Concise report

Clinical improvements in proliferative vs membranous lupus nephritis following B-cell depletion: pooled data from two cohorts

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Abstract

Objective. To compare the clinical results after treatment with B-cell depleting therapy in patients with membranous (WHO Class V) vs proliferative (WHO Class III or IV) lupus nephritis (LN).

Methods. Data were compiled from two European centres on all patients with LN who were treated with i.v. rituximab (RTX) in a combination protocol with i.v. cyclophosphamide and steroids. Laboratory and serological evaluations were performed at 3, 6 and 12 months of follow-up. No immunosuppressive drugs were given before B-cell repopulation.

Results. Forty-three patients, 28 with proliferate and 15 with membranous LN by renal biopsy, were evaluated. Six months after treatment with RTX, both the membranous and the proliferative LN patients had a significant reduction in proteinuria and an increase in serum albumin. The main improvements were observed during the first 6 months and only minor non-significant changes in albumin and proteinuria were observed thereafter. As expected, the patients with membranous nephritis had lower anti-dsDNA titres and higher complement C3 levels at baseline, but in both groups a significant reduction in anti-dsDNA titre and improvements in complement C3 levels were seen during the first 6 months after treatment; the kinetics of improvement were similar in both groups.

Conclusion. The clinical course following B-cell depleting therapy is strikingly similar between patients with membranous and those with proliferative LN. These observational data suggest that, if controlled studies confirm the efficacy of B-cell depleting therapy in proliferative nephritis, clinicians may reasonably consider such therapy in membranous LN.

Key words: Systemic lupus erythematosus, Lupus nephritis, Rituximab, Treatment, Anti-CD20.

Introduction

B-cell depleting therapy using rituximab (RTX; MabThera, Welwyn, Great Britain) has been proposed as a therapy for SLE based on mechanistic considerations as well as uncontrolled observational data from several groups [1–6].

Recently, a double-blinded randomized controlled trial in lupus nephritis (LN) was completed and a press release indicated that the trial had not achieved its primary end-point. The report did not, however, reveal any data. Proliferative LN (i.e. WHO Classes III and IV) and membranous LN (WHO Class V) share some clinical characteristics but are also dissimilar, not only in histology (by definition) but also in that the latter patients more frequently exhibit the nephrotic syndrome rather than typical nephritic symptoms. Membranous LN has a less clear association with anti-DNA antibodies and hypocomplementaemia than proliferative LN, and do not benefit as clearly from immunosuppressive therapies including cyclophosphamide (CYC). Thus, even if RTX was to be proved effective for the treatment of proliferative LN, it
could still not be assumed that such efficacy would also apply to membranous LN.

At the two rheumatology units that we represent, a total of 43 patients with LN have been treated with RTX, 28 with proliferative and 15 with membranous disease. The indication for treatment in all cases was active disease and failure to respond to at least one conventional immunosuppressive agent.

In this report, which entails pooled data from our two cohorts, we show that there is no difference in the clinical outcome in terms of biochemical markers of renal function between patients with membranous (WHO Class V) and those with proliferative (WHO Class III or IV) LN after treatment with B-cell depleting therapy.

Patients and methods

The characteristics of our patients and the protocol used to treat them in both units have been described previously [1, 3]. Briefly, patients with SLE and active LN were treated after having failed common immunosuppressive therapy, including CYC in most patients. The treatment protocol included i.v. RTX 375 mg/m^2 body surface area given weekly, four times or i.v. RTX 100 mg twice given 2 weeks apart, with standard pre-medications; i.v. CYC 500–1000 mg given twice (3 weeks apart); i.v. methylprednisolone 250 mg given twice (3 weeks apart); and a taper of oral glucocorticoids. No additional immunosuppressive therapy was given during B-cell depleting therapy.

The assessments undertaken during follow-up that are reported here include visits at 3, 6, 9 and 12 months, which included determinations of serum creatinine (μmol/L), serum albumin (g/L), 24-h proteinuria (g/24 h), serum complement C3 (g/L) and serum anti-DNA (IU/ml). All subjects gave their written informed consent before entering. The study was approved by the Local Ethics Committee (Karolinska Institutets Etikråd) and by the Swedish Medical Product Agency.

