CASE REPORT

Low-dose ofatumumab for rituximab-resistant nephrotic syndrome

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SUMMARY

Drug resistant idiopathic nephrotic syndrome (DRNS) remains a therapeutic dilemma. In this pilot study, the efficacy of the new fully humanised, anti-CD20 monoclonal antibody ofatumumab was tested in 4 children with persistence of proteinuria for at least 12 months in spite of a full drug approach (including rituximab). We used a low-dose 2-infusion ofatumumab model (300+700 mg/1.73 m² 2 weeks apart) using specified premedication. Transient normalisation of proteinuria (persisting for 2 months) was achieved in 1 child while another presented stable remission after 12 months; both had normal renal function. The outcome was not modified in the remaining 2 children presenting an impaired renal function. These results demonstrate that low-dose ofatumumab may induce remittance of proteinuria in children with a long story of DRNS and normal renal function. Further studies are needed to test whether higher doses of ofatumumab can also modify proteinuria in patients with impaired renal function.

BACKGROUND

Idiopathic nephrotic syndrome (INS) is a condition with a variable clinical expression and response to drugs.¹ Standard therapy for INS includes oral steroids and calcineurin inhibitors (CNI) as second-line in those who do not respond to steroids, and rituximab as a steroid-CNI-sparing drug in patients with long-lasting dependence on the association.^{2–8} Children who are or become resistant to the above schedule are usually tapered from any intervention to minimise the risk of complications, however, still maintaining ACE inhibition (ACE-I) as an antihypertensive and antiproteinuric approach.

In spite of rituximab being first proposed as an alternative in most difficult cases, based on the indications of clinical trials,^{5–6} its use has been limited to patients having proven sensitivity to steroids and CNI. Resistance to both drugs is now considered critical to its use and it is currently not indicated in these patients.⁹

Recent results in a small series on children with INS resistant to steroids/cyclosporine indicate an option with the new anti-CD20, ofatumumab.¹⁰ Ofatumumab is a fully humanised last generation anti-CD20 monoclonal antibody (human IgG1(k) mAb). It is expected to be more effective than other similar compounds since its antigen combining site is composed of a deep pocket interacting with an epitope enriched with hydrophobic residues. This binding site is very close to the cell membrane and may attach the CD20 residue more closely,

potentially leading to more efficient complement-dependent cytotoxicity.^{11–12} Ofatumumab is currently in phase III clinical trials for the treatment of chronic lymphocytic leukaemia, relapsing lymphoma and rheumatoid arthritis, with apparently improved results.^{13–14} Basu¹⁰ first used ofatumumab to treat five children who had nephrotic syndrome and resistance to all drug options (cyclosporine/tacrolimus, cyclophosphamide and rituximab). All the children had a histological diagnosis of focal segmental glomerulosclerosis (FSGS). Renal function was normal in all the cases. After six pulses of ofatumumab (1 with 300 mg/1.73 m² and 5 with 2000 mg/1.73 m²), the proteinuria normalised and was stably normal after 6 month follow-up in all the cases. The strong therapeutic scheme was designed on the basis of studies on leukaemia and lymphoma. It is conceivable that the outset of a new drug should follow a therapeutic scheme designed for other clinical conditions. However, it also seems reasonable to tentatively prove lower-dose schemes once high-dose efficacy is proven. This logical line was historically followed for rituximab in INS since it started with high-dose schedule in early studies (from 4 to 16 infusions)^{15–16} while, later on, clinical trials demonstrated the equivalence of one rituximab infusion in cases with documented sensitivity, reducing *de facto* the possibility of side effects.

On the basis of the aforementioned evidence and following the logical approach to test the minimum efficient dose, we designed a small pilot study to confirm the efficacy of ofatumumab in children with drug resistant INS (DRNS), keeping the option of a low-dose scheme in mind and also considering patients with altered renal function.

CASE PRESENTATION

Four children (3 male/1 female) were recruited after having documented the persistence of proteinuria in them for at least 1 year (median 3, range 1–13 years), during which time they had received a combination of steroids, cyclosporine/tacrolimus and mofetile mycophenolate. The definition of drug resistance was based on consolidated criteria according to which proteinuria in the nephrotic range persisted after a cycle of steroids of at least 3 months and an association with cyclosporine/tacrolimus for at least another 6 months. Mofetile mycophenolate was associated with the above drugs in some cases. Subsequently, all the patients also received 1–3 doses rituximab (375 mg/m²/dose, cumulative dose ranging from 300 to 1350 mg), administered as an off-label therapy (table 1), following which the steroids and cyclosporine were

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Table 1 Characteristics of patients and therapeutic history

