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(Article begins on next page)
Retreatment regimen of rituximab monotherapy given at the relapse of severe HCV-related cryoglobulinemic vasculitis: Long-term follow up data of a randomized controlled multicentre study

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Abstract

Objective
To evaluate the efficacy and safety in the long term of a retreatment regimen with Rituximab (RTX) alone administered at clinical relapse in cryoglobulinemic vasculitis (CV).

Methods
Thirty patients with severe HCV-related CV, previously enrolled in the multicentre Italian trial on RTX in the treatment of CV, were retrospectively evaluated after the end of the trial. All of them were managed with RTX alone at clinical relapse, if any. Disease activity at the last available follow up was defined as complete remission (absence of active disease), partial remission (response > 50% of at least one manifestation among glomerulonephritis, peripheral neuropathy or skin ulcers) or active disease.

Results
The mean follow up after the first RTX cycle was 72.6 (20.4) months. After the end of the trial, 21/30 (70%) patients showed an active follow up [81.7 (10.9) months], 3/30 (10%) lost follow up and 6/30 (20%) died. 12/21 (57.1%) patients were in complete disease remission, if any. Disease activity at the last available follow up was defined as complete remission (absence of active disease), partial remission (response > 50% of at least one manifestation among glomerulonephritis, peripheral neuropathy or skin ulcers) or active disease.

Conclusions
A long-term regimen of retreatment with RTX alone given at clinical relapse seems to be effective and safe in CV, with a low rate of infections and severe hypogammaglobulinemia.
Introduction
Cryoglobulinemic vasculitis (CV) is a systemic vasculitis, usually triggered by HCV infection [1], and characterized by an expansion of oligo-monoclonal B cells that produce IgM with rheumatoid factor (RF) activity, which can lead to the formation of immune complexes consisting of RF, HCV and polyclonal HCV-specific IgG, precipitating in blood vessel walls or glomerular capillaries. CV is characterized by the typical clinical triad of purpura, weakness, and arthralgia and often by severe organ involvement including glomerulonephritis, peripheral neuropathy, and skin ulcer [2]. Treatment of HCV-related CV may target either the viral trigger or the downstream B cell arm of autoimmunity. Anti-viral therapy has a strong rationale, is effective in many milder cases, but it may also prove ineffective, contraindicated, or not tolerated, and sometimes may worsen CV. The new direct acting antiviral drugs for HCV are being investigated in HCV-related CV. Importantly, antiviral treatment is presently not the first choice, based on clinical priorities, in HCV-positive patients with severe CV organ involvement [3], [4], [5], [6], [7] and [8]. Rituximab (RTX) is an anti CD20 monoclonal antibody, which depletes the expanded population of B cells, and proved to be an effective strategy in CV. Recently, two independent controlled randomized trials reported a large efficacy and good safety of RTX in severe manifestations of CV [9] and [10]. In the Italian study, 59 patients with severe manifestations of CV (skin ulcers, active glomerulonephritis or refractory peripheral neuropathy), either HCV related or not, were randomized to receive RTX or the best available treatment (high-dose glucocorticoids, azathioprine or cyclophosphamide, or plasmapheresis), and then they were followed for 24 months. In HCV-positive patients, treatment with antiviral agents had previously failed or was not indicated. Patients who did not respond to conventional treatment could be rescued by RTX [9]. Survival of treatment was always statistically higher in the RTX group at 3, 6, 12 and 24 months [9]. As compared to conventional therapy, the overall rate of serious adverse events was similar in the RTX treated patients, with severe infections occurring in patients who had previously received high-dose glucocorticoids or with hypogammaglobulinemia. Interestingly, the median time to relapse after RTX treatment was 1.5 years [9]. Since the issue of RTX retreatment in systemic vasculitis (as well as in other rheumatic diseases) is still open, the aim of the present study was to evaluate the very long-term efficacy and safety of a retreatment regimen with RTX alone administered only in the case of clinical relapse in CV. Patients who were treated with RTX in the course of the aforementioned study [9], and managed with RTX alone also after the end of the trial were evaluated.

