کارگاه‌های آموزشی مرکز اطلاعات علمی

مقاله نویسی علوم انسانی

اصول تنظیم قراردادها

آموزش مهارت های کاربردی در تدوین و چاپ مقاله
Rituximab in Steroid-dependent Nephrotic Syndrome

Mohamed El Koumi

Treatment of steroid-dependent nephrotic syndrome, particularly in patients who have failed to respond to multiple immunosuppressive drugs, remains challenging. Rituximab represents a new off-label therapeutic option. Here, we report the use of rituximab in 7 children with steroid-dependent nephrotic syndrome with various histological backgrounds who failed to maintain remission with other immunosuppression regimens. All patients received rituximab infusion, 750 mg/m² in 2 doses, 2 weeks apart, and the subsequent doses were adjusted by clinical response. In all patients, complete B-cell depletion was observed after the first course of rituximab. Follow-up for at least 12 months showed sustained remission in 6 children. We conclude that rituximab can reduce the risk of relapses, reduce the burden of immunosuppression, and at least, offer a better control of steroid-dependent nephrotic syndrome with minimal doses of immunosuppressive agents and steroids.

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INTRODUCTION

Idiopathic nephrotic syndrome is the most frequent glomerular disease during childhood. It is classically viewed as a primary disorder of T-cell function mediated by a glomerular permeability factor that functionally alters the sieving coefficient of plasma proteins across the glomerular wall. The contribution of B cells and the potential role of immunoglobulin chains in modifying the glomerular permeability to protein in children with steroid-sensitive nephrotic syndrome have been repeatedly reported. Most patients with nephrotic syndrome respond to steroid therapy. However, still a significant number develop steroid dependency and some severe cases remain difficult to treat, and prolonged courses of steroids and a long-lasting multidrug immunosuppressive therapy is needed.

Frequently relapsing patients who develop steroid dependency require alternative therapy. Of proven efficacy, mycophenolate mofetil and calcineurin inhibitors (cyclosporine A and tacrolimus) are usually effective, but long-term treatment with these agents is necessary, raising concerns of a possible accumulation of side effects. In addition, many cases of steroid-dependent nephrotic syndrome (SDNS) remain unresponsive to these options. Rituximab is a genetically engineered chimeric murine/human monoclonal immunoglobulin G1 kappa antibody directed against the CD20 antigen. Several case reports have suggested that rituximab may be effective in SDNS patients. It has been postulated that children with severe SDNS or cyclosporine-dependent nephritic syndrome, treatment with rituximab has allowed the discontinuation of one or more immunosuppressive treatments. Rituximab was also reported to be efficient in children with steroid-resistant nephritic syndrome. In this study, we report our results of using rituximab as a rescue therapy for children with SDNS after failure of other therapies to keep maintained remission.

CASE REPORT

Seven children (3 boys and 4 girls) suffering from recalcitrant SDNS received rituximab at the renal unit of the Royal Hospital of Sick Children, Glasgow. Their ages ranged from 10.8 to 18.6 years (mean, 14.4 ± 2.9 years), and their mean time period of nephrosis prior to rituximab was 8.3 ± 3.7 years (range, 3.9 to 15.8 years) and mean total
number of relapses was 17. They had previously received therapy with combined prednisone and mycophenolate mofetil (all patients), cyclosporine A (2 patients), or tacrolimus (4 patients; Table 1). Pathologic examination of the kidney showed minimal change disease in 5 children, minimal change disease evolving into focal segmental glomerulosclerosis in 1, and focal segmental glomerulosclerosis with interstitial fibrosis in 1. All parents provided their consent to use rituximab as a rescue therapy.

Prior to rituximab, chronic active infections or current severe infection were actively excluded. Baseline lymphocyte subsets, CD19 (using flow cytometry) and serum immunoglobulin were checked and repeated on a monthly basis after rituximab infusion. The first rituximab infusion was given after steroid-induced remission (6 patients) or when presenting with low-range proteinuria without biological nephritic syndrome (1 patient). Indication for rituximab therapy was based on frequent relapses, persistent proteinuria, and steroid side effects (all patients), in addition to drug-induced hypertension (4 patients), cosmetic side effects and unusual infections (3 patients each). Initial treatment with rituximab was 750 mg/m² for 2 doses, 2 weeks apart (maximum dose, 1 g). Each infusion was preceded by dexchlorpheniramine (2.5 mg to 5.0 mg) and hydrocortisone (50 mg/kg to 100 mg/kg) given intravenously.10,11 Subsequent doses were given for nephrotic relapse as defined by 3 consecutive days of 3+ to 4+ proteinuria measured by urinary dipstick and confirmed by urine protein-creatinine ratio in conjunction with CD19 reconstitution.

