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par

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OFATUMUMAB DANS LE TRAITEMENT DES SYNDROMES NEPHROTIQUES CORTICO-DEPENDANTS ET CORTICO-RESISTANTS DE L'ENFANT

OFATUMUMAB TREATMENT IN CHILDREN WITH STEROID-DEPENDENT AND STEROID-RESISTANT NEPHROTIC SYNDROME

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Présidente : Madame la Professeure Christèle GRAS-LE GUEN

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Table des matières

I. Contexte et présentation générale

Le syndrome néphrotique idiopathique (SNI) est une maladie définie par une protéinurie importante (rapport protéine/créatinine urinaires > 0,2 g/mmol), une hypoalbuminémie < 30 g/ L et caractérisée cliniquement par des œdèmes. Son incidence est estimée à 1-4/100 000 enfants/an et le diagnostic est habituellement fait chez des enfants âgés de 2 à 7 ans [1, 2]. Dans la plupart des cas, il survient après un événement immunitaire ou allergique. Environ 90% des SNI répondent à la corticothérapie et sont donc dits « cortico-sensibles » (SNCS). Cependant, 10% des patients développent un syndrome néphrotique cortico-résistant (SNCR), pouvant conduire à une insuffisance rénale terminale [3]. L'histologie rénale dans le SNCS montre principalement des lésions glomérulaires minimes. Dans le SNCR, elle peut révéler une hyalinose segmentaire et focale. Au sein des SNCS, certains enfants présentent un syndrome néphrotique cortico-dépendant (SNCD), qui nécessite souvent l'utilisation d'autres médicaments afin de limiter les effets indésirables des corticostéroïdes [4]. Une origine immunitaire est suspectée depuis longtemps et serait liée à un facteur circulant augmentant la perméabilité de la membrane basale glomérulaire par lésion des podocytes [3, 5]. Ce facteur circulant n'a pas encore été identifié. Plusieurs médicaments immunosuppresseurs, tels que les anticalcineurines et le mycophénolate mofétil, ont montré une efficacité [4, 6]. Malheureusement, ces traitements sont associés à des effets indésirables et des études ont été menées afin de trouver un moyen d'éviter leur utilisation [4, 6–9]. Le rituximab (RTX), un anticorps monoclonal chimérique anti-CD20, en est un exemple, mais il n'est pas efficace dans tous les cas (50 à 100% de rémission dans le SNCD et environ 50% dans le SNCR) [10, 11] et plusieurs perfusions peuvent être nécessaires pour obtenir une déplétion

prolongée des lymphocytes B, associée à de meilleurs résultats [12–17]. Plus récemment, l'ofatumumab, un anticorps monoclonal anti-CD20 humain de deuxième génération, a été décrit dans le traitement du SNI et pourrait être intéressant dans cette indication [8, 18-23]. Dans certains cas, il semble induire une rémission, notamment lorsque le RTX n'a pas été efficace. Ce travail présente la plus grande cohorte de patients atteints de SNI traités par ofatumumab à ce jour.

Quatorze patients ont été inclus dans cinq centres en France, parmi lesquels cinq avaient un SNCD, trois un SNCR sur reins natifs et six une récurrence après transplantation, avec une durée médiane de suivi de 10,5 mois. Trois régimes d'ofatumumab différents ont été administrés. Le critère de jugement principal était la protéinurie à 6 mois de la dernière dose d'ofatumumab. Au total, 11 patients (79%) étaient en rémission, complète pour 6 (43%) et partielle pour 5 d'entre eux (36%). L'ofatumumab a été efficace chez 3 enfants sur 6 traités pour une récurrence de SN après transplantation. Huit patients ont présenté une réaction allergique mineure lors de la première perfusion. Un enfant est décédé suite à une infection survenue à cause de multiples facteurs. Aucune tumeur n'a été observée mais le recul n'est pas assez important pour observer ce type de maladie.

Globalement, ces résultats suggèrent une efficacité ainsi qu'une bonne tolérance de l'ofatumumab dans le SNI, notamment après échec du RTX. Toutefois, des études complémentaires sont nécessaires pour les confirmer et déterminer un protocole standardisé ainsi que la dose dans cette indication.

Ce travail fait l'objet d'un article soumis au journal *Pediatric Nephrology* le 28/08/2019 et est actuellement en cours de révision.

II. Article

1. Title page

Ofatumumab treatment in children with steroid-dependent and steroid-resistant nephrotic syndrome

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2. Abstract

Steroid-dependant (SDNS) and steroid-resistant nephrotic syndromes (SRNS) can be a challenge to treat, and the result of the consequent long-lasting proteinuria is end-stage renal disease. Recently, ofatumumab, a second-generation and fully human anti-CD20 monoclonal antibody, has been shown to be effective in children with multidrug-resistant nephrotic syndrome (NS).

We retrospectively collected data from the medical records of children with SDNS or SRNS treated with ofatumumab in this indication in France.

Fourteen patients were included in this study in five centers, of whom five had SDNS and nine had SRNS, with a median duration of follow-up of 10.5 months. Three different ofatumumab regimens were administered. Six children were treated after kidney transplantation. The primary outcome was the proteinuria at 6 months after the last dose of ofatumumab. A total of 11 patients (79%) were in remission, which was complete for 6 patients (43%) and partial for 5 of them (36%). Only 3 out of 6 children treated for a recurrence of NS after transplantation responded to ofatumumab. Eight patients exhibited a minor allergic reaction with the first infusion. One patient with severe post-transplantation recurrence died of infection, as a consequence of multiple factors. No malignancies were observed, however the time of follow-up was not sufficient to see such disease.

Altogether, these results suggest the possible effectiveness and the tolerability of ofatumumab for multidrug-resistant NS. It seems to be a suitable alternative in case of allergy to rituximab. However, there is a need for further studies to confirm these findings and safety and to determine a standardized protocol in this indication.

Keywords: nephrotic syndrome, children, ofatumumab, FSGS

3. Abbreviations

CD: cluster of differentiation

CNI: calcineurin inhibitor

CNIL: National Commission of Information Technology and Liberties

ESRD: end-stage renal disease

FRNS: frequently relapsing nephrotic syndrome

FSGS: focal and segmental glomerular sclerosis

IAds: immunoadsorption sessions

INS: idiopathic nephrotic syndrome

IV: intravenous

IVIG: intravenous immunoglobulins

mAb: monoclonal antibody

MCD: minimal change disease

MMF: mycophenolate mofetil

NS: nephrotic syndrome

RTX: rituximab

SDNS: steroid-dependent nephrotic syndrome

SRNS: steroid-resistant nephrotic syndrome

SSNS: steroid-sensitive nephrotic syndrome

UPCR: urine protein/creatinine ratio

4. Introduction

Idiopathic nephrotic syndrome (INS) is a disease defined by pronounced proteinuria (urine protein-to-creatinine ratio -or UPCR- > 0.2 g/mmol), and hypoalbuminemia < 30 g/L and clinically characterized by edema. Its incidence is estimated to be 1-4/100 000 children/year, and INS is usually first diagnosed in children between 2 and 7 years of age [1, 2]. In most cases, it occurs after an immune or an allergic event. Approximately 90% of INS respond to corticosteroid therapy and are classified as steroid-sensitive nephrotic syndrome (SSNS), although 10% of the patients develop steroid-resistant nephrotic syndrome (SRNS), which can lead to end-stage renal disease (ESRD) [3]. The renal histology in SSNS mostly shows minimal change disease (MCD), although it can reveal focal and segmental glomerular sclerosis (FSGS) in SRNS. Even in SSNS, some children exhibit steroid-dependent nephrotic syndrome (SDNS), which often requires the use of other medications in order to limit the adverse effects of corticosteroids [4]. An immune origin has been suspected for a long time, linked to a circulating factor that increases the permeability of the glomerular basal membrane [3, 5] through alteration of the podocytes. This circulating factor has yet to be identified. Several immunosuppressive drugs, such as calcineurin inhibitors (CNI) and mycophenolate mofetil (MMF), have exhibited a certain degree of efficacy [4, 6]. Unfortunately, these treatments are associated with adverse effects, and studies have been undertaken to find a way to avoid their use [4, 6–9]. Rituximab (RTX), a chimeric anti-CD20 monoclonal antibody (mAb), is an example, but it is not effective in every case (resulting in approximately 50 to 100% remission in SDNS and around 50% in SRNS) [10, 11] and several infusions may be needed to accomplish prolonged B-cell depletion, associated with better outcome [12–17]. More recently, a second-generation

fully human anti-CD20 mAb, ofatumumab, has been described in the treatment of INS and it may be of considerable relevance in this disease [8, 18–23]. In some cases, it appears to induce remission, notably when RTX has been ineffective. This study comprised the largest cohort to date of children exhibiting INS treated by ofatumumab.

