

# Ofatumumab in two pediatric nephrotic syndrome patients allergic to rituximab

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## Abstract

**Background** Rituximab, a chimeric anti-CD20 monoclonal antibody, is an effective treatment in steroid-dependent nephrotic syndrome (SDNS). However, some patients develop adverse reactions.

**Case-Diagnosis/Treatment** Patient 1, a 14-year-old boy with SDNS since the age of 2, was treated with oral prednisone, cyclosporine A (CsA) and mycophenolate mofetil. A first infusion of rituximab at age 12 years was well tolerated, but this was followed by a prolonged relapse unresponsive to oral prednisone, mycophenolate mofetil and CsA. A second rituximab infusion was attempted, but treatment was interrupted due to severe dyspnea. Treatment with a humanized anti-CD20 monoclonal antibody, ofatumumab, was then attempted. The patient experienced a mild allergic reaction and maintained remission despite interruption of all treatment at >12 months of follow-up. Patient 2, a 3-year-old boy who presented at 18 months with nephrotic syndrome initially resistant to treatment with oral prednisone, was given with three intravenous boluses of methylprednisolone followed by CsA and achieved remission. Upon steroid discontinuation, the NS relapsed. Prednisone was restarted and treatment with a single dose of rituximab was never completed due to a severe allergic reaction. Ofatumumab infusion was uneventful, and he maintained remission during the follow-up period (>12 months)

despite interruption of prednisone therapy. B cells reappeared at 7 months in both patients.

**Conclusions** Ofatumumab may be a therapeutic option in severe forms of NS with allergy to rituximab.

**Keywords** Ofatumumab · Steroid-dependent nephrotic syndrome · Steroid-resistant nephrotic syndrome · Adverse reaction · Rituximab · Children

## Introduction

The chimeric anti-CD20 monoclonal antibody (mAb) rituximab, a B-cell depleting agent, is effective in inducing and maintaining a prolonged remission of nephrotic syndrome in children with frequently relapsing or steroid-dependent nephrotic syndrome (SDNS) [1, 2]. However, some patients can experience important adverse events during infusion, such as hypotension, cardiac arrhythmia and severe anaphylactic reactions [3]. The frequency of mild infusion reactions is around 54 %, whereas severe infusion reactions requiring interruption are exceptional [4]. In this report we describe the use of the humanized anti-CD20 mAb ofatumumab in two pediatric patients, one with SDNS and one with NS which was initially steroid-resistant (SRNS) but sensitive to combination treatment with calcineurin inhibitors, and evaluate its efficacy and safety during a follow-up of at least 1 year.

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## Case reports

### Patient 1

Patient 1 was a 14-year-old boy with SDNS since the age of 2 years. Due to steroid dependency, treatment with 5 mg/kg/

day cyclosporine A (CsA) was introduced, allowing prednisone therapy to be interrupted, with infrequent relapses. Renal function was normal, and two renal biopsies performed during this period and showing minimal change disease excluded calcineurin-induced toxicity. Therefore, this treatment was continued, due to obesity and a family history of diabetes, in order to minimize the chance of relapse. After 5 years the patient was switched to mycophenolate mofetil (MMF, 1200 mg/m<sup>2</sup>/day). On this therapeutic regimen he experienced infrequent relapses but did not achieve prednisone discontinuation and presented with an increasing body mass index, ultimately developing severe obesity, hypertension and initial osteopenia. For this reason, 8 years after onset, the patient received one dose of intravenous (IV) rituximab (375 mg/m<sup>2</sup>). There was no relevant adverse event during infusion, and the patient achieved complete CD19<sup>+</sup> B-cell depletion, leading to prednisone discontinuation after 5 months without relapse. Total B cells returned to >5 % of total peripheral blood lymphocytes (6.3 % CD19<sup>+</sup> B cells) at 6 months post-rituximab and to 22.3 % CD19<sup>+</sup> B cells at 23 months. Two years after rituximab infusion, during MMF tapering, he experienced a relapse during an episode of pneumonia, and remission was induced by treatment with prednisone, subsequently discontinued. Six months later, during tapering of MMF, he experienced a new prolonged relapse that did not respond to >30 days of prednisone (secondary steroid-resistance). Therefore, MMF dosage was increased, and he was given CsA in addition to prednisone and MMF, but remission was not achieved. A second rituximab infusion was then attempted, but was interrupted because of a severe allergic reaction, despite premedication with paracetamol, clorphenamine and slow infusion as per protocol, with the occurrence of a rash and dyspnea. Due to the severity of this reaction, as soon as remission was achieved by three boluses of IV methylprednisolone, the patient was treated with a humanized anti-CD20 mAb, ofatumumab (750 mg/1.73 m<sup>2</sup>); a mild allergic reaction did not preclude completion of the infusion. All concomitant immunosuppression therapy was tapered gradually, and the patient remained in stable remission for 15 months after the infusion, 7 months from discontinuation of all concomitant therapy. Total B cells, which were normal pre-ofatumumab administration and completely depleted at 1 month (CD19<sup>+</sup> cells 0 % of total lymphocytes), returned to >5 % of total peripheral blood lymphocytes 7 months after the infusion of ofatumumab.

