Systematic Review:

A Systematic Review of Efficacy and Safety of Ofatumumab Therapy in Children With Difficult-to-treat Nephrotic Syndrome

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ABSTRACT

Context: Different studies have been done so far on drug safety and efficacy in children with refractory nephrotic syndrome (NS). Ofatumumab might be an effective drug for this syndrome; however, the long-term effects and cost-effectiveness of ofatumumab treatment have not been comprehensively assessed.

Objectives: This study aims to perform a systematic review of the efficacy and safety of ofatumumab in children with difficult-to-treat NS.

Study Selection: An electronic literature search was conducted to identify appropriate studies. The search key terms were as follows: ("nephrotic syndrome" OR "minimal change disease" OR "focal segmental glomerulosclerosis" OR "membranous") AND ("Ofatumumab" or "CD20" or "Arzerra" or "HuMax-CD20").

Data Extraction: Data were extracted from the articles according to the selection criteria by two independent reviewers.

Results: A total of 83 potentially relevant articles were identified. Thirty-two articles were removed due to duplication. Then 26 more articles were excluded because they were book sections and review papers and therefore not relevant. Another 14 items were removed after reviewing the full text of selected papers because the topics did not fit our study subject. Finally, 11 studies were selected in our systematic review. The benchmark considered to assess the efficacy of ofatumumab in children with nephrotic syndrome in most of the studies was a complete remission rate.

Conclusions: In conclusion, our systematic review showed that ofatumumab may be an effective drug in refractory NS treatment in children and could bring down the use of steroids and immunosuppressants. However, further large randomized trials are suggested.

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1. Context

Nephrotic Syndrome (NS) is the most common glomerular disease in children and its treatment is challenging (1) five patients were treated with ofatumumab. One patient had post-transplant recurrent Focal Segmental Glomerulosclerosis (FSGS). The main complications of the disease consist of heavy proteinuria, hypoalbuminemia (serum albumin <2.5 g/dL) , dyslipidemia, and hypercoagulability. According to NS clinical guidelines, a daily low-dose alternate steroid regimen is useful as the initial treatment for children diagnosed with Frequently Relapsing Nephrotic Syndrome (FRNS) or Steroid-dependent Nephrotic Syndrome (SDNS) (2) hypoalbuminemia and dyslipidemia. Low-dose alternate-day steroid regimen is the standard of care. In case of relapse or significant adverse events, steroid-sparing agents may be used.

This analysis was aimed at assessing the efficacy and safety of rituximab for the treatment of children with nephrotic syndrome. Four studies were included in the final meta-analysis. The end-point of our analysis was the percentage of patients in remission at 6 months. Pooled data from the four studies favours the use of rituximab (RR 5.25, 95 % CI: 3.05-9.06; P<0.0001. In FRNS/SDNS patients, using glucocorticoids for a long time may result in hypertension, hypercholesterolemia, and low bone mineral density, augmented risk of infection, and adverse steroid effects such as impaired glucose tolerance, growth retardation, cataract, striae, and pseudotumor cerebri (3) a monoclonal antibody against the B-lymphocyte surface protein CD20, leads to the depletion of B cells. Recently, rituximab was reported to effectively prevent relapses of glucocorticoid-dependent or frequently relapsing Minimal Change Disease (MCD). Approximately 20% of children diagnosed with NS have Steroid-resistant Nephrotic Syndrome (SRNS) and do not respond to regular treatments completely. Relapses have been reported in 80%-90% of children with Steroid-sensitive Nephrotic Syndrome (SSNS) and 50% of them may develop SDNS in the future (4) the efficacy and safety of rituximab in treating childhood refractory nephrotic syndrome remain inconclusive.