5. Materials and Methods

We retrospectively analyzed the patients under 20 years of age who exhibited either SRNS or SDNS and who were treated with ofatumumab in France during the period 2015-2018. Five pediatric nephrology centers participated in this study: the University Hospitals of Bordeaux, Marseille, Nantes, Necker Enfants Malades (Paris), and Toulouse. The clinical and biological data of each patient were extracted from their medical records. We report the initial description of the NS for each patient, the successive treatments that were administered, the doses of ofatumumab, the number of infusions and their timing, the serum creatinine, the UPCR, and the albuminemia 6 months after the last dose of ofatumumab, as well as the duration of the B-cell depletion.

The primary study endpoint to assess the efficacy of ofatumumab was urinary protein excretion 6 months after the last dose. Complete remission was defined as UPCR < 0.02 g/mmol or proteinuria < 1+ 3 days consecutively on a urinary dipstick. Partial remission was defined as follows: UPCR > 0.02 g/mmol but < 0.2 g/mmol, or the need of immunoadsorption sessions (IAds) to maintain a UPCR < 0.02 g/mmol. A failure was defined as a persistent UPCR > 0.2 g/mmol.

The reported ofatumumab regimens were assigned to one of three groups: “standard doses”, as described in the treatment of chronic lymphocytic leukemia and used by Basu in 2014 (300 mg/1.73 m² then 5 infusions of 2,000 mg/1.73 m² performed weekly) [18], ”low doses” (4 to 5 infusions of 750 mg/1.73 m² performed weekly), and “other doses” for those that were neither standard nor low doses. This last group mainly refers

to an 18-month long protocol of administration, with a dose of 300 mg/1.73 m^2 at first, then 2,000 mg/1.73m^2 at day 7 (D7), D14, month 6 (M6), M12, and M18.

GraphPad Prism software (version 7.04) was used for the statistical analysis and to generate the graphs.

The data were coded and used in accordance with the rule MR004 of the French data protection authority (CNIL).

6. Results

Fourteen patients were included in this study. Their characteristics are listed in Table 1 and a brief description of each patient is available online (Annexe: Supplementary material/Online Ressource 1). The male/female sex ratio was 2.5/1. The median age at the time of diagnosis was 6.8 [4.6-10.3] years. Ofatumumab was introduced at a median age of 13.8 [9.2-16.5] years. Four patients were classified in the ofatumumab “low dose” group, six in the “standard dose” group, and four in the “other dose” group.

The median time of follow-up after the first dose of ofatumumab was 10.5 [7.0-13.0] months.

Five of the patients (36%) exhibited SDNS, 3 (21%) had SRNS with native kidneys and 6 (43%) presented a post-transplantation recurrence of SRNS. All of them received steroids and a CNI as previous therapy; RTX was administered to 13 patients (93%). The median time between the last RTX infusion and introduction of ofatumumab was of 3.0 [2.5-19.2] months. Seven patients (50%) needed IAds to control the proteinuria before being placed on ofatumumab. IAds were provided to six patients who still had their own kidneys and one patient who had already been transplanted. IAds were ineffective in six of the patients, who were then transplanted (or retransplanted), before receiving ofatumumab. In these cases, the NS relapsed immediately post-transplantation and was again managed by IAds, which were then more successful at controlling the proteinuria.

The treatment and outcomes of the patients are presented in Table 2 and data on additional treatments and biology are showed in Table 3. Ofatumumab led to remission (either complete or partial) in 11 patients (79%). Complete remission was achieved in

six cases (43%), 5 with SDNS and 1 with SRNS. A partial remission or a reduction of the IAds frequency was observed in five cases (36%), 2 with SRNS and 3 with a post-transplantation recurrence. Of note, for patient 10, the IAds were still being provided 6 months after the last dose of ofatumumab but sustained complete remission persisted after discontinuation of IAds. No remission was observed 6 months after the last dose of ofatumumab for three of the patients, who all presented a recurrence of the NS after transplantation.

B-cell depletion was obtained in 12/14 cases and lasted for a median time of 9.3 [5.3-11.8] months. The B-cell count was not monitored in two patients because ofatumumab was not effective. Unexpectedly, the duration of the B-cell depletion was reduced with the standard doses compared with the two other regimens (Figures 1A and 1B).

Comparison of the groups of patients in “complete remission, “partial remission”, and “no remission” showed that the median time of B-cell depletion seemed to be longer in the group in “complete remission”: 11.5 [8.3-14.3] months versus 6.0 [4.0-7.5] months in “partial remission”, and 9 months in “no remission” (Figure 1C).

All patients who exhibited SDNS were in complete remission after ofatumumab (Figure 2A) whereas the absence of remission was only observed in the post-transplantation recurrence group. Ofatumumab was clearly more effective with native kidneys, as all the of patients in this group were in remission after the treatment, whereas 50% (3/6) of the transplanted patients were not in remission (Figure 2A). All of the patients in remission (either complete or partial) received low or other doses (Figure 2B). Moreover, most of the patients without remission received standard doses (2/3).

An allergic reaction was observed in eight patients (57%) during the first infusion. The reported symptoms were mostly urticaria, pharyngeal itching, and abdominal pain. These were resolved by the administration of steroids and antihistamine. None of the patients needed administration of adrenaline.

One patient developed chronic anemia while he had chronic kidney disease, and another patient exhibited neutropenia after ofatumumab treatment that lasted several weeks despite the withdrawal of potentially responsible medications. In five out of eight cases (data was missing for six patients) there was hypogammaglobulinemia < 7 g/L. One patient with severe post-transplantation recurrence of NS died of infection 4 months after the last dose of ofatumumab, as a consequence of multiple factors. No malignancies were observed at time of report but the patients have to be followed-up longer to see if such diseases will happen.

7. Discussion

This is the largest cohort of children with severe NS treated with ofatumumab described to date. Eleven patients (79%) out of 14 achieved either partial or complete remission at 6 months.

NS is usually initially managed with steroids and 90% of the children respond to corticosteroids within 4 weeks of therapy. However, some SDNS or the remaining SRNS can be a challenge to treat. The ensuing chronic proteinuria leads to glomerular fibrosis and diffuse mesangial sclerosis [3]. This gives rise to chronic renal disease, which entails a multitude of complications, in addition to the complications stemming from the NS itself. Even after a kidney transplantation, up to 50% of SRNS cases relapse [24–28], with a risk of graft loss due to persistent proteinuria.

