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ORIGINAL ARTICLE

Ofatumumab for the treatment of childhood nephrotic syndrome

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Abstract
Background Ofatumumab is a humanized anti-CD20 monoclonal antibody that has recently garnered interest as a potential therapeutic agent for nephrotic syndrome. We report our center's experience in administering ofatumumab to five pediatric patients with idiopathic nephrotic syndrome.
Methods Between March 2015 and November 2016, five patients were treated with ofatumumab. One patient had post-transplant recurrent focal segmental glomerulosclerosis (FSGS) which had been resistant to plasmapheresis and numerous immunosuppressive agents. Four patients had nephrotic syndrome in their native kidneys, one with initial steroid-resistant disease and the others with subsequent development of steroid resistance. Two of the patients were treated with a desensitization protocol after experiencing hypersensitivity reactions to ofatumumab.
Results One patient did not complete ofatumumab treatment due to infusion reactions. Of the four remaining patients, three achieved complete remission after treatment, and one achieved partial remission. One of the patients achieving complete remission represents the first reported case of successful treatment of post-transplant recurrent FSGS using ofatumumab. Two patients who received ofatumumab with our desensitization protocol were able to complete their treatments after initially experiencing hypersensitivity reactions.
Conclusions Ofatumumab may be an effective treatment for refractory childhood nephrotic syndrome and post-transplant recurrent FSGS. A desensitization protocol may be helpful to address hypersensitivity reactions.

Keywords Ofatumumab · Nephrotic syndrome · Focal segmental · Glomerulosclerosis · Children

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Introduction

Treatment of nephrotic syndrome (NS) in children remains challenging. The current mainstay of therapy is prednisone/prednisolone given for weeks to months at presentation and with each disease relapse, exposing children to the adverse effects of steroids on metabolism, growth, and behavior [1]. Furthermore, 7.4–19.6% of children are resistant to corticosteroid therapy [2–4]. Second-line immunosuppressive agents used for those intolerant of or resistant to corticosteroids confer additional side-effects and have expected response rates of only 20–50% [5]. Patients who have treatment refractory NS inevitably progress to end-stage renal disease (ESRD) [6]. A further challenge is that focal segmental glomerulosclerosis (FSGS), one of the most common histologic subtypes of childhood NS, has a 15–30% risk of recurrence in transplanted kidneys [7]. Thus, identifying additional therapeutic agents is critical.

Ofatumumab is a human anti-CD20 monoclonal antibody indicated for the treatment of chronic lymphocytic leukemia. Recently, three reports on a total of 11 children were published on the use of ofatumumab for the treatment of refractory NS [8–10]. Remission was induced in nine of the reported 11 children with multi-drug resistant NS [8–10]. This has spurred the off-label use of ofatumumab for childhood NS treatment,

despite little information on dosing, efficacy, and side-effects in this disease.

We reviewed our center's experience with ofatumumab in childhood NS. Between March 2015 and November 2016, five patients were treated with ofatumumab, including four patients with NS involving their native kidneys and one patient with recurrence of FSGS in his transplanted kidney. Our approach to administering ofatumumab safely to those who had hypersensitivity reactions is also described.

Materials and methods

We performed a retrospective review of all pediatric NS patients treated with ofatumumab between March 2015 and November 2016 at the Children's Healthcare of Atlanta. There were five patients in total. All patients presented with NS between ages 1 and 18 years and had the clinical diagnosis of idiopathic NS {edema; urine protein/creatinine ratio (UPCR) > 2 mg/mg, or ≥ 300 mg/dL or 3 + protein on urine dipstick; and hypoalbuminemia ≤ 2.5 g/dL [1]}, without evidence of secondary causes (e.g., lupus). Clinical course and laboratory results were collected from the electronic medical records. Ofatumumab dosing, administration, and reported side-effects were obtained from the electronic medical records and confirmed with the dispensing pharmacy.