This meta-analysis aimed to investigate the efficacy and safety of rituximab treatment compared with other immunosuppressive agents in children with refractory nephrotic syndrome. Three randomized controlled trials and two comparative control studies were included in our analysis. The included studies were of moderately high quality. Compared with other immunotherapies, rituximab therapy significantly improved relapse-free survival (hazard ratio=0.49, 95% Confidence Interval (CI), 0.26-0.92, P=0.03). Refractory nephrotic syndrome usually occurs in patients with SDNS, FRNS, and SRNS difficult to treat by variable immunosuppressants FRNS (5).

2. Objectives

Ofatumumab is a human monoclonal antibody against CD20+cells, and it was first used in chronic lymphocytic leukemia treatment (1) five patients were treated with ofatumumab. One patient had post-transplant recurrent FSGS. Today, ofatumumab has attracted researchers as a potential treatment for NS. Since no systematic review on the effect of this drug on NS has been done, we aimed to do a systematic review on the efficacy and safety of ofatumumab as well as its influence on children diagnosed with difficult-to-treat NS.

3. Data Sources

An extensive search was done for this systematic review in PubMed, Science Direct, Web of Science, Scopus, and the Cochrane Library for the relevant articles up to January 2020. The research terms were as follows: (“nephrotic syndrome” OR “minimal change disease” OR “focal segmental glomerulosclerosis” OR “membranous”) AND (“Ofatumumab” OR “CD20” OR “Arzerra” OR “HuMax-CD20”). Bibliographies in relevant articles and conference proceedings were scanned. We also controlled studies by the same author for possible overlapping participant groups. If the study was reported as duplicate, we only included the most recent or more complete study. The following selection criteria were applied: all studies about using ofatumumab in children diagnosed with difficult-to-treat NS.

4. Data extraction

Data were extracted from the articles according to the selection criteria by two independent reviewers. Disagreements were resolved by discussion between two reviewers considering the opinion of a third reviewer. Then we abstracted the following information from each study: first author, publication year, study design, sample size, the mean age of patients, intervention regime, follow-up duration, concomitant treatment, and outcome measures for each group.

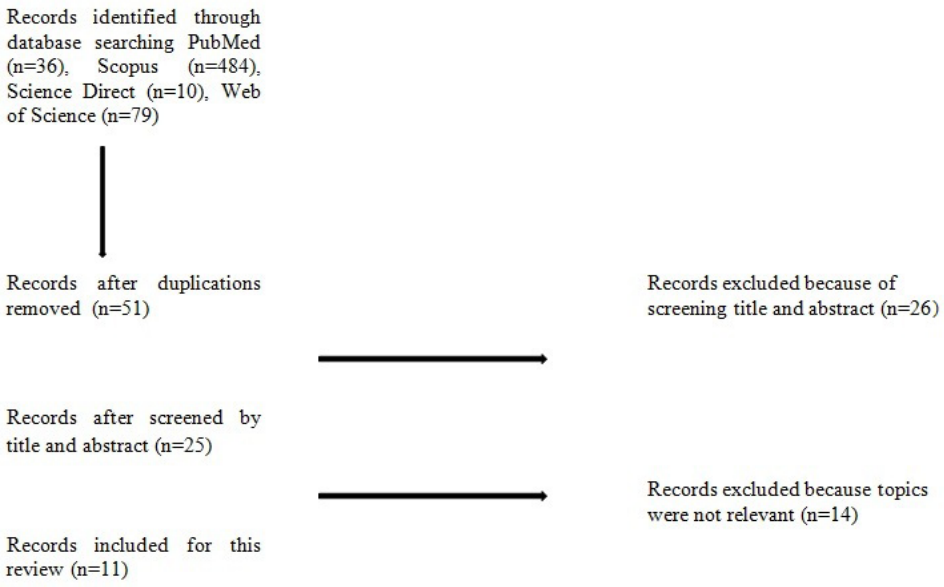

Figure 1. Flowchart of the study selection process *Journal of Pediatrics Review*

FSGS: Focal Segmental Glomerulosclerosis; SDNS: Steroid-dependent Nephrotic Syndrome; MN: Membranous Nephropathy; MCD: Minimal Change Disease; NS: Nephrotic Syndrome; RTX: Rituximab; SRNS: Steroid-resistant Nephrotic Syndrome.