Results

Twenty-eight patients with proliferative LN and 15 with membranous LN were included in this analysis. Mean baseline values for the proliferative and membranous groups are given in Table 1. Significant baseline differences were seen for anti-DNA titre but the groups were otherwise very similar.

In patients with proliferative and membranous LN, similar changes occurred over time in biochemical markers of renal function following the B-cell depleting therapy. The changes for serum albumin and proteinuria are shown in Fig. 1.

Six months after treatment with RTX both the membranous and the proliferative LN patients had a significant increase in serum albumin ($P < 0.005$). A reduction in proteinuria was observed in both groups ($P < 0.05$ at 9–12 months of follow-up). The main improvements were observed during the first 6 months and only minor non-significant changes in serum albumin and proteinuria were observed thereafter.

As expected, the patients with membranous nephritis had lower anti-dsDNA antibody titres and higher complement C3 levels at baseline (although the only significant difference was for anti-dsDNA antibody). During the first 6 months after treatment significant improvements in complement C3 levels were seen in both groups ($P < 0.01$), whereas the reduction in anti-dsDNA titres was only significant for the patients with proliferative nephritis ($P < 0.02$); the kinetics of improvement were similar in both groups.

Mean serum creatinine levels improved in the membranous LN patients but worsened in the group of patients with proliferative LN; the latter trend could be attributed to two patients who developed end-stage renal disease following treatment. Anti-DNA titres, which were dissimilar at baseline, converged upon follow-up.

Discussion

We present pooled data on over 40 patients with LN treated with B-cell depleting therapy and show that there is no difference in the clinical outcome in terms of biochemical markers of renal function between patients with membranous (WHO Class V) and those with proliferative (WHO Class III or IV) LN after treatment with B-cell depleting therapy.

The purpose of this report is not to analyse the efficacy of this treatment modulation as such, but to show that the time course of clinical changes following B-cell depleting therapy is similar for patients with proliferative and membranous LN.

The only differences noted between the two subgroups are readily seen as implicit in these two subtypes of LN: patients with proliferative disease tend to have higher anti-DNA titres and are at higher risk of worsening serum creatinine.

With the caveat when analysing pooled data from different cohorts it should be pointed out that all the patients did meet ACR criteria and all had a biopsy-proven renal disease. The number of patients with proliferative vs membranous LN mirrors the number of refractory patients in these two subgroups in our clinics.

Observational studies from our centres along with others have previously shown good clinical outcome in patients with LN treated with B-cell depleting therapy [1, 3, 4, 6]. Most patients included in these studies had proliferative LN, with laboratory as well as serological improvements during the first 6 months of follow-up. Few patients with membranous LN have been reported [7] and no comparisons have been made about the rate of improvement in biochemical markers of renal function in the two different groups of LN. Additional support for the efficacy of B-cell depleting therapy in membranous LN, beyond data from uncontrolled observations as indicated above, comes from observations in the Karolinska cohort showing resorption of extracapillary immune deposits in patients with membranous LN following treatment with RTX (Jónsdóttir et al., Karolinska Institutet, unpublished data). In summary, we conclude that, if B-cell depleting therapy with RTX were to be proved effective...
for the treatment of proliferative LN, a reasonable clinical extrapolation to membranous LN can be made.

**Rheumatology key message**
- The same kinetics of improvement was seen in patients with proliferative and membranous LN after treatment with B-cell depleting therapy.

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**References**


**Table 1** Mean baseline values for the proliferative and membranous groups

<table>
<thead>
<tr>
<th>Baseline characteristics</th>
<th>Proliferative LN</th>
<th>Membranous LN</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>32 (10) (17–56)</td>
<td>32 (11) (15–58)</td>
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<tr>
<td>C3, g/l</td>
<td>0.65 (0.31) (0.15–1.1)</td>
<td>0.57 (0.26) (0.24–1.47)</td>
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<tr>
<td>Anti-dsDNA, IU/ml</td>
<td>541 (672) (7–2560)</td>
<td>174 (286) (10–1058)</td>
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<tr>
<td>Serum albumin, g/l</td>
<td>28.7 (7.5) (17–45)</td>
<td>28.8 (7.5) (16–41)</td>
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<tr>
<td>24-h proteinuria, g</td>
<td>3.6 (3.7) (0.1–17)</td>
<td>4.6 (4.9) (0.4–18.5)</td>
</tr>
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Values are represented as mean (s.d.) (range).