The B cell count was systematically controlled by flow cytometry using anti-CD19 monoclonal antibody before and following the first injection and prior to the second injection of rituximab B cell count (reference value, 200 to 1600 B cell per milliliter) was followed every month along with biological criteria of nephritic syndrome remission. For relapsed cases after B cell recovery (over 10 cell/mm³), another single injection of rituximab (750 mg/m²) was given to keep B cell depletion. The follow-up period for a minimum period of 12 months was reviewed for both efficiency and safety of rituximab.

Complete B cell count at baseline were 325 ± 154 B cell per milliliter, and CD19 depletion (< 5 cell/mm³) was observed after the first course of rituximab infusion in all of the patients. The duration of B cell depletion after therapy ranged from 4 to 16 months (Table 2). Five patients had sustained remission at

<table>
<thead>
<tr>
<th>Patient</th>
<th>CD19 Count Before Rituximab Therapy (%)</th>
<th>Timing of Depletion, mo</th>
<th>Timing of Reconstitution, mo</th>
<th>Relapse on Reconstitution</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>180 (10)</td>
<td>1</td>
<td>6</td>
<td>Yes</td>
</tr>
<tr>
<td>2</td>
<td>231 (11)</td>
<td>1</td>
<td>15</td>
<td>No</td>
</tr>
<tr>
<td>3</td>
<td>573 (23)</td>
<td>1</td>
<td>9</td>
<td>No</td>
</tr>
<tr>
<td>4</td>
<td>342 (16)</td>
<td>1</td>
<td>18</td>
<td>No</td>
</tr>
<tr>
<td>5</td>
<td>176 (27)</td>
<td>1</td>
<td>12</td>
<td>No</td>
</tr>
<tr>
<td>6</td>
<td>490 (27)</td>
<td>1</td>
<td>7</td>
<td>No</td>
</tr>
<tr>
<td>7</td>
<td>283 (15)</td>
<td>1</td>
<td>None till 5</td>
<td>Relapse despite depletion</td>
</tr>
</tbody>
</table>

*Normal CD19 count was 200 to 600 × 10⁶/L (8% to 24% of total lymphocytes). CD19 depletion was considered if CD19 was less than 5% in peripheral circulation, CD19 reconstitution was considered if CD19 was greater than 5%.
the time of B cell reconstitution, which allowed reduction of the immunosuppressive afterwards, while relapse occurred only in 2 patients, one at the time of B cell reconstitution (patient 1), and the other, 5 weeks after the first course of rituximab therapy, clearly before reconstitution of B cell (patient 7); therefore, he did not receive further doses of rituximab and continued on conventional immunosuppressive drugs. Kidney biopsy of this patient was that of evolving FSGS and interstitial fibrosis.

Four patients needed 2 doses of rituximab therapy to achieve remission and 2 patients needed 3 doses, while only 1 patient needed 5 doses (Table 3). Over a period of 6 months since initiation of rituximab course, immunosuppression had dramatically altered (as shown in Table 3). Mycophenolate mofetil and calcineurin inhibitors, which were universal in all of the patients, were systematically reduced and eventually stopped, but unfortunately, they were secondarily resumed in only 1 patient (patient 7), in whom proteinuria was sustaining despite CD19 depletion.

Rituximab was very well tolerated. None of the patients had serious infections or adverse events on the follow-up. Apart from self-limited dizziness and chest discomfort (2 patients) and unexplained epistaxis (1 patient), spontaneous recovery was observed within hours following withdrawal of rituximab infusion, suggesting anaphylactic shock.