One of the alternatives is the administration of a CNI [4, 6–8, 29, 30]. These are used as steroid-sparing agents, limiting their adverse effects (growth delay in particular) that can occur especially when they are administered for a long time. The use of CNI can also induce a complete remission without any relapse. In clinical practice, CNI are usually given for a minimum of two years, although they can be maintained longer if there is a relapse upon dose reduction or withdrawal. Unfortunately, CNI also have adverse effects, such as acute and chronic nephrotoxicity, through thrombotic microangiopathy, arteriolar hyalinosis, and interstitial fibrosis [31], limiting their use for years. In this cohort, none of the patients remained in complete remission with a CNI, and all of them required other treatments, such as MMF, an anti-CD20 mAb, and/or IAds.

Plasmapheresis and IAds have been reported to be effective when previous therapies fail to result in a complete remission, especially in a post-transplantation context [32–

36]. This finding supports the notion of an immunological origin of the INS, with the presumed elimination of a circulating factor that has yet to be identified.

RTX is a chimeric anti-CD20 mAb and it is an option when a CNI is not sufficient to achieve a complete remission, or when the patient is dependent on this medication with side effects [12–15, 17, 37]. However, RTX is not always successful (50 to 100% remission in SDNS and approximately 50% in SRNS) [10, 11] and there is no consensus regarding alternative treatments.

Ofatumumab is a second-generation anti-CD20 mAb that was first used in chronic lymphocytic leukemia [38, 39]. Unlike RTX, which is a chimeric immunoglobulin composed of a murine Fab fragment paired with a human Fc fragment, ofatumumab is a fully human mAb [40, 41]. It is produced in a recombinant murine cell line from transgenic mice and is composed of both human Fab and Fc fragments. It binds to an epitope on the CD20 transmembrane protein on B lymphocytes and results in a higher affinity than RTX [40]. Ofatumumab is also better at recruiting C1q and hence at activating the classical complement pathway [42]. This enhances complement-dependent cytotoxicity in vitro [43, 44]. The aim is to deplete CD20+ B cells for longer. The efficacy of these anti-CD20 mAbs is being assessed in steroid-dependent NS in a phase II clinical trial (ClinicalTrials.gov Identifier: NCT02394119) currently ongoing [45].

The hypothesis of a direct effect of RTX on podocytes, protecting actin cytoskeleton and viability by binding to sphingomyelin-phosphodiesterase-acid-like-3b, is not supported by the molecular mechanisms of the effect of anti-CD20 mAbs [46]. Indeed, the epitopes targeted by ofatumumab and RTX are different, although both may induce a remission in some cases. In addition, no data have been published to date regarding

an effect of ofatumumab on podocytes. The activity observed in this cohort suggests that there may be an effect on CD20+ cells.

Prior to the present study, 19 children with resistant NS treated with ofatumumab had been reported, including 3 in a post-transplantation context [18–23, 47]. Ofatumumab was introduced due to RTX resistance in 15 of them (7 had initial resistance, 4 had late resistance, and 4 were undetermined) and due to poor tolerance of the RTX in 4 cases. In 16 cases, ofatumumab led to remission (12 complete, 4 partial). Two patients did not respond to the treatment and the infusion could not be carried out in one patient due to a severe allergic reaction.

In this French cohort, ofatumumab led to total B-cell depletion in at least 12 cases, with a median time of depletion of more than 9 months. For the patients who received the higher doses, the renewed increase in B-cell numbers occurred earlier than for the others, and the patients with systematic infusions at D0-D7-D14-M6 still had B-cell depletion at 6 months. This result needs to be interpreted with a degree of caution in light of the small number of the reported cases and the unequal durations of follow-up. The optimal dose and the schedule for administration of ofatumumab infusions is a matter of debate and is not consensual in this indication in children.

Six months after the last dose of ofatumumab, six of the patients (43%) were in complete remission and five (36%) were in partial remission. The patients with SDNS presented a better response to the treatment than the ones with SRNS on native kidneys or post-transplantation recurrence. Unfortunately, ofatumumab was not successful in three of the transplanted patients. The doses used in SDNS in this study were high compared to the ones that are found in the literature [20] or used in the clinical trial assessing the efficacy of ofatumumab vs RTX (1500mg/1.73m^2, one pulse) [45]. This could part of the efficacy of ofatumumab after RTX failure. Moreover, RTX

may be partially contributing to the control of the disease as the time between last RTX and ofatumumab introduction was short (3 months) in patients with SDNS. However, there must be other determining factors of the response to ofatumumab, such as the duration of the B-cell depletion, the initial steroid-resistance, the histological findings, and the context of the transplantation.

Regardless, the efficacy of ofatumumab is of clear relevance (almost 80% of the patients were in complete or partial remission) in these patients who exhibited severe NS, after failure of all of the previous therapies, and who no longer appeared to derive a benefit from the usual and conventional treatments.

The infusions were well tolerated overall, despite the fact that severe adverse effects have been reported previously [48, 49]. We only noticed mild or minor drug reactions during the first infusion in more than half of patients, such as a rash, pharyngeal itching, abdominal pain, vomiting, and dyspnea. There were no severe reactions, and none were life-threatening. This is thought to be due to humanization of the mAb, which may hence be less antigenic. In all of the cases, the symptoms decreased after the administration of an antihistamine and steroids. Another advantage of ofatumumab is that it may be less prone to the development of a secondary immunization against a murine fragment. Despite these characteristics, it requires the administration of a premedication [21], especially prior to the first infusion, and a lower dose can be administered initially to evaluate the tolerance [18].

No malignancies were reported after the infusions, with a median time of follow-up of 10.5 months, which is short to see such complication, and 1 transplanted patient died of infection. This last one had a severe NS and imputability of ofatumumab is difficult to assess, but it has to be reported. Five patients presented hypogammaglobulinemia

after ofatumumab treatment. As a result, supplementation with immunoglobulins may be warranted after ofatumumab treatment.

8. Conclusion

Ofatumumab appears to be a suitable alternative in multidrug-resistant nephrotic syndromes in children and in case of allergy to RTX. It can lead to a complete or a partial remission in most of the patients who are otherwise hard to treat and often dependent on IAds. In post-transplantation recurrences, its use remains an option, although it does appear to be less effective, probably as a result of the severity of the disease. The infusions were well tolerated. However, these findings should be confirmed in further studies. Moreover, the doses still need to be established with a standardized protocol for children in this indication.

The merchandizing authorization for ofatumumab was removed. It is still available in some situations but requires a special request.

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10. Tables

Table 1: Characteristics of the patients.

Characteristics		SDNS		SRNS		Post-tx recurrence		Total	
		n or median	% or IQ range	n or median	% or IQ range	n or median	% or IQ range	n or median	% or IQ range
Number of patients		5	36%	3	21%	6	43%	14	100%
Male/Female		3/2	21%/14%	3/0	21%/0%	4/2	29%/14%	10/4	71%/29%
Age at diagnosis (years)		7.5	2.8-10.3	10.0	5.0-13.0	5.5	4.4-10.4	6.8	4.6-10.3
Age at OFA introduction (years)		11.7	9.2-15.5	12.9	5.6-15.1	16.0	9.2-17.8	13.8	9.2-16.5
Age at report (years)		13.0	10.0-16.5	13.0	6.5-16.0	17.3	10.5-20.0	14.0	10.0-17.6
Time diagnosis-OFA (years)		5.2	1.2-9.9	2.1	0.6-2.9	6.7	4.8-9.7	5.3	2.0-8.0
Previous therapy:	Steroids	5	36%	3	21%	6	43%	14	100%
	Calcineurin inhibitor	5	36%	3	21%	6	43%	14	100%
	MMF	5	36%	2	14%	4	29%	11	79%
	RTX	4	29%	3	21%	6	43%	13	93%
	Abatacept	0	0%	0	0%	1	7%	1	7%
	IAds/Plasmapheresis	0	0%	1	7%	6	43%	7	50%
	Tocilizumab	1	7%	0	0%	1	7%	2	14%
	IVIG	1	7%	0	0%	1	7%	2	14%
Time last RTX-OFA introduction (months)		3.1	1.0-11.2	2.2	1.8-2.8	14.5	3-28.2	3.0	2.5-19.2
Number of RTX		1.0	0.5-3.5	4.0	2.0-4.0	2.0	2.0-2.3	2.0	1.0-3.3
B-cell depletion before OFA (yes/no)		3/2	21%/14%	3/0	21%/0%	1/5	7%/36%	7/7	50%/50%
Ofatumumab regimen:	low dose	2	14%	1	7%	1	7%	4	29%
	standard dose	0	0%	2	14%	4	29%	6	43%
	other	3	21%	0	0%	1	7%	4	29%
Time of follow-up (months)		12.0	10.5-15.5	7.0	7.0-7.0	10.5	6.0-14.0	10.5	7.0-13.0
Response at 6 months:	complete remission	5	36%	1	7%	0	0%	6	43%
	partial remission	0	0%	2	14%	3	21%	5	36%
	no remission	0	0%	0	0%	3	21%	3	21%