## Patient 2

Patient 2 was a 3-year-old boy with onset of nephrotic syndrome at 30 months of age. Initial steroid resistance at 4 weeks of prednisone therapy led to treatment with three boluses of IV methylprednisolone and oral CsA (5 mg/kg/day) with complete remission. The patient stopped prednisone therapy after

a total of 6 months from onset, and after 2 months he relapsed while receiving CsA. Remission was induced by treatment with prednisone, and after another 6 months tacrolimus (0.07 mg/kg/day) was added to the therapeutic regimen. Four months later, in an effort to discontinue prednisone, the patient was given an infusion of rituximab (375 mg/m<sup>2</sup>). Baseline B-cell counts were normal (CD19<sup>+</sup> cells 25 % of total lymphocytes). Despite premedication with prednisolone, clorphenamine and paracetamol and slow infusion as per protocol, the patient presented an almost immediate severe allergic reaction, with urticaria and respiratory distress that required treatment interruption. Due to the severity of this reaction, 2 months later the humanized anti-CD20 mAb ofatumumab (750 mg/1.73 m<sup>2</sup>) was administered with no adverse reaction. The patient subsequently remained in stable remission. He tapered prednisone that was interrupted in 2 months and remained in remission under tacrolimus 19 months later. As with Patient 1, the total B cell count (the CD19<sup>+</sup> cells were depleted at the time of the ofatumumab infusion; 0 % total lymphocytes) returned to >5 % of total peripheral blood lymphocytes 7 months after the infusion.

## Discussion

Idiopathic nephrotic syndrome (INS), the most frequent glomerular disease in childhood, is characterized by intense proteinuria, associated with edema, hyperlipidemia and hypoalbuminemia that is due to glomerular alterations. Non-genetic forms of INS generally respond to steroid treatment and are defined as steroid-sensitive nephrotic syndrome, whereas frequent relapsing/remitting episodes can occur and result in SDNS or SRNS [5]. Immunosuppression can be achieved with second-line treatments, such as calcineurin inhibitors, CsA or tacrolimus, and the antiproliferatives azathioprine or MMF can be used in combination, but some patients experience treatment-related toxicity and multi-drug resistance [6, 7]. The efficacy of rituximab, a chimeric mouse-human anti-CD20 mAb, was initially tested in B-cell lymphoma and hematological disorders. The crosslinking of specific mAbs with CD20 can result in the recruitment of immunological factors that induce strong cytotoxic effects, such as antibody-dependent cellular cytotoxicity or complement-dependent cytotoxicity, which ultimately cause the depletion of B cells [8]. Rituximab has recently been described as an effective treatment for the management of severe forms of INS [1, 2], but a few patients experience rituximab-related adverse events and, rarely, resistance [9, 10]. Indeed, whereas mAbs are generally well tolerated in humans, they may be recognized as non-self by the immune system and may induce immune activation, which in turn causes acute reactions such as anaphylactic [immunoglobulin E (IgE)-mediated] and anaphylactoid reactions against the mAb, serum sickness, tumor lysis syndrome and

cytokine release syndrome. This is the case with rituximab, as its murine components can be recognized as foreign. Late adverse effects have been reported in the literature and include late-onset neutropenia, defects of immune reconstitution with associated immune compromise, infections such as *Pneumocystis carinii* pneumonia, progressive multifocal leukoencephalopathy, reactivation of hepatitis, intestinal perforation and interstitial pneumonitis [11]. The development of anti-rituximab antibodies in patients receiving repeated infusions, the so-called HACAs (human anti-chimeric antibodies) has been described, leading to a reduced level of circulating rituximab and to an impaired B-cell depletion [12]. In this report, we describe two patients affected by SDNS and initially SRNS but SDNS in association with CsA, respectively, who experienced severe anaphylactic reactions against rituximab treatment. Due to the severity of the allergic reaction in both patients, treatment with ofatumumab was considered. Ofatumumab is a new fully-humanized mAb directed against a different epitope of CD20 than rituximab. This permits a prolonged binding to its target, which translates to a more efficient CDC compared to the same concentration of rituximab [13]. Its safety profile is rather similar to that of rituximab, with infusion-related reactions and long-term neutropenia, hypogammaglobulinemia and infections being described [14]. Ofatumumab infusion induced a mild allergic reaction in patient 1 and no adverse reaction in patient 2, and allowed complete discontinuation of all concomitant immunosuppressive treatment in patient 1 for more than 7 months and discontinuation of prednisone in patient 2, with both patients maintaining a prolonged remission for >12 months. Of note, patient 1 had fully reconstituted B cells prior to starting on ofatumumab therapy, while patient 2 underwent ofatumumab infusion with already depleted B cells due to the partial infusion of rituximab that he had received 2 months previously. Therefore, for patient 2 in particular, an added effect of rituximab prior to ofatumumab cannot be excluded in determining the favourable clinical outcome. HACAs were not dosed in our patients as patient 1 had received only one previous rituximab infusion and patient 2 none at all, and the timing of reaction observed in both patients suggests an acute IgE-mediated or anaphylactoid mechanism. Interestingly, as recently reported [10] our observations demonstrate that a single infusion of ofatumumab is as effective as six weekly infusions previously reported for five patients with SRNS monitored for 9 months [9]. Of note, despite its reported increased efficiency in inducing B-cell depletion compared to rituximab, reconstitution of total B cells was evident 7 months after ofatumumab infusion in both patients, resembling the previously shown post-rituximab recovery of B cells [15].

In conclusion, our clinical experience strongly suggests that ofatumumab could be a therapeutic option in managing severe forms of drug-resistant nephrotic syndrome in pediatric patients who have developed an allergy to rituximab. Long-

term follow-up and an increased number of observations are necessary to evaluate the safety and efficacy of ofatumumab in these patients.

#### Compliance with ethical standards

**Conflict of interest** The authors declare that they have no conflict of interest.

**Ethical approval** All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

**Informed consent** Informed consent was obtained from all individual participants included in the study.

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