Patient number	1	2	3	4
Sex	F	M	M	M
Age (years)	7	16	14	14
Age at onset (years)	4	3	13	10
Histological pattern	FSGS	FSGS	MCD	MCD
Previous steroid-sparing therapy	CsA, FK, RTX	CYC, CsA, FK, IL-2, RTX	CsA, PEX, FK, RTX	CsA, FK, RTX, IL-2
Number of RTX	1	3	3	2
RTX total dose (mg)	300	600	1350	930
Months from last RTX	13	34	5	39
Antiproteinuric therapy at time of ofatumumab infusion	Steroid (1.2 mg/kg/day from 1 month), FK, ACE-I	Steroid (0.16 mg/kg/day from 1 month), CsA, ACE-I	Steroid (0.5 mg/kg/day from 1 month), FK, ACE-I	ACE-I

ACE-I, ACE inhibitors; CsA, cyclosporine; CYC, cyclophosphamide; F, female; FK, tacrolimus; FSGS, focal segmental glomerulosclerosis; IL, interleukin; M, male; MCD, minimal change disease; PEX, plasma exchange; RTX, rituximab; uPCR, urinary protein creatinine ratio.

tentatively tapered off. However, steroids were started again in case of abrupt worsening of renal function (patient 1, 2 and 3). Renal histology showed FSGS in two patients and minimal lesions in the other two. Following our clinical approach to patients with nephrotic syndrome with resistance to drugs, all four patients were characterised for mutations in one of the principal genes involved in the pathogenesis (ie, NPHS1, NPHS2 and WT1), which are detected in 90% of all molecular forms. All the patients were negative for these mutations.

At the time of treatment, the patients were either receiving ACE-I or angiotensin-receptor blocker (ARB). Renal function was altered in two cases ($60 >$ estimated glomerular filtration rate >30 mL/min/1.73 m², calculated according to revised Schwartz formula), while it was normal in the remaining two (table 2).

TREATMENT

We used two infusions of ofatumumab (300+700 mg/1.73 m² 2 weeks apart) using a specified premedication with intravenous methylprednisolone 2 mg/kg, oral paracetamol 15 mg/kg and intravenous cetirizine 0.4 mg/kg. Speed of infusion followed a standardised scheme, according to which a solution of ofatumumab 1 g/L or less was infused at 12 mL/h (initial 30 min) with doubling of the infusion rate every 30 min, up to a maximum of 200 mL/h. The entire protocol had the approval of our Institutional Review Board, which authorised an off-label administration of ofatumumab; the patients were assigned to treatment without randomisation; informed consent was given

by the parents or by a legal guardian and by the patients as appropriate for age. No side effects were observed.

OUTCOME AND FOLLOW-UP

After infusion of the second dose of ofatumumab, progressive remission (ie, uPCR <200 mg/g or 0–1+ of protein on urine dipstick for 3 consecutive days)¹⁷ was achieved in one patient (patient 3), who presented progressive reduction of proteinuria after 1 month and stable normalisation after 6 and 12 months (table 2). A second child (patient 1) achieved transient reduction of proteinuria, which did not reach normal levels and lasted for less than 2 months; serum albumin never normalised in this patient and cholesterol levels were stably high for the whole period. The other two patients had no response to the ofatumumab (table 2).

The unique important difference between the partial and total responder (patient 3 and patient 1, respectively) versus the non-responder (patient 2 and patient 4), was renal function, which was normal in the former cases (table 2) and not modified by ofatumumab infusion. CD20 count was, in all cases, 0 after 1-month of using ofatumumab, which then increased during the successive follow-ups, with the time course in CD20 cell depletion and reconstitution comparable to what was already observed following treatment with rituximab.

DISCUSSION

This is the second report describing the use of the new generation anti-CD20 monoclonal antibody, ofatumumab, in nephrotic syndrome resistant to drugs. This drug has already been used in

Table 2 Laboratory values

Patient number	Proteinuria (mg/m ² /h) uPCR (mg/g)				Serum albumin (g/dL)				eGFR (mL/min/1.73 m ²)*				Cholesterol (mg/dL)			CD19 (n/μL)		
	M0	M1	M6	M12	M0	M1	M6	M12	M0	M1	M6	M12	M0	M1	M6	M0	M1	M6
1	135	14	73	50.9	2.5	2.5	2.1	2.2	71	87	100	112	600	736	558	1570	14	612
	7407	678	NA	3542														
2	123	110	181	NA	3.1	3.3	3.0	3.5	30	31	NA	NA	124	117	219	1355	82	594
	1892	1346	5658	NA														
3	114	40	14	3.4	3.4	3.1	3.1	NA	123	118	113	115	244	266	186	0	0	6
	2348	1180	305	111														
4	195	167	82	168	2.0	2.2	2.9	2.0	35	38	31	10	221	219	222	568	0	234
	5980	6464	7283	NA														

*Calculated according to revised Schwartz formula.