OFA: Ofatumumab, SDNS: Steroid-dependent nephrotic syndrome, SRNS: Steroid-resistant nephrotic syndrome, tx: transplantation, IQ: interquartile, CNI: Calcineurin inhibitor, MMF: Mycophenolate mofetil, RTX: Rituximab, IAds: Immunoadsorption sessions, IVIG: Intravenous immunoglobulins

Table 2: Summary of the clinical and biological features of the patients.

Cases	Age at dg (years)	Age at tor (years)	NS	Tx	Previous therapy	Nb RTX	Time last RTX-OFA introduction (months)	B-cell depletion pre-OFA	OFA regimen	Response at M6	Duration of the response (months)	B-cells depletion (months)	Follow-up (months)
1	11	13	SDNS	0	CTC, MMF, CNI, RTX	1	2.9	Yes	750 mg/1.73 m² 4 times weekly	complete remission	12	12	12
2	3.5	17		0	CTC, MMF, CNI	0	No RTX	No	30 mg/1.73 m² (incomplete, stopped because of a severe allergic reaction) then 300 mg/1.73 m² then 2,000 mg/1.73 m² weekly then 1,600 mg/1.73 m² at 6 months from the last infusion	complete remission	13	13	13
3	2,1	10		0	CTC, MMF, CNI, RTX	1	0.3	No	300 mg/1.73 m² then 2,000 mg/1.73 m² then 2,000 mg/1.73 m² weekly then 1,300mg/1.73 m² at 6 months from the last infusion	complete remission	8	10	10
4	9.5	16		0	CTC, MMF, CNI, Tocilizumab, IVIG, RTX	6	13.8	Yes	2,000 mg/1.73 m² 3 times weekly, then 2,700 mg/1.73 m² at 6 months, then 2,000 mg/1.73 m² at 12 months and 1,300 mg/1.73 m² at 18 months	complete remission	18	18	18
5	7.5	10		0	CTC, MMF, CNI, RTX	1	3.3	Yes	750 mg/1.73 m² 5 times weekly	complete remission	11	11	11
6	10	13	SRNS	0	CTC, MMF, CNI, RTX	4	2.8	Yes	750 mg/1.73 m² 4 times weekly	complete remission	7	3	7
7	5	6.5		0	CTC, CNI, RTX, IAds	2	1.8	Yes	300 mg/1.73 m² then 2,000 mg/1.73 m² 5 times weekly	partial remission (IAds)	7	3	7
8	13	16		0	CTC, MMF, CNI, RTX, IAds	4	2.2	Yes	300 mg/1.73 m² then 2,000 mg/1.73 m² 5 times weekly	partial remission (IAds)	7	6	7
9	5	20	Post-tx rec	2	CTC, MMF, CNI, IAds, RTX, Aba	3	27.4	No	300 mg/1.73 m² then 2,000 mg/1.73 m² 5 times weekly then a single dose of 2,000 mg/1.73 m² due to the increase of the CD19	partial remission	9	9	14
10	2.5	6		1	CTC, MMF, CNI, IAds, RTX	2	3.0	No	300 mg/1.73 m² then 2,000 mg/1.73 m² 5 times weekly then a single dose of 2,000 mg/1.73 m² due to the increase of the CD19	partial remission (IAds)	8	6	13
11	6	15		1	CTC, MMF, CNI, IAds, RTX	2	30.7	No	750mg/1.73 m² 4 times weekly	partial remission (IAds)	6	5	6
12	13	20		1	CTC, MMF, CNI, Tocilizumab, IVIG, IAds, RTX	2	24.5	No	2000 mg/1.73 m² 3 times weekly, then 2,000 mg/1.73 m² at 6 months	no remission	4 months of partial remission	9.5	13
13	5	12		1	CTC, CNI, IAds, RTX	2	3.0	No	300 mg/1.73 m² then 2,000 mg/1.73 m² 5 times weekly	no remission	NA	MD	8
14	9.5	19.5		1	CTC, CNI, IAds, RTX	2	4.4	Yes	300 mg/1.73 m² then 2,000 mg/1.73 m² 5 times weekly	no remission	NA	MD	6

Dg: diagnosis, tor: time of report, NS: nephrotic syndrome, Tx: transplantation, Nb: number of, RTX: Rituximab, OFA: Ofatumumab, M: months, SDNS: Steroid dependent nephrotic syndrome, SRNS: steroid-resistant nephrotic syndrome, CTC: corticosteroids, MMF: mycophenolate mofetil, CNI: calcineurin inhibitor, IAds: immunoadsorption sessions, Aba: Abatacept, IVIG: intravenous immunoglobulins, NA: not applicable, MD: missing data

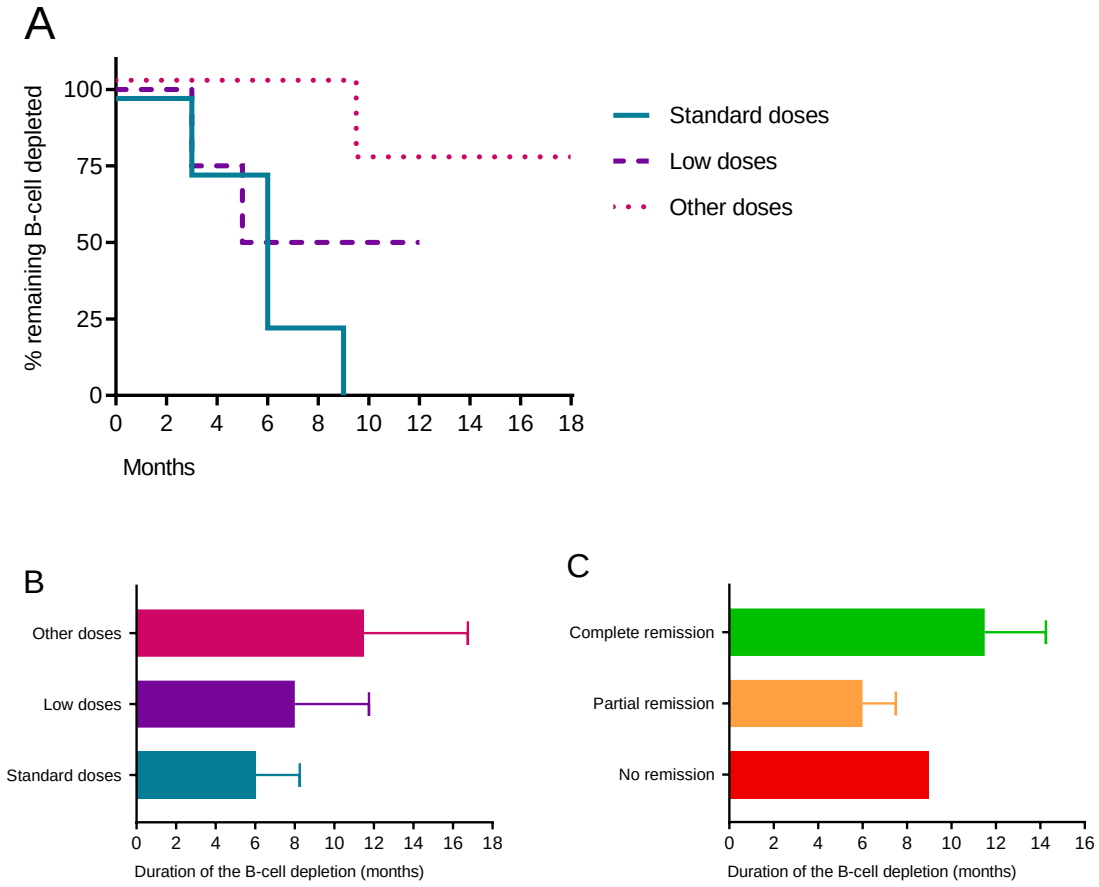
Table 3: Treatment at ofatumumab introduction and 6 months after the last infusion.