Ofatumumab regimen and desensitization protocol

We based our ofatumumab treatment protocol on the report by Basu, with a first dose of 300 mg/1.73 m^2 followed by 5 weekly doses of 2000 mg/1.73 m^2 [8]. Our dosing regimen and administration is described in Table 1. We subsequently developed a desensitization protocol (Table 1) for patients who developed hypersensitivity reactions with our standard ofatumumuab regimen. This protocol is adopted from that reported by Galvão and Castells [11] and was utilized for Patients 4 and 5. The protocol was used for those who had mild-to-moderate infusion reactions—i.e., skin and subcutaneous tissue findings only or features suggesting respiratory, cardiovascular, or gastrointestinal involvement without hypoxia, hypotension, or neurologic compromise, as defined by Brown [12].

Results

Patient 1

The patient is a 16-year-old male with onset of steroid-dependent (SD) NS at age 9 years. Renal biopsy showed minimal change disease (MCD) with mesangial immunoglobulin A deposition and mild mesangial hypercellularity. Mycophenolate mofetil (MMF), tacrolimus, and intravenously administered (IV) methylprednisolone failed to improve disease control, but adherence was poor. Two doses of IV rituximab 375 mg/m^2 were given in the fourth year after diagnosis (course #1), followed by a remission lasting approximately 8 months. Relapse occurred within 3 months after B-cell recovery (defined as CD19 > 5% of lymphocytes), whereupon he received another two doses of IV rituximab 375 mg/m^2 (course #2). This second course of rituximab did not result in depletion of B cells (defined as CD19 < 1% of lymphocytes), and the NS persisted despite ongoing high-dose prednisone therapy. He suffered numerous complications, including pulmonary emboli, deep vein thromboses, and arterial thromboses. Ofatumumab treatment was initiated 3 months after the second course of rituximab. He received a first dose of ofatumumab of 300 mg/1.73 m^2, followed by four weekly doses of 2000 mg/1.73 m^2. B-cell depletion was achieved by 1 week and persisted 5 months after the first dose. Remission was achieved within 3 weeks and lasted 13 months, whereupon a third course of IV rituximab, three doses of 375 mg/m^2, were given over a 6-week period. B-cell depletion was again achieved with the third course of rituximab, and NS remitted 2 months later. At his last follow-up, he had been in remission for 3 months.

Patient 2

The patient is a 13-year-old male with onset of steroid-resistant NS at age 3 years. Renal biopsy showed MCD. He experienced severe medication side-effects while on multiple immunosuppressants (prednisone, cyclosporine, MMF, and tacrolimus). IV rituximab 375 mg/m^2 was thus given 5 years after diagnosis, followed by some improvement in relapse frequency. Eight years following diagnosis, treatment with a second dose of rituximab was complicated by symptoms consistent with serum sickness. Thus, treatment with ofatumumab was initiated, but subsequently aborted when the patient developed rash and nasal congestion with the first dose. These symptoms resolved with IV methylprednisolone and diphenhydramine. At his last follow-up, he was having infrequent relapses on tacrolimus, MMF, and prednisone.

Patient 3

The patient is a 13-year-old male who was diagnosed with SDNS at 3 years of age. Renal biopsy showed diffuse foot process effacement and mesangial hypercellularity, suggestive of early FSGS. A therapeutic regimen of tacrolimus and IV methylprednisolone failed to improve disease control, and he suffered from severe steroid side-effects and disease complications, including pulmonary emboli. His condition progressed to ESRD 6 years after diagnosis, and the patient underwent deceased-donor renal transplantation 2 years later