Patients and methods
Thirty patients, 24 females and 6 males, with a mean (SD) age of 63 (11) years (median 65, range 37–78 years), suffering from severe HCV-related CV and treated with RTX during the 24-month trial, were studied [9]. All the patients were HCV-positive and they remained untreated with antiviral drugs during the published 24-month study [9] and also in the available follow-up. After the end of the trial, patients were managed with RTX alone (1 g intravenous infusion two weeks apart) only in the case of clinical relapse. Three patients in whom a maintenance treatment with RTX was chosen after the end of the trial [9] were excluded from the present study. Additional 18 patients who received RTX during the trial [9] were not included since died (5/18), interrupted RTX infusion due to drug reaction at the first infusion (2/18) during the trial itself [9], or since further follow-up after the end of the trial was not available (11/18). Patients were categorized into three groups, based on the response to RTX evaluated at the last available follow-up visit, as in complete remission (absence of active disease), partial response (response, as defined previously [9], observed in >50% of at least one manifestation among glomerulonephritis, peripheral neuropathy or skin ulcers) or active disease. For each retreatment with RTX, the time at which retreatment was administered, the number of retreatments, the clinical indications for retreatment, the clinical efficacy and biologic response within 6 months from retreatment were assessed. Biologic response was present when serum cryoglobulins disappeared, or RF decreased >50% or C4 increased >50% if compared to the value immediately before the retreatment. The criteria for indication to RTX retreatment for CV relapse after the end of the trial, always included the clinical judgment, were the same leading to RTX retreatment during the trial [9]. Long-term
survival of RTX therapy stratified by one of the three organ manifestations, which represented the main indication for RTX treatment at the beginning of the 24-month trial (i.e., glomerulonephritis, peripheral neuropathy or skin ulcers) [9], was assessed by Kaplan Meier curve. Clinically relevant adverse events and deaths were registered. Data are presented as mean and standard deviation (SD) or frequencies, as appropriate.

**Results**

**Long-term follow-up and survival of the rituximab regimen**

The mean follow up after the first RTX cycle given during the trial [9] was 72.6 (20.4) months. As concerns the follow-up after the end of the trial [9], 24/30 patients (80%) were observed for more than 24 months after the trial [mean follow up 79.3 (10) months] and 6/24 (20%) for less than 24 months [mean follow up 35.8 (6.7) months]. At the last follow-up, 21/30 (70%) patients were still under an active follow-up from the same Centre, 3/30 (10%) patients were lost during the follow-up, and 6/30 (20%) died. At the last available follow-up visit, CV disease remission was recorded in more than half of the patients (12/21, 57.1%), a partial response in 5/21 (23.8%), while an active disease in 4/21 (19%) patients. The mean survival time of the whole RTX treatment (i.e., the interval time from the first RTX to the end of RTX therapy, including retreatment, due to retreatment RTX failure) was 7.6 (0.3) years; as shown in Fig. 1, this survival was slightly longer for nephritis [7.9 (0.4) years] than for neuropathy [6.7 (0.4) years]; while it could be not evaluated in the subgroup of patients where the indication to retreatment were the skin ulcers, since only 5 patients were included.

**Retreatment regimen**

**No retreatment required, due to the lack of relapse**

13 out of 30 (43.3%) patients had no clinical relapse from the initial cycle of RTX at the beginning of the trial [9] to last follow up visit, i.e., had a very long term response to RTX [mean follow-up of 62.4 (22.9) months].

**Retreatment for relapse**

17 out of 30 patients (56.7%) needed at least one RTX retreatment after the initial RTX cycle (9). Of these 17 patients, the majority needed only a single retreatment, i.e., 10/17 (58.8%), while 7/17 (41.2%) needed more than one RTX retreatment (2 retreatments in 6/17; 3 retreatments in 1/17) (Fig. 2), with a total of 25 retreatments during 80.7 (15.3) months from the beginning of the trial [9]. Retreatment with RTX was effective in two thirds of the patients, with complete remission in one third (6/17, 35.3%), partial response in 5/17 (29.4%) and no response in 6/17 (35.3%; this lack of response refers, however, only to the last RTX retreatment, since previous RTX retreatments were effective in 2/6 patients). Of these 6 patients with no response to the last RTX retreatment, 1 patient died for intestinal CV, and 5 patients showed no improvement in skin ulcers. The mean time to retreatment after the initial RTX cycle in the trial was 22.3 (12.1) months. Thus, the efficacy of the RTX initial therapy usually lasted for a long time. High doses of glucocorticoids were never used concomitantly with RTX retreatment, and medium doses, quickly reduced and suspended, were administered only in a minority (3/17, 17.6%).