Patients	NS	At OFA introduction	At 6 months after the last OFA				
		Treatment	Treatment	UPCR (g/mmol)	Alb (g/L)	Serum creatinine (µmol/L)	Response
1	SDNS	CTC, CNI	CNI	0.018	34.7	55	complete remission
2		CTC, CNI, MMF	None	< 0.02	46	58	complete remission
3		CTC, CNI	None	< 0.02	> 30	35	complete remission
4		CTC, CNI	CTC	< 0.02	MD	MD	complete remission
5		CTC, CNI	CTC (lower dose), CNI	0.02	34.9	42	complete remission
6	SRNS	CTC, CNI	MD	0.017	40	38	complete remission
7		CTC, CNI, IAds	CNI, IAds (spaced)	0.1	30.6	MD	partial remission (IAds)
8		IAds	IAds (spaced)	0.009	40.8	47	partial remission (IAds)
9	Post-tx recurrence	CNI, MMF, IAds	CNI, MMF	0.13	35	94	partial remission
10		CTC, CNI, MMF, IAds	CNI, MMF, IAds (spaced)	0.03	44	77	partial remission (IAds)
11		CTC, CNI, MMF, IAds	CTC, CNI, MMF, IAds (spaced)	0.094	35.3	79	partial remission (IAds)
12		CNI, MMF, IAds	CNI, MMF, CTC, IAds (spaced)	0.23	35	94	no remission
13		CTC, CNI, IAds	CTC, CNI, IAds	0.44	29	58	no remission
14		CTC, CNI, IAds	Deceased	M4: 1.26	M4: 30.7	M4: 248	no remission

NS: nephrotic syndrome, OFA: Ofatumumab, UPCR: Urine protein/creatinine ratio, Alb: Albumine, SDNS: Steroid dependent nephrotic syndrome, SRNS: steroid-resistant nephrotic syndrome, tx: transplantation, CTC: corticosteroids, MMF: mycophenolate mofetil, CNI: calcineurin inhibitor, IAds: immunoadsorption sessions, M: months, MD: missing data

11. Figures

Figure 1: B-cell depletion

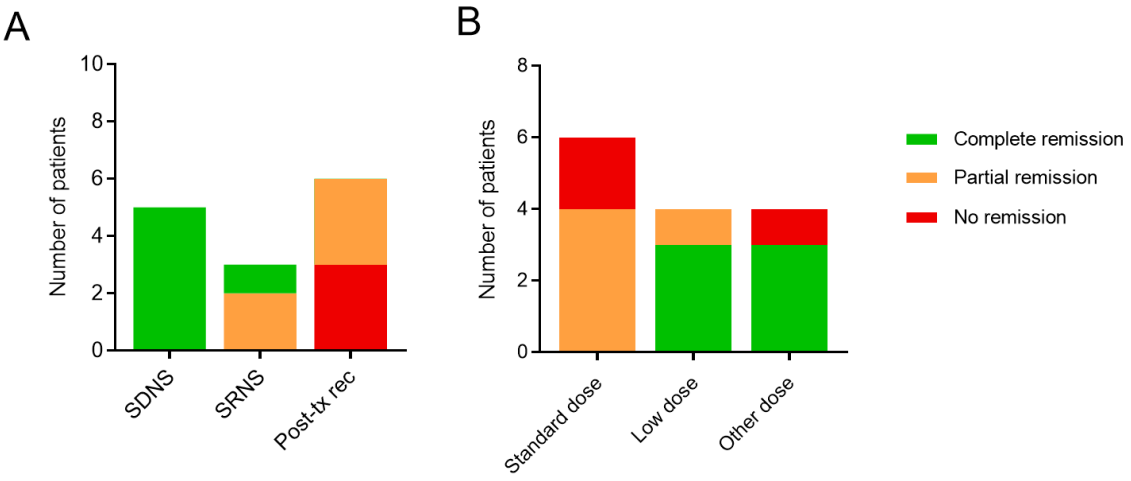


A: Survival curve comparing the percentage of patients with sustained B-cell depletion in the 3 treatments groups (n=4 in each group). Standard doses: 300 mg/1.73 m² then 2,000 mg/1.73 m² x5 weekly, Low doses: 750 mg/1.73 m² x4-5 weekly, Other doses: variable doses with systematic infusions at D0, D7, D14, and M6.

B: Histogram showing the median of the duration of the B-cell depletion with the interquartile range in the 3 treatments groups (n=4 in each group). Standard doses: 300 mg/1.73 m² then 2.000 mg/1.73 m² x5 weekly, Low doses: 750 mg/1.73 m² x4-5 weekly, Other doses: variable doses with systematic infusions at D0, D7, D14, and M6.

C: Histogram showing the median of the duration of the B-cell depletion depending on the response at 6 months after the last dose of ofatumumab. Complete remission n=6, partial remission n=5, no remission n=1 (data not available for the 2 other patients without remission).

Figure 2: Response



A: Histogram showing the response at 6 months after the last dose of ofatumumab depending on the type of nephrotic syndrome. SDNS: Steroid-dependent nephrotic syndrome (n=5), SRNS: Steroid-resistant nephrotic syndrome (n=3), Post-tx rec: post-transplantation recurrence (n=6).

B: Histogram showing the response at 6 months after the last dose of ofatumumab depending on the doses that were administered. Standard dose: n=6, Low dose: n=4, Other dose: n=4.

III. Discussion et conclusion

Il s'agit de la plus grande cohorte d'enfants atteints de SN grave traités par ofatumumab décrite à ce jour. Onze patients sur 14 (79%) étaient en rémission partielle ou complète à 6 mois.

La prise en charge initiale du SN consiste en l'administration de corticostéroïdes. Parmi ces patients, 90% y répondent dans les 4 semaines suivant l'instauration du traitement. Cependant, certains SNCD et les SNCR peuvent être difficiles à traiter. La protéinurie chronique qui en résulte conduit à une fibrose glomérulaire [3]. Cela à pour conséquence une maladie rénale chronique, qui entraîne une multitude de complications, ajoutées aux complications du SN en lui-même. Après une transplantation rénale, jusqu'à 50% des cas de SNCR rechutent [24–28], avec un risque de perte du greffon du fait de la protéinurie persistante.