Table 1 Ofatumumab regimen and desensitization protocol

Standard ofatumumab regimen[a]						
Premedications						
Drug	Route	Dose				
Acetaminophen	Oral	15 mg/kg (max 650 mg)				
Diphenhydramine	IV	0.5–1 mg/kg (max 50 mg)				
Methylprednisolone	IV	1 mg/kg (max 60 mg)				
Ofatumumab dose	Concentration	Rate (mL/h)				
Dose 1: 300 mg/1.73 m^2	300 mg/1.73 m^2 in 1000 mL 0.9% NaCl	Six incremental steps, 30 min each: 12, 25, 50, 100, 200, 300; Final step: 400				
Dose 2: 2000 mg/1.73 m^2 (max 2000 mg)	2000 mg/1.73 m^2 in 1,000 mL 0.9% NaCl	Same as Dose 1				
Dose 3: same as Dose 2	Same as Dose 2	4 incremental steps, 30 min each: 25, 50, 100, 200 Final step: 400				
Dose 4: same as Dose 2	Same as Dose 2	Same as Dose 3				
Dose 5: same as Dose 2	Same as Dose 2	Same as Dose 3				
Dose 6: same as Dose 2	Same as Dose 2	Same as Dose 3				
Desensitization protocol for patients with allergic reactions to ofatumumab						
Premedications						
Drug	Route	Dose				
Acetaminophen	Oral	15 mg/kg (max 650 mg)				
Diphenhydramine	IV	0.5–1 mg/kg (max 50 mg)				
Methylprednisolone	IV	1 mg/kg (max 60 mg)				
Cetirizine	Oral	5–10 mg				
Montelukast	Oral	5–10 mg				
Ranitidine	Oral	75–125 mg				
Infusion protocol for each ofatumumab dose[b]						
Step	Concentration (mg/mL)	Rate (mL/h)	Time (min)	Dose per step (mg)	Cumulative dose (mg)	Cumulative time (min)
1	0.04	2.5	15	0.025	0.025	15
2	0.04	5	15	0.05	0.075	30
3	0.04	10	15	0.1	0.175	45
4	0.04	20	15	0.2	0.375	60
5	0.40	5	15	0.5	0.875	75
6	0.40	10	15	1	1.875	90
7	0.40	20	15	2	3.875	105
8	0.40	40	15	4	7.875	120
9	1.98	10	15	4.96	12.835	135
10	1.98	20	15	9.92	22.755	150
11	1.98	40	15	19.84	42.595	165
12	1.98	80	15	39.68	82.275	180
13	1.98	120	15	59.53	141.805	195
14	1.98	160	15	79.37	221.175	210
15	1.98	200	15	99.21	320.385	225
16	1.98	240	210.6	1671.73	1992.115	435.6

IV, Intravenous; max, maximum

[a] Six weekly dose regimen as described by Basu [8]

[b] Adopted from protocol described by Galvão and Castells [11]

with basiliximab and methylprednisolone induction. Maintenance immunosuppression comprised MMF, tacrolimus, and prednisone. He rapidly displayed signs of disease recurrence with a UPCR of 8.04 mg/mg within 24 h following the procedure. He was then started on daily plasmapheresis beginning post-operative day (POD) 1. The plasmapheresis frequency was decreased to 4 days a week after nearly 3 weeks of daily treatment. Rituximab 375 mg/m^2 was given on POD 20 and 28, with no plasmapheresis for 48 h following each treatment to prevent drug removal. Additional treatments for the FSGS recurrence included twice weekly IV methylprednisolone 20 mg/kg and conversion of tacrolimus and MMF to cyclosporine and cyclophosphamide. Eight months after transplant, despite ongoing immunosuppressant therapy plus four sessions of plasmapheresis per week, severe proteinuria and edema persisted. Ofatumumab was then given at 300 mg/1.73 m^2 for the first dose, followed by five weekly doses of 2000 mg/1.73 m^2. Plasmapheresis sessions were withheld for at least 48 h following each ofatumumab dose to prevent drug removal. The patient developed itching and rash with the first infusion which resolved with a brief pause and treatment with IV diphenhydramine. The urine protein level dramatically downtrended thereafter (Fig. 1), becoming subnephrotic within 12 weeks following administration of the first ofatumumab dose. Plasmapheresis was stopped after completion of ofatumumab, and the patient was able to remain free of edema and maintain nearly normal serum albumin levels despite no longer receiving albumin replacement with plasmapheresis.