**Retreatment for relapse within 24 months**

The 17 patients needing a retreatment with RTX due to CV relapse were further distinguished into 2 groups, including those needing retreatment within the first 24 months (i.e., during the trial), or only later. Seven out of the 17 retreated patients (41.2%) were retreated during the 24 months of the trial [9] and all of them, except one, did not require any further treatment in the follow-up after the trial (Fig. 2). Peripheral neuropathy was the clinical indication for retreatment in 6/7 patients, while nephritis in the remaining patient. Compared to the CV manifestations present at the beginning of the trial, the same clinical manifestation of CV relapsed in all cases. High or medium doses of glucocorticoids were never used concomitantly with RTX to treat relapse.

**Retreatment for very late relapse**
Most of the retreated patients (10/17: 58.8%) needed only a very late retreatment after the end of the trial. The clinical indications were skin ulcers in five patients, nephritis in three patients, and peripheral neuropathy in two patients. The mean time to retreatment from the initial RTX cycle was 29 (10.4) months. Compared to the CV manifestations present at the beginning of the trial, the same clinical manifestation of CV relapsed in 7/10 patients, while in 3/10 patients CV relapsed with a different clinical manifestation. A short course of glucocorticoids (25 mg/day of prednisone tapered and then suspended in one month) was added to RTX in three retreated patients. 3.3. Biologic response to retreatment after the end of the trial Early biological response was assessed in 11 patients after the end of the trial, and is shown in Table 1. Disappearance of serum cryoglobulins was observed in 2/11 (18%), a decrease >50% of RF or an increase >50% of serum C4 was recorded in 7/11 (64%). Almost 80% of the patients showing significant biologic effects presented long-term clinical benefits (Table 1).

Long-term tolerance
After the end of the trial, we registered 9 clinically relevant adverse events (30%) (Table 2), in particular recurrent infections (urinary or upper respiratory infections) occurred in 3/30 (10%) patients and chronic hypogammaglobulinemia (serum IgG below 3 g/L) in 2/30 (7%) patients. Death occurred in 6/30 (20%) patients (Table 2); 2 patients died due to new onset intestinal CV precipitated by concurrent infections. One patient died for systemic complications due to liver failure in HCC, 2 patients for heart failure not related to RTX infusion, and in one patient the cause of death was unknown. All of these 6 patients showed an active disease at the last available follow-up.