5. Study Selection

A total of 83 potentially relevant articles were identified. Thirty-two articles were removed due to duplication. Also, 26 more articles were excluded because they were book sections and review papers and therefore not relevant. Another 14 items were removed after reviewing the full text of papers because the topics did not fit our study subject. Finally, 11 studies were selected in our systematic review (1, 6-16). Figure 1 demonstrates the study selection approach. In this systematic review, all 11 included studies were case reports, so we could not do a quantitative synthesis (meta-analysis).

6. Results

Table 1 shows the papers' characteristics and outcomes in detail. Note that no meta-analysis has been conducted. Efficacy of ofatumumab in children with nephrotic syndrome in most of the studies was assessed with complete remission. Almost all studies revealed that ofatumumab is a promising agent in refractory NS treatment in children and could also be a potential drug that limits the use of corticosteroids and immunosuppressants. Bonnani A. et al. (7) described the first case of acute pneumonitis associated with ofatumumab and other studies reported minor side effects for ofatumumab such as rash and allergic reactions (1) five patients were treated with ofatumumab. One patient had post-transplant recurrent FSGS (6, 11). Gastrointestinal complications such as nausea, vomiting, and abdominal pain were reported in some studies (1, 13, 16).

7. Discussion

Ofatumumab is the last generation of anti-CD20 monoclonal IgG (k) which binds strongly to CD20 and can cause a more effective complement-dependent cytotoxicity. It is currently in the third phase of clinical trials for the treatment of rheumatoid arthritis, chronic lymphocytic leukemia, and relapsing lymphoma. In some studies, it has been reported that in children with SRNS who did not respond to rituximab, ofatumumab could create remission and it is more effective and have a better tolerance in pediatric SRNS in case of an allergic reaction to rituximab (10) which is characterised by severe proteinuria and hypoalbuminaemia. Some children become Steroid-dependent (SD). However, in studies discussed in this systematic review, with the use of ofatumumab, the side effects such as a rash (1, 11) and allergic reactions (6, 15) were observed too.

In another study on ofatumumab for childhood NS treatment, authors indicated that it is unclear how B-cell deplete agents such as ofatumumab and rituximab affect the pathogenesis of nephrotic syndrome and believed that their experience with ofatumumab for refractory NS treatment and recurrent post-transplant FSGS was an incentive. They also realized that the desensitization protocol might be helpful to address hy-

Table 1. General characteristics and outcomes of studies included in this systematic review

Ref. No.	Authors name	Year	Country	Study design	Frequency	Age (y)	Gender (male) (n)	Type	Follow-up period(month)	Complete remission events (n)	Side effect (n)	Results
(1)	Wang, C. S.	2017	USA	Retrospective review	5	14.2	5	FSGS resistant to plasmapheresis and immunosuppressive agents=1 nephrotic syndrome with steroid-resistant disease=4		3	Rash=4 angioedema, nausea , emesis=1	For post-transplant recurrent FSGS and refractory childhood nephrotic syndrome, ofatumumab may be an effective treatment
(6)	Vivarelli, M.	2017	Italy	Case report	2	8.5		SDNS =1	>12	2	Allergic reaction=1	Ofatumumab may be a therapeutic option in severe forms of nephrotic syndrome with an allergy to rituximab.
(7)	Bonanni, A	2017	Italy	Case report	1	14	1	Nephrotic syndrome dependent on prednisolone plus cyclosporine A	2			They described the first case of acute pneumonitis associated with ofatumumab
(8)	Bonanni, A	2015	Italy	Case report	4	12.75	3	FSGS=2 MCD=2	12	2	Not reported	Low-dose ofatumumab may induce remittance of proteinuria in children
(9)	Basu, B	2014	India	Case report	5	9.38	Not reported	Not reported	12	5	None	Ofatumumab may be an effective treatment in managing refractory SRNS
(11)	Bonnani	2018	Italy	Original article	37	11.1	21	MCD =3 FSGS =14 IgM Nephropathy= 1	12	Not reported	1-Infusion reactions (fever=1, rash=7, dyspnea= 3) 2-Early adverse events (≤3 months) : Infections=4 3-Late adverse events (>3 months) : Infections =4, Neurological manifestation=1	Data from the article supports the use of anti-CD20 to maintain steroid-free remission of idiopathic nephrotic syndrome
(12)	Shuichiro	2017	japan	Case report	1	5	1	MCD	8	1	Infusion reaction not seen	A single infusion of low dose ofatumumab appears to be safe and effective in children with complicated RTX-resistant nephropathy
(13)	Manuel Alfredo Podestà	2019	Italy	Case report	1	18	1	MN	4	Partial remission	Mild flushing, viral enteritis with high-grade fever	Ofatumumab could be a valuable alternative to rituximab for the treatment of patients with MN