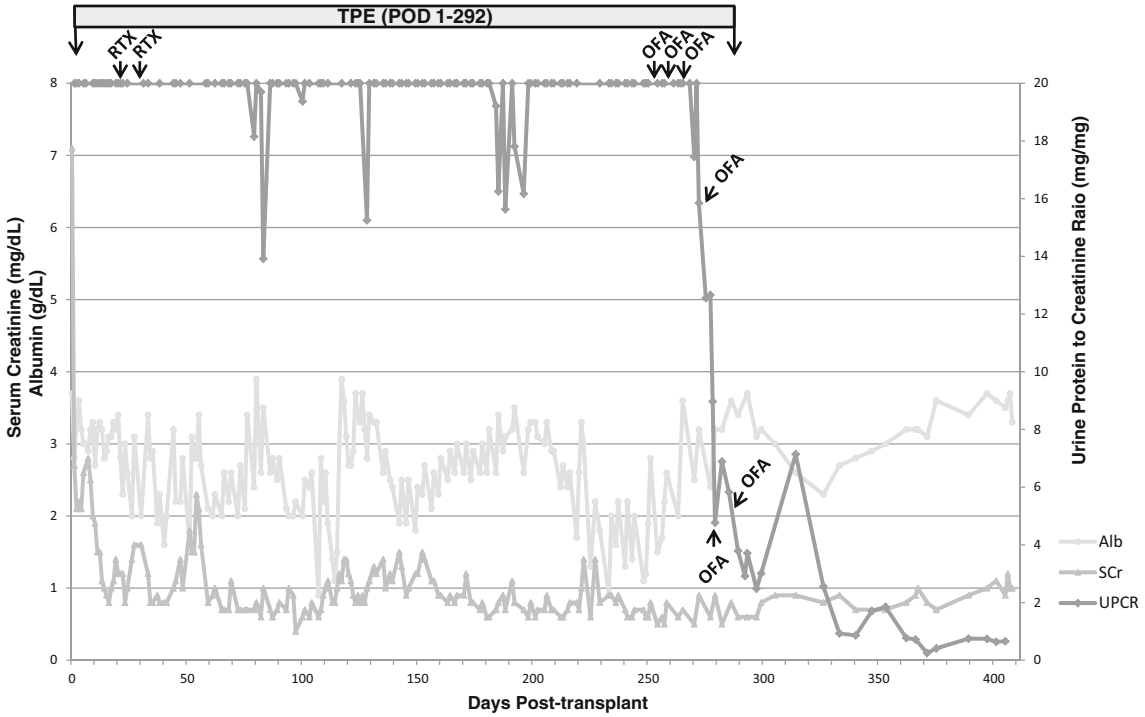

Fig. 1 Post-transplant recurrence treatment and laboratory results for patient 3. *Alb* albumin, *CsA* cyclosporine, *MP* methylprednisolone, *OFA* ofatumumab, *POD* post-operative day, *RTX* rituximab, *SCr* serum creatinine, *TPE* plasmapheresis, *UPCR* urine protein/creatinine ratio

UPCR reached a nadir of 0.16–0.41 mg/mg and remained in this range at last follow-up 9 months after ofatumumab treatment.

Patient 4

The patient is a 16-year-old male who presented with SDNS at age 11 years. Renal biopsy was consistent with MCD. By the second year after diagnosis, he was on a multi-drug regimen of MMF, tacrolimus, prednisone, and lisinopril to control relapses. Three years after diagnosis, he displayed persistent disease, for which two doses of IV rituximab 375 mg/m^2 were given. Post-rituximab therapy, the UPCR transiently improved to a subnephrotic range, but did not normalize. We therefore initiated the patient on ofatumumab, but he developed an urticarial rash and lip swelling with the first dose, which resolved with IV diphenhydramine treatment and stopping of the infusion. Therapy was switched to IV methylprednisolone and IV cyclophosphamide, and he was able to achieve remission. However, he quickly relapsed when IV methylprednisolone doses were spaced. We developed a desensitization protocol based on published experience [11] (Table 1) and gave the patient ofatumumab at an initial dose of 300 mg/1.73 m^2, followed by five weekly infusions of 2000 mg/1.73 m^2. He experienced transient nausea and emesis with the first dose but was able to complete the remainder of the treatments uneventfully. The UPCR prior to ofatumumab was 4.32 mg/mg and improved to 1.88 mg/mg after the first dose. Subsequent UPCR values ranged from 0.64 to 2.24 mg/mg over the ensuing 6 months of follow-up. The serum albumin normalized 2 months following the initiation of ofatumumab therapy.