L'une des alternatives est l'administration d'un anticalcineurine [4, 6–8, 29, 30]. Ceux-ci sont utilisés pour diminuer et/ou arrêter les corticostéroides, limitant leurs effets indésirables (retard de croissance en particulier), survenant surtout en cas d'administration prolongée. L'utilisation des anticalcineurines peut également induire une rémission complète sans aucune rechute. En pratique clinique, les anticalcineurines sont généralement administrés pendant au moins deux ans, mais ils peuvent être maintenus plus longtemps, en cas de rechute après réduction de la dose ou après leur interruption. Malheureusement, ces traitement présentent aussi des effets indésirables, notamment une néphrotoxicité aiguë et chronique, par microangiopathie thrombotique, hyalinose artériolaire et fibrose interstitielle des reins [31], limitant leur utilisation sur le long terme. Dans cette cohorte, aucun patient n'est resté en rémission complète avec un anticalcineurine et tous ont eu besoin d'autres

traitements, tels que le MMF, le rituximab (un anticorps monoclonal anti-CD20) et/ou des IAds.

La plasmaphérèse et les IAds ont montré leur efficacité lorsque les traitements antérieurs ne permettaient pas d'obtenir une rémission complète, en particulier dans un contexte post-transplantation [32–36]. Cet élément est en faveur d'une origine immunologique du SN, avec l'élimination présumée d'un facteur circulant qu'il reste à identifier.

Le RTX est un anticorps monoclonal anti-CD20 chimérique. Il est envisagé lorsque l'utilisation d'un anticalcineurine n'est pas suffisante pour obtenir une rémission complète ou lorsque le patient est dépendant de ce médicament avec des effets secondaires [12-15, 17, 37]. Cependant, le RTX est parfois inefficace (rémission dans 50 à 100% des cas dans les SNCD et environ 50% dans les SNCR) [10, 11] et il n'existe pas de consensus quant aux traitements alternatifs.

L'ofatumumab est un anticorps monoclonal anti-CD20 de deuxième génération qui a été utilisé pour la première fois dans la leucémie lymphoïde chronique [38, 39]. Contrairement au RTX, qui est une immunoglobuline chimérique composée d'un fragment Fab murin couplé à un fragment Fc humain, l'ofatumumab est un anticorps monoclonal entièrement humain [40, 41]. Il est produit dans une lignée de cellules murines recombinantes provenant de souris transgéniques et est composé de fragments Fab et Fc humains. Il se lie à un épitope de la protéine transmembranaire CD20 des lymphocytes B et comporte une affinité supérieure à celle du RTX [40]. L'ofatumumab est également plus efficace dans le recrutement du C1q et donc dans l'activation de la voie classique du complément [42]. Cela améliore la cytotoxicité dépendante du complément in vitro [43, 44]. L'objectif est d'aboutir à une déplétion des cellules B CD20+ pendant une plus longue durée. L'efficacité de ces anticorps

monoclonaux anti-CD20 est en cours d'évaluation chez les patients atteints de SNCD dans le cadre d'un essai clinique de phase II (ClinicalTrials.gov Identifier: NCT02394119) [45].

L'hypothèse d'un effet direct du RTX sur les podocytes, en préservant leur cytosquelette d'actine et leur viabilité via une liaison à la sphingomyelin-phosphodiesterase-acid-like-3b, n'est pas étayée par les mécanismes moléculaires de l'effet des anti-CD20 [46]. En effet, les épitopes ciblés par l'ofatumumab et le RTX sont différents, bien que les deux induisent une rémission dans certains cas. De plus, aucune donnée n'a été publiée à ce jour concernant un effet de l'ofatumumab sur les podocytes. Les effets observés dans cette cohorte suggèrent un effet direct de ces traitements sur les cellules CD20+.

Avant cette étude, 19 cas d'enfants atteints de SN résistants traités par ofatumumab avaient été rapportés, dont 3 dans un contexte post-transplantation [18–23, 47]. L'ofatumumab a été introduit en raison d'une résistance au RTX chez 15 d'entre eux (7 présentaient une résistance initiale, 4 une résistance tardive) et en raison d'une mauvaise tolérance du RTX dans 4 cas. Dans 16 cas, l'ofatumumab a permis une rémission (12 complètes, 4 partielles). Deux patients n'ont pas répondu au traitement et la perfusion n'a pas pu être réalisée chez un patient en raison d'une réaction allergique grave.

Dans cette cohorte française, l'ofatumumab a permis une déplétion totale des lymphocytes B dans 12 cas sur 14, avec une période de déplétion médiane supérieure à 9 mois. Le compte de lymphocytes B n'avait pas été suivi chez les 2 patients restants du fait de l'absence de réponse. De façon inattendue, pour les patients qui ont reçu les doses les plus élevées, la réascension des lymphocytes B est survenue plus tôt que pour les autres. Les patients avec des perfusions systématiques à J0-J7-J14-M6

ont présenté une persistance de la déplétion en lymphocytes B à 6 mois. Ce résultat doit être interprété avec une certaine prudence compte tenu du petit nombre de cas rapportés, des modalités différentes et des durées inégales de suivi. La posologie optimale et le rythme d'administration des perfusions d'ofatumumab font l'objet de discussions et ne sont pas consensuels dans cette indication chez l'enfant.

Six mois après la dernière dose d'ofatumumab, six patients (43 %) étaient en rémission complète et cinq (36%) étaient en rémission partielle. Les patients présentant un SNCD ont mieux répondu au traitement par rapport à ceux qui avaient un SNCR ou une récurrence après transplantation. Malheureusement, l'ofatumumab n'a pas été efficace chez trois des patients transplantés. Les doses utilisées dans cette étude dans le SNCD sont élevées par rapport à celles décrites dans la littérature [20] ou utilisées dans l'essai thérapeutique évaluant l'efficacité de l'ofatumumab contre le RTX (1500mg/1.73m², une seule injection) [45]. Ceci peut expliquer en partie l'efficacité de l'ofatumumab après un échec du RTX. De plus, le RTX pourrait contribuer partiellement au contrôle de la maladie puisque le délai entre la dernière injection de RTX et l'introduction de l'OFA était court (3 mois) dans le groupe SNCD. Cependant, il doit exister d'autres facteurs conditionnant la réponse à l'ofatumumab, tels que la durée de déplétion des lymphocytes B, la résistance initiale aux corticostéroïdes, l'histologie à la biopsie rénale et le contexte de transplantation.

Quoi qu'il en soit, l'ofatumumab semble être une alternative intéressante (avec près de 80% de rémission complète ou partielle) chez ces patients qui présentaient un SN grave, après échec des traitements conventionnels.

Les perfusions ont été globalement bien tolérées, bien que des effets indésirables graves aient été rapportés précédemment [48, 49]. Lors de la première perfusion, nous avons observé des réactions bénignes ou mineures chez plus de la moitié des patients,

telles une éruption cutanée, un prurit pharyngé, des douleurs abdominales, des vomissements et une dyspnée. Il n'y a pas eu de réactions graves et aucune n'a été mortelle. Nous supposons que cela est dû au caractère humain de l'anticorps, qui serait donc probablement moins antigénique. Dans tous les cas, les symptômes ont répondu à l'administration d'un antihistaminique et de corticostéroïdes. Un autre avantage de l'ofatumumab est qu'il serait moins suceptible à une immunisation secondaire contre un fragment murin de l'anticorps. Malgré ces caractéristiques, une prémédication reste nécessaire [21], en particulier avant la première perfusion, et une dose plus faible peut être administrée initialement pour évaluer la tolérance [18].