Ref. No.	Authors name	Year	Country	Study design	Frequency	Age (y)	Gender (male) (n)	Type	Follow-up period(month)	Complete remission events (n)	Side effect (n)	Results
(14)	Manuela Colucc	2019	Italy	Case report	2	15	2	FSGS	12	2	Malaise	Ofatumumab may be a therapeutic option for post-transplant FSGS recurrence in patients who respond poorly to rituximab.
(15)	Josselin Bernard	2018	France	Case report	1	17	Not reported	FSGS	14	0	Minor allergic reaction	Ofatumumab may be an alternative treatment for post-transplantation rituximab-resistant SRNS
(16)	Sonia Solomon	2018	USA (New York)	Case report	1	13	1	FSGS	13	Partial remission	Abdominal pain and emesis	Ofatumumab may be a safe and effective option for post-transplant recurrence of FSGS.

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persensitivity reactions common in the use of ofatumumab and suggested that prospective studies with larger sample sizes be required to determine the safety of this therapeutic agent as well as its efficacy FRNS (5).

Manuel Podestà reported a case of a young male patient with NS refractory to steroids and cyclosporine. However, rituximab (375 mg/m^2) induced remission of the first episode and six relapses of Nephrotic Syndrome (NS). The seventh infusion was complicated by delayed serum sickness, which was resolved with steroids. On subsequent relapse, ofatumumab (300 mg) achieved remission of the NS, without significant side effects. Overall, this patient received 3 times ofatumumab in approximately four years interval, and one year after the second injection he experienced viral enteritis with high-grade fever and finally with the third infusion of ofatumumab, partial remission was achieved (13).

Ofatumumab in post-transplantation recurrence of focal segmental glomerulosclerosis plays a very important therapeutic role (14-16). Patients with nephrotic syndrome due to idiopathic FSGS are at high risk of recurrence. It has been observed that patients with FSGS due to genetic mutations typically do not develop recurrence after kidney transplantation. The combination of CsA and plasmapheresis is reported to induce remission in 60% of patients (17, 15). In patients with either SRNS or recurrent FSGS after kidney transplantation, who failed to respond to rituximab, the administration of ofatumumab results in either partial or complete remission (15). It is well described that even a partial remission of NS improves long-term outcomes in patients with FSGS (18).

8. Conclusion

Of a tu mum ab may be an effective drug in refractory NS treatment in children and could bring down the use of steroids and immunosuppressants. However, the limitations of the study are the size and nature of the studies. Thus, further large randomized trials are suggested.

Ethical Considerations

Compliance with ethical guidelines

All analyses were based on previously published studies, thus no ethical approval or patient consent was required.

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Authors' contributions

All authors contributed in preparing this article.

Conflicts of interest

The authors declared no conflict of interest.

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