Patient 5

The patient is a 13-year-old male who presented with SDNS at age 6 years. Renal biopsy performed 5 months after diagnosis showed MCD. A therapeutic regimen of tacrolimus, IV cyclophosphamide, and cyclosporine failed to reduce the frequency of relapses. Two doses of IV rituximab 375 mg/m^2 were given 5 years after diagnosis (course #1). Thereafter, he achieved a sustained remission of 8 months. He was given a second course of IV rituximab, two doses of 375 mg/m^2 after recovery of B cells and the development of subnephrotic range proteinuria. Full relapse occurred 6 months later, whereupon a third course of IV rituximab was given, with depletion of B cells with one dose of IV rituximab 375 mg/m^2. However, steroid-resistant relapse persisted, with numerous complications. Ofatumumab was first given 5 months later, but the patient developed diffuse hives with the first dose. The rash resolved with stopping the infusion and administering IV diphenhydramine. We subsequently re-administered IV ofatumumab with our desensitization protocol in an initial dose of 300 mg/1.73 m^2, followed by five weekly doses of 2000 mg/1.73 m^2. Remission was achieved 4 weeks after the first dose

Table 2 Review of reported cases of ofatumumab treatment in nephrotic syndrome

Author/year	Cases	Age (years)	Previous therapy	Ofatumumab regimen	Response	Duration	Adverse reaction
Basu/2014 [8]	1	19	CTX, Tac, RTX	300 mg/1.73 m^2, then 5 weekly doses of 2000 mg/1.73 m^2	Remission	50 weeks (at time of report)	None[c]
	2	8	CTX, CsA, Tac, RTX	Same as above	Remission	42 weeks (at time of report)	None
	3	7	CTX, Tac, RTX, galactose	Same as above	Remission	8 weeks	None
	4	5	CTX, CsA, Tac, RTX, galactose	Same as above	Remission	38 weeks (at time of report)	None
	5	6	Tac, MMF, RTX	Same as above	Remission	25 weeks (at time of report)	None
Bonanni et al./2015 [9]	6	7	CsA, Tac, RTX	300 mg/1.73 m^2, then 700 mg/1.73 m^2 2 weeks apart	Partial remission	<2 months	Not reported
	7	16	CTX, CsA, Tac, interleukin, RTX	Same as above	No response	–	Not reported
	8	14	CsA, plasma exchange, Tac, RTX	Same as above	Remission	12 months (at time of report)	Not reported
	9	14	CsA, Tac, RTX, interleukin	Same as above	No response	–	Not reported
Vivarelli et al./2016 [10]	10	14	CsA, MMF, RTX,	750 mg/1.73 m^2	Remission	15 months (at time of report)	Mild allergic reaction
	11	3	CsA, Tac, RTX	750 mg/1.73 m^2	Remission	19 months (at time of report)	None
Current report	Patient 1	16	MMF, Tac, IV MP, RTX	300 mg/1.73 m^2, then 4 weekly doses of 2000 mg/1.73 m^2	Remission	13 months	None
	Patient 2[a]	13	CsA, MMF, Tac, RTX	N/A	N/A	N/A	Rash and nasal congestion
	Patient 3[b]	13	Tac, IV MP, CsA, CTX, RTX, plasma exchange	300 mg/1.73 m^2, then 5 weekly doses of 2000 mg/1.73 m^2	Remission	9 months to date	Itching and rash
	Patient 4	16	MMF, Tac, RTX, CTX	Same as above	Partial remission	6 months to date	Rash, angioedema, nausea, emesis
	Patient 5	13	Tac, IV MP, CTX, CsA, RTX	Same as above	Remission	3 months to date	Rash

CsA cyclosporine, CTX cyclophosphamide, FR frequency relapsing, IV intravenous, MMF mycophenolate mofetil, MP methylprednisolone, N/A not applicable, RTX rituximab, SD steroid dependent, SR steroid resistant, Tac tacrolimus, Tx treatment

[a] Patient did not complete ofatumumab therapy

[b] Patient with post-transplant focal segmental glomerulosclerosis recurrence who had also received post-transplant immunosuppression therapy (basiliximab, solumedrol, mycophenolate mofetil, tacrolimus)

[c] One case of "transient infusion reaction" was reported, but the author did not state which patient had the reaction

of ofatumumab and has been sustained for 3 months at the time of this report.