Discussion
The indication for retreatment with RTX is an open issue in rheumatic diseases, including some systemic vasculitis where RTX has become a cornerstone of the treatment strategy [11], [12] and [13]. Based on the results of this study, a retreatment regimen, which implies the use of RTX only at clinical relapse, appears beneficial in CV. No large data have been published up to now about the retreatment schedule of RTX in a complex disease as CV, where the clinician has to take into account also the concomitant presence of the chronic infection by HCV in the majority of the cases [14] and [15]. In the 24-month Italian multicenter study evaluating the efficacy and safety of RTX in severe CV (presence of glomerulonephritis, peripheral neuropathy, or skin ulcers) if compared to the best immunosuppressive treatment available for CV (i.e., azathioprine, cyclophosphamide, high-doses glucocorticoids or plasma exchange) [9], the retreatment with RTX was always allowed at clinical relapse, based on the judgment of the expert. This retreatment with RTX was needed in about one third of the patients in 24 months, after a median interval of about 12–18 months, and with an efficacy observed in about 75% of cases [9]. In the other randomized trial with RTX in CV [10], the median duration of remission for the 10 patients responding to RTX was 7 months. The 3 patients who relapsed were retreated with a second course of rituximab, and all 3 patients achieved remission and remained in remission for more than 6 months following this retreatment [10]. The present retrospective study reports the very long-term followup of 30 patients with severe CV enrolled in the 24-month Italian trial [9]. In this study, the mean follow up from the first RTX cycle administered [9] was 6 years, and the large majority of the patients showed a follow-up lasting more than 2 years after the end of the trial. As during the trial [9], these patients were managed also after the end of the trial with retreatment with RTX alone, only if clinical relapse occurred. First, the overall mean survival of the regimen of retreatment with RTX given only at CV relapse was long, about seven years, when considering the whole followup from the first RTX administration [9]. Secondly, RTX retreatment was needed in less than 50% of the CV patients, more frequently in the first two years after the beginning of RTX therapy. Third, RTX retreatment, when needed, was effective in about two thirds of the patients (one third with full remission, one third with partial response). Fourth, the duration of response to RTX retreatment usually lasted for more than one year, confirming the results already reported in the first 24 months [9]. Finally, high-dose steroids were never used at the time of RTX retreatment, while medium doses of steroids, i.e., 25 mg/day of prednisone or equivalent, were used in only three patients: this confirms a major advantage of RTX in CV, i.e. that it may
be effective also in the lack of glucocorticoids [9] and [14]. Of note, the absence of response to RTX retreatment was usually observed in patients showing skin ulcers. This manifestation of CV might then become progressively resistant to RTX; however, coexisting local co-morbidities, such as infections or chronic venous insufficiency, might have contributed, supporting the concept that an integrated treatment approach (local and systemic, immunosuppressive and antibiotic) is needed for the optimal treatment of skin ulcers in CV. As concerns the renal and the neurological manifestations, the efficacy of RTX resulted somewhat longer for nephritis than for peripheral neuropathy in this study. This appears relevant since nephritis, rather than neuropathy, is a key risk factor for mortality in CV [16]. An increased frequency of RTX retreatment for peripheral neuropathy, mainly due to the worsening of neuropathic symptoms, should be also considered. Differently from renal and skin involvement, where relapse may be easier to be recognized objectively, peripheral nerve involvement in CV is frequently based on symptoms, while electrophysiological tests, even if useful [17], may be operator-dependent and not easy to be performed in a routine clinical setting. A regimen with retreatment at relapse may be safer than a fixed maintenance therapy with RTX, but a maintenance regimen may be superior to maintain remission: thus, the balance between efficacy and safety must be carefully weighted in the single disease. Overall, the present study and the past study [9] support the concept that retreatment at relapse regimen may be useful for most cases of severe CV. In ANCA-associated vasculitis (AAV), RTX has an established role for remission induction. It is now an approved alternative to cyclophosphamide in severe AAV. In addition, a maintenance retreatment period with RTX, to maintain remission, appears useful in AAV. With standard therapies, 50% of patients with newly diagnosed AAV relapse by 5 years. For remission maintenance, trials are comparing repeated RTX maintenance treatment (500 mg of RTX on days 0 and 14 and at months 6, 12, and 18 after study entry) or daily azathioprine [18]. More patients with AAV had sustained remission at month 28 with maintenance RTX than with azathioprine; however, the frequencies of severe adverse events were similar in the two groups. In particular, eight patients in the azathioprine group (13.8%) and 11 in the RTX group (19.3%) had severe infections [18]. In the present study, with the RTX retreatment regimen at relapse, death could be attributed to severe clinical relapse in CV in only two cases (both cases with intestinal vasculitis). Of note, in both of these cases a severe infection anticipated and possibly triggered the relapse of CV, with subsequent abdominal involvement of vasculitis. Infections must be promptly recognized and adequately treated in order to avoid severe and difficult-to-manage relapses in CV. The other 4 deaths were not related to RTX treatment. Concomitant morbidities (e.g., cardiovascular disease, chronic liver damage, lymphoproliferative disorders, infectious complications) and the concomitant chronic infection by HCV contribute to a high mortality in severe CV, which was also observed in this study. Recurrent infections of the upper respiratory airways or the lower urinary tract occurred in only three patients in this study, and two of these patients had a severe hypogammaglobulinemia (IgG below 3 g/l), secondary to B-cell depletion. Overall, infections (both severe and non-severe) were registered in about 15% of the patients, and the rate of severe hypogammaglobulinemia requiring chronic immunoglobulin replacement was low (7%) with the RTX regimen at relapse in CV. Overall, as concerns infections and hypogammaglobulinemia, the safety of this RTX-at relapse regimen in CV appeared superior to that of a RTX-maintenance regimen in ANCA-associated vasculitis. In fact, RTX is associated with an increased risk of hypogammaglobulinemia even if recovery of IgG level can occur [19]. Hypogammaglobulinemia occurred in one-quarter of granulomatosis with polyangiitis patients during RTX re-treatment with either 2 g once annually, 1 g biannually or a combination of both [20]. Thus, a RTX regimen with retreatment at clinical relapse may be suggested in some ANCA-associated vasculitis [21]. Liver toxicity or failure due to flare of HCV infection were not reported in this study. This is crucial for CV, which is both a systemic autoimmune disease and a chronic infectious viral disease in the large majority of cases. A regimen of RTX alone at relapse might be more cautious in HCV-infected individuals than a chronic B-cell depletion with a RTX maintenance regimen. HCV-RNA serum levels were not collected in this study, since previous work from our group and others reported the safety of intermittent RTX therapy on HCV replication [10] and [22]. On the other hand, the clinician should evaluate very well the risk/benefit ratio of the RTX regimen chosen in the individual case [23]. In very severe CV, in...
particular in relapsing patients with motor peripheral neuropathy or rapidly progressing glomerulonephritis, or in patients with life-threatening presentations (e.g., hemorrhagic alveolitis or intestinal vasculitis), a maintenance regimen with RTX, at least for some time, may be more adequate [24]. Interestingly, in the present study the CV patients with early biological response (within the first 6 months), characterized by the disappearance of serum cryoglobulins or significant decreases of RF or increases of serum C4, were more likely to respond in the long-term. By contrast, we were not able to detect any predictors of long-term response in the previous study [9]. Of note, the absence of complete immunological response during follow-up was associated with early relapse in non-infectious CV [25]. Bone marrow analysis of B-cell clonal expansion might also be useful to predict the response to RTX therapy in CV, and its duration, but it is not routinely done [26]. Finally, the new highly effective antiviral agents for the treatment of HCV would likely improve also the treatment of HCV-related CV [27]. The good safety profile of interferon-free regimens might also open the possible combination of RTX with these agents in severe CV. On the other hand, HCV-related CV may also be a true autoimmune-driven disorder in some cases, becoming biologically independent from the initial triggering HCV infection [23] and [28]; therefore, treatments acting downstream to the viral infection, as RTX, will likely remain a cornerstone of therapy in CV, at least in selected patients.