Figures in bold indicate a significant response to therapy.

eGFR, estimated glomerular filtration rate; M, month; NA, not available.

patients with chronic lymphocytic leukaemia, relapsing lymphoma and rheumatoid arthritis, with apparently improved results in respect to other immunodepressors,^{13 14} this first experience giving the rationale for the extension to nephrotic syndrome. In their earlier report, Basu¹⁰ repeated five infusions with high-dose ofatumumab (300 mg followed by 4 infusions of 2000 mg/1.73 m²) in five children with documented nephrotic syndrome unresponsive to all treatments, including rituximab. Actually, this category of patients represents the most difficult to be treated among patients with nephrotic syndrome, and they invariably undergo worsening of renal function predisposing to dialysis and renal transplant. Therefore, the report by Basu¹⁰ represented a breakthrough in the clinical management of otherwise intractable cases. However, the use of repeated high-dose ofatumumab (overall 8.300 mg/1.73 m²) potentially increases the risk of side effects in terms of immunosuppression, which may even persist in the long term. Our brief report demonstrates that low-dose ofatumumab (1000 mg/1.73 m²) was effective in reducing proteinuria in one child with long-term DRNS, and partially and transiently modified proteinuria in another child, where both children had normal renal function. Normalisation of proteinuria took 2–3 months, but persisted after 12 months (patient 3). Although the presence of normal renal function limits, in our cases, the use of low ofatumumab to only a portion of the patients with FSGS, it is also clear that our report contains some elements of innovation in respect to the Basu report, with major reference to dosages and potential side effects. Moreover, our report does not exclude the fact that higher doses of ofatumumab can also modify proteinuria in other patients, but studies must be dedicated to this aspect.

There is a general consensus about innovative therapeutic strategies for nephrotic syndrome that involve anti-CD20 monoclonal antibodies. Most recent studies suggest the early use of rituximab in children with documented steroid dependence.¹⁸ The key issue of safety is, however, of relevance and must be considered in pilot studies (such as the present one) designed in view of clinical trials. On the basis of the present results, we are planning to treat patients affected by steroid-dependent and steroid-resistant nephrotic syndrome, with preserved renal function, using a low-dose scheme (ofatumumab 1.500 mg/1.73 m² single pulse, compared, in steroid-dependent and steroid-resistant patients, respectively, with rituximab 375 mg/m² single pulse and placebo, in two different randomised clinical trials—EUDRACT n 2015-000624-28, *ClinicalTrials.gov* ID NCT02394119; EUDRACT n 2015-000569-30, *ClinicalTrials.gov* ID NCT02394106). In those cases with reduced renal function, high-dose ofatumumab will be considered only after performing a renal biopsy, in order to exclude a histological pattern of severe fibrosis, which could determine a resistance to therapy.

Patient's perspective

We asked the patient who achieved stable remission about his perspective:
During the first infusion of ofatumumab I experienced some side effects, such as nasal congestion, itchy throat and ears. During the next infusion and also in the months after treatment I did not experience any side effect. Already after the first infusion my clinical condition improved week after week and my proteinuria decreased until complete remission. I think ofatumumab is the only therapy which can allow me a complete steroid withdrawal.

Learning points

- ▶ Nephrotic syndrome resistant to steroids and calcineurin inhibitors is a clinical condition with bad prognosis, usually evolving to renal failure.
- ▶ In the past, rituximab has been proposed as a possible alternative. However, clinical trials failed to show an antiproteinuric effect in patients with proven resistance to other drugs.
- ▶ Ofatumumab, a new fully humanised anti-CD20 monoclonal antibody, has been used at high dosages (total of 8000 mg/1.73 m²) with success in five patients with nephrotic syndrome resistant to all drugs. Proteinuria was normalised after the last infusion and remained low for several months.
- ▶ This study shows that ofatumumab can reduce proteinuria in the same category of patients when also used at low-dosages (1000 mg/m²), provided they have normal renal function.
- ▶ Ofatumumab should be considered as a therapeutic approach to nephrotic syndrome resistant to all types of drugs. Clinical trials will evaluate low-dose ofatumumab for patients with normal renal function.

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Contributors AB, RR, CM and GMG contributed to the therapeutic protocol and study design, patients' management and clinical data collection. AB and GMG were involved in the manuscript writing. All the authors participated in the manuscript revision.

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