Aucune complication tumorale n'a été signalée après les perfusions, avec un temps de suivi médian de 10,5 mois, ce qui est insuffisant pour affirmer l'absence de ce type de complication, et 1 patient transplanté est décédé suite à une infection. Ce dernier présentait un SN très sévère et l'imputabilité de l'ofatumumab est difficile à démontrer, mais cet événement doit être pris en compte. Cinq patients ont présenté une hypogammaglobulinémie après le traitement par ofatumumab. Par conséquent, une supplémentation en immunoglobulines peut être justifiée.

Au total, l'ofatumumab apparaît comme une alternative intéressante dans les SN multi-résistants de l'enfant et en cas d'allergie au RTX. Une rémission complète ou partielle est obtenue dans la majorité des cas, chez des patients qui sont difficiles à traiter et souvent dépendants des IAds. Dans les récurrence post-transplantation, son utilisation reste une option, cependant il semble être moins efficace dans ce contexte, probablement en lien avec la sévérité de la maladie chez ces patients. Les injections ont été bien tolérées dans l'ensemble. Néanmoins, ces éléments doivent être

confirmés dans d'autres études. En particulier, il reste à définir les doses optimales et un protocole standardisé dans cette indication chez l'enfant.

L'autorisation de mise sur le marché de l'ofatumumab a été retirée. Il est toujours possible de se procurer le médicament dans certaines situations mais nécessite une autorisation particulière.

IV. Annexe : Supplementary material

Patient 1

Patient 1 was diagnosed with NS at 11 years of age. As he exhibited SDNS, he was treated with MMF and a CNI was then introduced. After several months, RTX was initiated in order to withdraw the steroids and the CNI, but a single infusion did not lead to complete and persistent remission, despite effective B-cell depletion. Four infusions of 750 mg/1.73 m² of ofatumumab were performed 8 months after the diagnosis of the NS. These resulted in a complete remission with good tolerance of the treatment, despite transient hypogammaglobulinemia. At 6 months after the last dose of ofatumumab, the patient's UPCR was 0.018 g/mmol, the albuminemia was 34.7 g/L, and the serum creatinine was 55 µmol/L.

Patient 2

Patient 2 was diagnosed with NS at 3.5 years of age. It progressed towards SDNS. A CNI was introduced only 2 months after the diagnosis and maintained for more than 12 years due to relapses whenever the treatment was reduced. A renal biopsy revealed MCD 11 years after the diagnosis. Ofatumumab was administered 12 years after the diagnosis and led to a severe allergic reaction (30 mg/1.73 m² at the first infusion, uncomplete because of the reaction, then 300 mg/1.73 m² at day 7, 2000 mg/1.73 m² at day 14 and M6). Despite this reaction, the patient responded to the treatment, and MMF and CNI could be withdrawn several weeks after the second infusion. The tolerance was better with the subsequent infusions, after a premedication. At the time

of the report, B-cell depletion remained, and the patient was still in complete remission. At 6 months after the last infusion of ofatumumab, the UPCR was 0 g/mmol, the albuminemia was 40 g/L, and the GFR was normal.

Patient 3

The diagnosis of NS in patient 3 was made at 2.1 years of age. Although she was dependent to steroids, leading to treatment with MMF and then with a CNI. Despite cyclosporin A, with through levels > 100 ng/mL, the NS was not controlled and RTX was administered (375 mg/m², 1 dose). Unfortunately, the infusion had to be stopped due to an immediate and severe allergic reaction. Ofatumumab was then initiated one week later. A first infusion of 300 mg/1.73 m² was followed by 2 infusions of 2,000 mg/1.73 m², weekly. There was an allergic reaction following the first infusion (a rash, pharyngeal itching), less severe than the previous one and it resolved with dexchlorpheniramine and prednisone. Further infusions were performed at 6, 12, and 18 months. B-cell depletion was achieved and the patient was still in complete remission without other treatments for several months. At 6 months after the last infusion of ofatumumab, the UPCR was < 0.02 g/mmol and the albuminemia was > 30 g/L. There was no data regarding the serum creatinine.

Patient 4

This patient was diagnosed at 9.5 years of age with NS that was steroid-dependent. Firstly, it was not possible to taper the prednisone to below 60 mg/m² 1d/2. MMF was ineffective and a CNI was introduced 2 years after the diagnosis. Each time the steroids

were withdrawn, the proteinuria increased to nephrotic levels. Six infusions of RTX were performed weekly 3 years after the diagnosis and led to a partial remission, but the NS continued to relapse as soon as the CNI and the steroids were reduced. The tocilizumab, an anti-IL6 mAb, associated with IVIG, was introduced 4 years after the diagnosis, but the UPCR remained above 0.2 g/mmol. A renal biopsy performed 5 years after the diagnosis indicated MCD. Ofatumumab was administered just after the renal biopsy, with three infusions of 2,000 mg/1.73 m^2 weekly, then every 6 months over an 18-month period. This led to a complete remission that allowed withdrawal of the steroids and the CNI, without relapse of the NS to date. At 6 months after the last dose of ofatumumab, the patient's proteinuria was negative on the urinary dipstick, but no biological data was available.

Patient 5

This patient exhibited SDNS at 7.5 years of age. MMF was switched with a CNI, and then an infusion of RTX was performed 1.5 years after the diagnosis. This single injection failed to maintain a complete remission despite an effective depletion of B cells. Ofatumumab was introduced several weeks later at a dose of 750 mg/1.73 m^2, 5 times weekly. The infusions were well tolerated and led to a complete remission. At 6 months after the last infusion of ofatumumab, the UPCR was 0.02 g/mmol, the albuminemia was 34.9 g/L, and the serum creatinine was 42 µmol/L. The patient was still treated with a CNI.

Patient 6

Patient 6 was diagnosed with NS at 10 years of age. He was steroid-sensitive at first but developed SRNS at the first relapse. This led to the introduction of MMF and then a CNI. In order to withdraw tacrolimus, RTX was introduced 2.5 years after the diagnosis (4 infusions). This was ineffective, however, despite 7 months of B-cell depletion. Thereafter, he received four infusions of ofatumumab (750 mg/1.73 m^2 each, weekly), which were well tolerated. A complete remission was observed. At 6 months after the last dose of ofatumumab, the patient's UPCR was 0.017 g/mmol, the albuminemia was 40 g/L, and the serum creatinine was 38 µmol/L.

Patient 7

This patient was diagnosed with NS at 5 years of age. Due to steroid-dependency, a CNI was introduced. Two renal biopsies revealed FSGS, and genetic testing indicated no mutations. Unfortunately, the NS relapsed and was managed with IAds to ensure a complete remission. However, even after two infusions of RTX, the IAds could not be stopped. Ofatumumab was administered 8 months after the diagnosis (300 mg/1.73 m^2 the first time, then 2000 mg/1.73 m^2 5 times weekly). This led to a partial remission and the IAds could be spaced further apart but were maintained once a week due to persistence of the proteinuria. The first infusion was tolerated poorly, with pharyngeal itching and abdominal pain. At 6 months after the last dose of ofatumumab, the UPCR was 0.1 g/mmol, the albuminemia was 30.6 g/L, and there was no data available regarding the serum creatinine.

Patient 8

This patient exhibited SRNS at 13 years of age. MMF and a CNI were introduced without success. Two infusions of RTX were then performed, which were not effective at maintaining persistent negative proteinuria. IAds were started 7 months after the diagnosis and two other infusions of RTX were provided while the patient was in remission. Unfortunately, the NS relapsed several weeks after the infusions, leading to resumption of the daily IAds. The renal biopsies revealed either MCD or FSGS. Soon after, ofatumumab was administered (300 mg/1.73 m^2 once and then 5 x 2,000 mg/1.73 m^2 25 months after the diagnosis), which allowed the IAds to be spaced further apart. The patient exhibited urticaria at the first infusion. A supplemental infusion was performed 6 months after the last one due to renewal of the CD20+ cells but without a relapse of the NS. The IAds could be spaced progressively to once a month at the last follow-up. At 6 months after the 6^{th} infusion of ofatumumab, the UPCR was 0.009 g/mmol, the albuminemia was 40.8 g/L, and the serum creatinine was 47 µmol/L.

