CASE REPORT

Minimal change disease with maximum immunosuppression: successful treatment of steroid-dependent minimal change disease with rituximab

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SUMMARY

Minimal change disease (MCD) is usually steroid sensitive, although in case of steroid dependent and multiple relapses we can struggle with different immunosuppressive agents, sometimes with no response. Rituximab has been emerging as an alternative therapeutic option.

We describe a case of a young patient with MCD that had frequent relapses and steroid dependency, with no response to several immunosuppressive agents during 15 years of disease. He was kept under high-dose steroids and ciclosporin. He started treatment with rituximab (two administrations of 1 g 2 weeks apart, repeating after 6 months). The steroids dose was gradually reduced and the ciclosporin was stopped. During the entire 2 years follow-up period, he remained in remission and had no adverse events.

This remarkable outcome reinforces the option of using rituximab in difficult cases, allowing the reduction of steroid burden and its adverse effects, which is of extreme importance, especially in young patients.

BACKGROUND

Minimal change disease (MCD) is the main cause of nephrotic syndrome in children and usually responds well to steroids. In case of steroid dependency or multiple relapses, we should use other agents such as cyclophosphamide, mofetil mycophenolate or ciclosporin. However, in a few particular cases, the use of those agents is not enough. Therapeutic options in those patients are sparse but the burden of prolonged steroid therapy and the use of nephrotoxic agents such as ciclosporin since a very young age should drive us to search for better options.^{1,2}

Rituximab has been used in some published case reports and small studies, with promising results either in inducing or maintaining remission in steroid-dependent or multiple relapsing patients with MCD.^{3–10}

CASE PRESENTATION

We present a case of a 20-year-old white male with inaugural nephrotic syndrome at the age of 3 years old. He responded well to steroid therapy with complete remission. However, the course of the disease has been marked by frequent relapses and high-dose steroid dependence. He had a renal biopsy performed at the age of 8, which was

compatible with MCD. After the biopsy, he underwent treatment with cyclophosphamide (twice) and with mofetil mycophenolate (2 years). During the last 6 years, he was kept under ciclosporin and corticosteroids. During all the time, he remained steroid-dependent and with frequently relapsing MCD, having one relapse in the previous 6 months and five relapses during the last 2 years, usually triggered by intercurrent illnesses or attempts to reduce immunosuppression.

TREATMENT

At the age of 18, he began being followed in our hospital. He had no other health problems and his medication was 100 mg ciclosporin twice a day and 27 mg deflazacort every other day. By that time, he was on remission and, apart from a small stature, he had no major adverse effects from previous or actual immunosuppressive agents. The baseline main analytical parameters are described in table 1. He started treatment with rituximab: two administrations of 1 g of rituximab, 2 weeks apart. The steroid's dose was reduced gradually until it reached 3 mg deflazacort every other day (for the last 14 months). After 6 months of the first administration, he received another two administrations of rituximab, also 2 weeks apart. During 1 year, the ciclosporin dose was slowly reduced and eventually stopped (6 months ago).

OUTCOME AND FOLLOW-UP

During the entire follow-up period (2 years after the beginning of rituximab and more than 1 year since the last administration), he remained on remission and had no adverse events. Present medication includes only deflazacort 3 mg, every other day.

DISCUSSION

Rituximab is a chimeric monoclonal antibody that was originally developed for the treatment of B cell non-Hodgkin lymphomas.¹¹

It recognises a 35-kD integral protein (CD20) that is present on the surface of B lymphocytes at several stages of differentiation, from the pre-B cells to the mature lineage. After binding to CD20, the complex CD20-rituximab is internalised and cross-reacts with sphingomyelin phosphodiesterase acid-like 3b protein (SMPDL-3b), inducing cell death by mechanisms that are not completely understood. Proposed mechanisms include inducing cell

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Table 1 Baseline main analytical parameters

Analytical parameters	Result	Normal range
Haemoglobin (g/dL)	16.3	13.0–17.0
Creatinine (mg/dL)	0.8	0.66–1.24
Serum albumin (g/dL)	4.1	3.7–5.6
Serum total proteins (g/dL)	7.1	6.3–8.6
Proteinuria (mg/24 hours)	160	42–255

apoptosis, complement-dependent cytotoxicity and antibody-dependent cellular toxicity through cells that have Fc receptors such as natural killer cells, monocytes and macrophages.¹²

Since then, its use has been extended to other antibody-mediated diseases, some of them affecting the kidney, such as lupus, antineutrophil cytoplasmic antibody-associated vasculitis or membranous glomerulonephritis. Although the pathogenesis of MCD is still poorly defined, it has been considered a T cell disorder for several years; therefore, the efficacy of rituximab in this entity was not expected.¹³

The first hint that rituximab could be an option in MCD was the observation that some cases of children who had nephrotic syndrome and received rituximab to treat idiopathic thrombocytopenic purpura or a post-transplant lymphoproliferative disorder had a dramatic reduction in proteinuria.^{14 15}