Discussion

In this report, we present our experience with using ofatumumab to treat five pediatric patients with idiopathic NS, including the first report of a patient successfully treated with ofatumumab for FSGS recurrence post-transplant (Patient 3). This patient's dramatic response to ofatumumab, given that aggressive and prolonged plasmapheresis and treatment with numerous immunosuppressants, including rituximab, had failed, is particularly encouraging for the management of this devastating disease. Similar to results published previously [8–10], the response in our pre-transplant patients is promising. The three patients who were able to complete at least five doses of ofatumumab (Patients 1, 4, and 5) each achieved partial or complete remission. These patients all had developed steroid resistance after initial steroid sensitivity and had poor responses to rituximab and numerous other immunosuppressants. Patient 1, for whom the duration of follow-up was the longest, enjoyed a relatively long period of remission of 13 months after ofatumumab therapy, including 8 months after recovery of B cells. The follow-ups for Patients 4 and 5 were quite short in comparison.

Of note, four of our five patients had hypersensitivity reactions to ofatumumab infusion despite pre-medication with diphenhydramine, methylprednisolone, and acetaminophen. Previous studies have reported an incidence of urticaria and rash of >5% [11]. Because we felt that virtually no other treatment options were available for these most difficult-to-treat NS patients, we developed a desensitization protocol based on that published by Galvão and Castells [11]. This protocol was used for Patients 4 and 5, who successfully completed the six doses of ofatumumab treatment. To our knowledge, this is the first published clinical experience with using a desensitization protocol for ofatumumab in pediatric patients.

Ofatumumab, like rituximab, is a B-cell depleting monoclonal antibody that targets the CD20 antigen expressed on all B cells, excluding plasma cells. Two recent randomized clinical trials found rituximab to be effective in maintaining remission and allowing steroid withdrawal in children with SDNS [13, 14]. At the current time, there are no published randomized trials of ofatumumab for the treatment of NS. The first case of ofatumumab use was reported by Basu [8] and involved a 19-year-old female with multidrug-resistant idiopathic NS who was treated with ofatumumab for chronic lymphocytic leukemia and serendipitously achieved NS remission. Subsequent reports of ofatumumab in NS also showed efficacy in inducing remission in multidrug- and rituximab-resistant NS [8–10]. The clinical features, ofatumumab treatment details, and patient responses of these early reports and the current cases are summarized in Table 2.

It is unclear how B-cell depleting agents like rituximab and ofatumumab affect the pathogenesis of NS. B cells have been shown to be elevated in the active phase of NS and are found in significantly higher numbers in FSGS glomeruli versus controls [15, 16], although whether this represents a direct role of B cells in the disease is not yet established. Immunoglobulins have also been implicated in the pathogenesis of NS. Dantal et al. showed in four patients with post-transplant recurrent FSGS that anti-immunoglobulin immunoadsorption resulted in the removal of factor(s) involved in proteinuria, suggesting that the putative factor(s) is bound to immunoglobulin. Rituximab may act mechanistically by B-cell depletion, although persistent remission after B-cell recovery suggests a disease-modifying effect beyond total B-cell depletion. Colucci et al. reported that delayed reconstitution of switched memory B cells after rituximab is predictive of sustained disease remission and suggests that this subpopulation may play a role in NS pathogenesis [17], although the exact mechanism is unclear. In Patients 1 and 3 of our study, we observed that the disease remission induced by ofatumumab persisted for 8 and 3 months, respectively, after recovery of B cells. Interestingly, Patient 3 in our series, as well as Patient 5 with his later courses of rituximab, did not achieve remission with rituximab despite B-cell depletion but did respond to ofatumumab. Our observations therefore suggest that the effects of ofatumumab and rituximab involve more than B-cell depletion. How ofatumumab is able to induce a more favorable response in some patients than rituximab is unclear. While ofatumumab is known to bind CD20 via a different epitope and with greater avidity than rituximab and promotes a more potent complement-dependent cytotoxicity [18], the relevance of these differences to the treatment of NS is unclear at this time.

Our experience with ofatumumab for the treatment of refractory NS and recurrent post-transplant FSGS is encouraging, and the desensitization protocol we describe may be helpful to address hypersensitivity reactions that appear to be common with this medication. Prospective studies with larger sample sizes will be required to determine the safety and efficacy of this novel therapeutic agent.

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Compliance with ethical standards

Ethical approval The study was approved by the Children's Healthcare of Atlanta Institutional Review Board. For this type of study, formal consent is not required.

Disclosure The authors declare that they have no potential conflicts of interest to disclose.

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