7
Peripheral neuropathy	–	4/17	10/14	–	6/15	12/14
Total	–	6/28	12/25	–	13/27†	22/26†

* Values are the median (range), except for active urinary sediment, which are the number positive/total number assessed, and any grade of improvement versus baseline (all categories), which are the number improved/total number with the feature at baseline.
† $P < 0.05$ versus the non-rituximab (non-RTX) group, by Mann-Whitney test (continuous variables) or Fisher's exact test (categorical variables).
‡ In the RTX group, differences in the visual analog scale (VAS; 0–100 mm) scores for pain were significant for baseline versus month 1 ($P = 0.003$) and for baseline versus month 2 ($P = 0.01$), and differences in the VAS scores for paresthesias were significant for baseline versus month 2 ($P = 0.01$), as determined by Wilcoxon's matched pairs signed rank test. In the non-RTX group, no significant differences in either parameter for month 1 or month 2 values versus baseline were observed.
§ $P < 0.01$ versus the non-RTX group, by Mann-Whitney test (continuous variables).
¶ Patients who withdrew during the first 2 months of study because of side effects were excluded. In the non-RTX group, data obtained immediately before the switch to RTX were used in the analyses.

Table 4. SAEs and deaths during the study period, by treatment group*

	Non-RTX group	RTX group	RTX-switch group
No. of SAEs/total no. of patients (%)	3/29 (10.3)	5/28 (17.9)	6/23 (26.1)
Rate of SAEs per drug exposure (no. of events/person-year)	0.48	0.12	0.22†
Infections	1	1	2
Pneumonia	1	0	1
Urosepsis	0	0	1
Cardiovascular events	1	2	3
Angina	1	0	0
Myocardial infarction	0	1	0
Heart failure	0	1	3
Acute liver failure	1	1	0
Gastrointestinal bleeding	0	1	0
Hemorrhagic alveolitis	0	0	1
Deaths‡	1	2	3

* There were no significant differences in serious adverse events (SAEs) between the non-rituximab (non-RTX) and the RTX group ($P = 0.47$ by Fisher's exact test) or between the RTX and the RTX-switch group ($P = 0.51$ by Fisher's exact test). Except where indicated otherwise, values are the number of SAEs.
† The rate of SAEs is 0.24 events/person-year if calculated for the entire interval after randomization (i.e., the time the patient spent in both the non-RTX and the subsequent RTX-switch groups).
‡ Deaths were due to acute liver failure (1 in the non-RTX group and 1 in the RTX group), myocardial infarction (1 in the RTX group), heart failure (2 in the RTX-switch group), and hemorrhagic alveolitis (1 in the RTX-switch group).