**DISCUSSION**

In our study, a series of 7 Scottish children with SDNS who had either responded unsatisfactorily to treatment with multiple immunosuppressive agents, including cyclophosphamide, levamisole, mycophenolate mofetil, cyclosporine, and tacrolimus, or had features suggestive of medication-related side effects or toxicity were treated with rituximab. Although minimal change disease is classically considered a primary disorder of T-cell immunity, the beneficial effect of rituximab was first reported in a patient who presented with SDNS for 13 years, and secondarily developed severe relapsing idiopathic thrombocytopenic purpura. Following this case report, several authors reported outstanding effects of rituximab in patients with long-lasting SDNS.

In our series, and in concert with other reports, two initial injections of rituximab were sufficient to induce complete B-cell depletion in all patients that sustained over 6 to 12 months. A sustained remission was achieved in 5 patients with difficult SDNS, which allowed succinct reduction of the immunosuppressive therapy afterwards. This result was in agreement with Guigonis and colleagues, in a multicenter report from France on the efficacy of rituximab in a heterogeneous group of 22 patients with SDNS who were receiving concomitant treatment with prednisone, calcineurin inhibitors, or mycophenolate mofetil. At a median follow-up of 9.5 months, 19 (86.3%) patients had a beneficial effect with sustained remission or reduction of proteinuria. Our series of patients were of a uniform ethnicity unlike the diverse ethnicity in the French study.

In our study, 5 patients had sustained remission at the time of B-cell reconstitution, which allowed reduction of the immunosuppressive afterwards, while relapse occurred only in 2 patients, one at the time of reconstitution and one relapsed 5 weeks after the first course of rituximab, when a 3rd dose of rituximab was attempted without any success. The kidney biopsy of this patient was that of FSGS...
and interstitial fibrosis. Fernandez-Fresnedo and colleagues concluded that adult patients with steroid-resistant nephritic syndrome secondary to FSGS may need more than 2 doses of rituximab to show response. They also reported that only 3 of 8 adult patients with steroid-resistant nephritic syndrome caused by FSGS responded to rituximab.18

In the present study, immunosuppressive drugs were successfully tapered over at least 6 months in all patients except in 1 patient. At the last follow-up, remission was sustained in 5 patients without any treatment, while having a normal circulating B-cell count. The overall tolerance of rituximab was good in our patients who were systematically treated without massive proteinuria and without biological nephritic syndrome. The most frequent adverse effect was a general dizziness at the time of the first infusion. These symptoms were attributed to a cytokine release and spontaneously recovered after the temporary withdrawal of the infusion and restarting again at a slower rate.12 Prytula and colleagues reported acute reactions in 27% patients and a high incidence of severe side effects including anaphylaxis and serious infections, fortunately, none of these side effects were reported in our case studies even with subsequent doses.19 Kamei and associates reported high incidence (36%) of severe respiratory injuries associated with the use of rituximab, such as interstitial pneumonitis, acute respiratory distress syndrome, or lung fibrosis. They recommend that a routine chest radiograph should be obtained before rituximab infusion is initiated in children and it should never be administered to patients already suffering from lung disease.20

Another case series reported occasional cases of reversible cytokine shock and neutropenia, with no risk of severe infections.6 In this study, there were no serious adverse events; only mild infusion-related reactions, none meriting discontinuation of therapy. However, physicians must also be aware of potentially life-threatening side effects, including the occurrence of progressive multifocal leukoencephalopathy and acute lung injury.21-23

From our study we concluded that rituximab resulted in complete B cell depletion in all patients which is proved to be efficient to prevent relapse of nephritic syndrome and allowed to decrease or to withdraw steroids and immunosuppressive drugs. The response to rituximab appears to be better if the patient is in remission at the time of the infusion and of minimal change nephritic syndrome histology. The tolerance of the treatment was good and no major side effects were reported. However, both the long term efficacy and safety of this drug in this group of patients remain unclear. Future studies are needed to analyze clinical, histological, and other features associated with a satisfactory response to rituximab.

Finally, in accordance to Gulati and colleagues,24 although there might be a bias for reporting favorable outcomes, findings from this and previous studies suggest that therapy with rituximab benefits a proportion of patients with difficult SDNS and further studies are needed to monitor treated patient for longer periods and correlate the favorable response with histological and genetic make-up.

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CONFLICT OF INTEREST

None declared.

REFERENCES


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