Initial retrospective studies, conducted between 2008 and 2011 recruited 211 patients with steroid-dependent nephrotic syndrome and 90 patients with steroid-resistant nephrotic syndrome. Variable doses of rituximab were used and follow-up was also variable (up 54 months). Response rates were 50% in steroid-dependent nephrotic syndrome (results from 10 studies) and 25% in steroid-resistant nephrotic syndrome (five studies).¹⁶

Since then, several prospective and randomised controlled trials have been published on the use of rituximab in idiopathic nephrotic syndrome. These trials were mainly conducted in children, although some included adult populations.^{7 17–20}

The response to rituximab seems to depend on the sensitivity to standard medication. In idiopathic nephrotic syndrome dependent only on steroids, rituximab achieves better results, with an overall 80% probability of oral drug-free remission at 12 months. However, in idiopathic nephrotic syndrome dependent on both steroids and calcineurin inhibitors, the probability of oral drug-free remission decreases to 50% at 6 months. Results in steroid and calcineurin inhibitors resistant patients are more controversial. Occasional case reports showed some promise, but the single prospective RCT conducted showed no benefit.^{16 19}

The evidence presented above suggests that in some cases (at least in patients that are steroid or steroid plus calcineurin inhibitor sensitive), the administration of rituximab may allow the discontinuation or dose reduction of either steroids and/or other immunosuppressive agents, reducing the burden of side effects resulting from the continued use of these agents. This was the main reason behind our own decision for trying the drug on our patient. The fact that our patient was essentially steroid sensitive/steroid dependent and the calcineurin inhibitor was mainly used to minimise the steroid burden, placed our case in the clinical setting in which the efficacy of rituximab seemed maximum, according to the available literature described above.

The dose and duration of the treatment with rituximab are still controversial. Some authors defend a single dose, others fixed multiple dose treatment and others maintain administrations every time CD19 count increases. There is also evidence that the administration while on remission has better long-term results.²¹ We chose a particularly intensive approach, according

to the opinion of an expert, as in this case, the long course of the disease was marked by unsuccessful therapeutic strategies and we were worried that the patient could have another relapse. This notion was also the reason for the slow taper of steroids to an almost residual dose and later also the slow taper of ciclosporin. Our option is questionable but we believe that without consensual literature an argument can be made for a more intensive rituximab therapy and a more cautious taper of previous immunosuppressive agents in patients who have a long course of the disease, with multiple immunosuppressive treatments (as was the case of our patient) or in patients who are not on remission. However, in other patients, perhaps a less intensive approach can be attempted. The next step in our case will be the discontinuation of the steroids that were kept in a minimal dose allowing both the patient and us and to feel more confident in his sustained remission.

As mentioned before, the mechanism of action is also not well understood. Some authors refer that the efficacy of rituximab in inducing sustained remission favours the hypothesis that B cells are involved in the physiopathology of MCD. However, the same authors point out that rituximab can affect T cell function both direct and indirectly, and, therefore, can also be the explanation for the success of the therapy in these cases of MCD.²²

More recent data also suggests that rituximab may interfere directly with the podocytes, via direct binding with SMPDL-3b, protecting the structure and function of podocytes. SMPDL-3b is also expressed on Th17 cells, and the activation of these cells is considered a fundamental step in the pathogenesis of nephrotic syndrome. It has been demonstrated that rituximab reduces Th17 cell response in rheumatoid arthritis; therefore, this may also be a pathway to explain the effectiveness of rituximab in minimal change disease.^{16 22–24}

Rituximab is generally well tolerated. Apart from an increased risk of infections, usual side effects include mainly infusion reactions, such as skin rash, hypotension, bradycardia or bronchospasm, which can be minimised through premedication or infusion rate adjustments. Some patients refer arthralgia or have cytopenias a few weeks after infusion. The most rare and serious complication after rituximab therapy is progressive multifocal leucoencephalopathy.^{20 22}

In our case, care was taken in insuring that the patient had vaccines against *Streptococcus pneumoniae*, influenza and Hepatitis B, well before starting rituximab therapy and, in all administrations, the patient received premedication with paracetamol, methylprednisolone and antihistamines.

Despite the fact that the main side effect of steroid therapy (low stature) could not be reversed, the prolonged exposure to both steroids and ciclosporin might lead in the future to the development of side effects such as osteopenia, dyslipidaemia and diabetes (with the subsequent increase in cardiovascular risk) and nephrotoxicity as a result of the prolonged exposure to the calcineurin inhibitor. As such, we believe that a preventive attitude is important, especially in such a young patient.

In conclusion, this is a complex case of MCD, in which the patient was submitted to multiple treatments, always with poor long-term efficacy and remaining with the need of high corticosteroids dose. Rituximab allowed the waning of both corticosteroids and ciclosporin with no relapse in a 2-year follow-up. This is a remarkable outcome that reinforces the use of rituximab in difficult cases like the one reported and maybe even earlier in the course of the disease. This is particularly important in young patients who are more significantly affected by the adverse effects of prolonged corticosteroid therapy.

Learning points

- ▶ Minimal change disease can become a therapeutic challenge.
- ▶ Rituximab can be a powerful weapon in treating multiple relapses and steroid-dependent minimal change disease.
- ▶ We should always try to minimise steroid burden, especially in young patients.

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