Patient 9

Patient 9 has already been described [22]. The patient was diagnosed with SRNS at 5 years of age. She developed ESRD, with FSGS, followed by a first renal transplantation. The NS relapsed, leading to a loss of the transplanted kidney within 3 years, and a second renal transplantation was performed 5 years later. Due to the recurrence of the NS, IAds were initiated and led to a complete remission. The patient remained dependent on IAds, however, despite treatments with CNI, corticosteroids, RTX, and abatacept. Ofatumumab was introduced and, as it maintained the remission, the IAds were stopped. Another infusion of ofatumumab was administered 8 months

after the last one, due to the recurrence of the NS and a renewed increase in B-cell numbers. Although it did not result in complete remission, the proteinuria was stabilized in the absence of IAds. One year after the last infusion of ofatumumab, the UPCR was 0.31 g/mmol, the albuminemia was 33 g/L, and the serum creatinine was 109 µmol/L.

Patient 10

Patient 10 was diagnosed with SRNS at 2.5 years of age. Tacrolimus was introduced shortly after the diagnosis but it lacked efficacy. A renal biopsy revealed MCD and no mutations were found in a panel of 26 specific genes. Therefore, daily IAds were provided, but they turned out not to be effective either. The patient progressed to ESRD and he was transplanted 2.5 years after the diagnosis. The NS relapsed immediately despite an immunosuppressive regimen with CNI, MMF, and steroids. IAds were provided again. These proved to be effective and allowed the use of RTX one-week post-transplantation. Two infusions were performed, but as the proteinuria persisted, the IAds were maintained, daily at first, then slowly tapered over the ensuing months. Ofatumumab was introduced 4 months after the transplantation (a first infusion of 300 mg/1.73 m^2 and 5 others of 2,000 mg/1.73 m^2, weekly). Another infusion was provided 9 months later due to a renewed increase in the number of B cells but without a relapse of the NS. The first infusion was followed by abdominal pain and vomiting. It led to a progressive withdrawal of the IAds, which were stopped eight months after the introduction of ofatumumab. The last transplant biopsy, performed 1 year post-transplantation, revealed cellular rejection and tubilitis, but no FSGS. One year after the last infusion of ofatumumab, the UPCR was 0.016 g/mmol, the albuminemia was

44.7 g/L, but the serum creatinine had increased to 94 µmol/L, probably due to toxicity of the calcineurin inhibitor and cellular rejection based on the renal biopsy.

Patient 11

Patient 11 was diagnosed with SRNS at 6 years of age, with no persistent or complete remission despite the use of MMF and CNI. IAds were initiated 4.5 years after the diagnosis, over a period of 18 months, but they were not sufficient to achieve a complete remission of the NS. The chronic and nephrotic proteinuria led to ESRD, and a first renal transplantation was performed 6 years after the diagnosis. As relapse of the NS occurred immediately on the graft, IAds were introduced and two infusions of RTX were administered. These did not result in remission and the patient remained dependent on IAds. Ofatumumab was considered 3 years post-transplantation. Four infusions of 750 mg/1.73 m² were performed, but they were only partially effective despite complete depletion of the B cells for 6 months. The patient was still dependent on IAds every 3 weeks at the last follow-up. At 6 months after the last infusion of ofatumumab, the UPCR was 0.09 g/mmol, the albuminemia was 35 g/L, and the serum creatinine was 79 µmol/L.

Patient 12

Patient 12 exhibited SRNS at 13 years of age. MMF, CNI, and tocilizumab with IVIG only reduced the proteinuria to around 0.2 g/mmol. IAds were introduced 8 months after the diagnosis every 2 days over a 3-week period, but they were not effective either. The renal biopsy revealed cellular proliferation and chronic tubulointerstitial

lesions. A double nephrectomy was carried out and a first transplantation was then performed 3.5 years after the diagnosis (1.5 years after the double nephrectomy). The NS relapsed within several days. This led to two infusions of RTX and IAds, which resulted in a partial response. Ofatumumab was administered 1 month after the transplantation (4 infusions of 2, 000 mg/1.73 m² were administered at D0-D7-D14-M6). This led to a partial remission, but it did not allow the IAds to be withdrawn (spaced to 1 session every 10 days). At 6 months after the last infusion of ofatumumab, the UPCR was in the nephrotic range (0.26 g/mmol), the albuminemia was 35 g/L, and the serum creatinine was 94 µmol/L.

Patient 13

This patient was diagnosed with SRNS at 5 years of age. Despite the introduction of a CNI, the proteinuria still exceeded the nephrotic range and IAds were performed 2 years after the diagnosis. Due to ESRD, a double nephrectomy and a first transplantation were performed 5 years after the diagnosis. A relapse of the NS occurred shortly thereafter and was only partially controlled by the IAds. Two infusions of RTX were not effective and ofatumumab was introduced 4 months after the transplantation. Six doses were administered, with urticaria occurring after the first dose. Unfortunately, this failed to result in remission, and 6 months after the last infusion, the UPCR was still in the nephrotic range (0.44 g/mmol), the albuminemia was 29 g/L, and the serum creatinine had increased to 58 µmol/L. Of note, there was transient neutropenia after the infusions of ofatumumab that persisted for several weeks despite interruption of the potentially responsible treatments.

Patient 14

This patient exhibited SRNS at 9.5 years of age. The renal biopsy revealed MCD. As he had only arrived in France in 2015, data prior to this date were not available. The chronic proteinuria led to ESRD and hemodialysis. A first transplantation was performed 7 years after the diagnosis, along with IAds and two infusions of RTX. As the proteinuria relapsed immediately, the IAds were continued on 6d/7. There was a partial response, but the proteinuria increased as soon as the sessions were spaced further apart. Therefore, ofatumumab was introduced 5 months after the transplantation (6 doses). Unfortunately, despite the infusions, there was no remission. At 4 months after the last dose of ofatumumab, the UPCR was 1.26 g/mmol, the albuminemia was 30.7 g/L, and the serum creatinine was 248 µmol/L. The patient died 4 months after the last dose of ofatumumab secondary to sepsis of digestive origin.

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Titre de Thèse :

Ofatumumab dans le traitement des syndromes néphrotiques cortico-dépendants et cortico-résistants de l'enfant

Ofatumumab treatment in children with steroid-dependent and steroid-resistant nephrotic syndrome

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RESUME (10 lignes)

Les syndromes néphrotiques cortico-dépendants (SNCD) et cortico-résistants (SNCR) peuvent être difficiles à traiter, avec une évolution vers l'insuffisance rénale terminale. L'ofatumumab, un anticorps monoclonal anti-CD20 humain, s'est révélé efficace chez des enfants atteints d'un SN résistant au rituximab. Quatorze patients ont été inclus rétrospectivement dans cette étude. Cinq avaient un SNCD et neuf un SNCR. Six enfants ont été traités après une transplantation rénale. Onze patients (79%) étaient en rémission à 6 mois de la dernière dose d'ofatumumab, complète pour 6 (43%) et partielle pour 5 (36%). Huit patients ont présenté une réaction allergique mineure. Ces résultats suggèrent une efficacité et la bonne tolérance de l'ofatumumab dans le SN résistant au rituximab mais nécessitent des études complémentaires.

MOTS-CLES

Syndrome néphrotique, enfants, ofatumumab, HSF