Conclusions
Although analysed retrospectively, a regimen where RTX is administered only at clinical relapse appears useful for the long-term management of most cases of severe CV. In these patients major safety concerns are usually represented by concomitant HCV infection and liver damage, by a more advanced age, lower serum immunoglobulin levels and co-morbidities, thus immuno suppressors and glucocorticoids should be spared, whenever possible.

References


Fig. 1. Overall survival of a regimen of retreatment with RTX at clinical relapse.

Fig. 2. Rituximab cycles and retreatments in the 30 patients.
### Table 1. Early biological response in 11 retreated patients.

<table>
<thead>
<tr>
<th>Biological response</th>
<th>N. (%)</th>
<th>Disease activity at last follow up</th>
</tr>
</thead>
<tbody>
<tr>
<td>Disappearance of serum cryoglobulins</td>
<td>2 (18.2)</td>
<td>CR = 1; PR = 1</td>
</tr>
<tr>
<td>C4 increased &gt;50% or RF decreased &gt;50%</td>
<td>8 (72.7)</td>
<td>CR = 3; PR = 3; A = 2</td>
</tr>
<tr>
<td>Absence of biological response</td>
<td>1 (9)</td>
<td>A = 1</td>
</tr>
<tr>
<td>Total</td>
<td>11 (100)</td>
<td>CR = 4; PR = 4; A = 3</td>
</tr>
</tbody>
</table>

Legend: CR, complete remission; PR, partial response; A, active disease; RF, rheumatoid factor.

### Table 2.
Adverse events and deaths occurring during the follow up period.

<table>
<thead>
<tr>
<th>N. of adverse events/total n. of patients (%)</th>
<th>9/30 (30)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recurrent infections (urinary, upper respiratory)</td>
<td>3/30 (10)</td>
</tr>
<tr>
<td>Chronic hypogammaglobulinemia</td>
<td>2/30 (7)</td>
</tr>
<tr>
<td>HCC</td>
<td>2/30 (7)</td>
</tr>
<tr>
<td>NHL</td>
<td>2/30 (7)</td>
</tr>
<tr>
<td>AMIb</td>
<td>1/30 (3)</td>
</tr>
<tr>
<td>Supraventricular extrasystoles</td>
<td>1/30 (3)</td>
</tr>
<tr>
<td>N. of deaths/total n. of patients (%)</td>
<td>6/30 (20)</td>
</tr>
<tr>
<td>Intestinal vasculitis</td>
<td>2/30 (7)</td>
</tr>
<tr>
<td>Heart failure</td>
<td>2/30 (7)</td>
</tr>
<tr>
<td>Liver failure in HCC</td>
<td>1/30 (3)</td>
</tr>
<tr>
<td>Not known</td>
<td>1/30 (6)</td>
</tr>
</tbody>
</table>

Legend: HCC, hepatocellular carcinoma; NHL, non-Hodgkin lymphoma; AMI, acute myocardial infarction.

a Relapse with new onset intestinal CV and concomitant infection.
b Not related to RTX.