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Systematic Review of Efficacy and Safety of Ofatumumab in Children with Difficult-to-Treat Nephrotic Syndrome

Running title: Efficacy of Ofatumumab in Pediatric Nephrotic Syndrome

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Abstract

Context: Different types of researches have been done so far on drug safety and efficacy in children with refractory nephrotic syndrome. 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 nephrotic syndrome.

Study Selection: An electronic literature search was conducted to identify appropriate studies. The search term was: (“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. Besides, 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 subject. Finally, 11 studies were selected in our systematic review. The metric 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 nephrotic syndrome treatment in children and could bring down the use of steroids and immunosuppressants. However, further large randomized trials are suggested.

Keywords: Ofatumumab, Nephrotic syndrome, Children, Treatment

1. Context

Nephrotic syndrome (NS) is the most common glomerular disease in children and its treatment is challenging (1). 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). 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 pseudo-tumor cerebri (3). Approximately 20% of children diagnosed with nephrotic syndrome 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). Refractory nephrotic syndrome usually occurs in patients with SDNS, FRNS, and SRNS difficult to treat by variable immunosuppressant (5).

2. Objectives: Ofatumumab is a human monoclonal antibody against CD20+ cells first used in chronic lymphocytic leukemia treatment (1). Today, Ofatumumab has attracted attention as a potential treatment for NS. Since no systematic review on the effect of this drug on nephrotic syndrome has been done, we aimed to design a systematic review on the efficacy and safety of Ofatumumab as well as its influence on children diagnosed with difficult to treat nephrotic syndrome.

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 updated up to January 2020. The research term was (“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 complete study. The following selection criteria were applied: all studies about using Ofatumumab in children diagnosed with difficult to treat NS were included.

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, and study design, sample size, the mean age of patients, intervention regime, follow-up duration, concomitant treatment, and outcome measures for each group.

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 selected papers because the topics did not fit our subject. Finally, 11 studies were selected in our systematic review (1,6,7,8,9,11,12,13,14,15,16). Figure 1 demonstrates the study selection approach. In this systematic review, all 11 included studies were case reports, so we couldn't do a quantitative synthesis (meta-analysis).

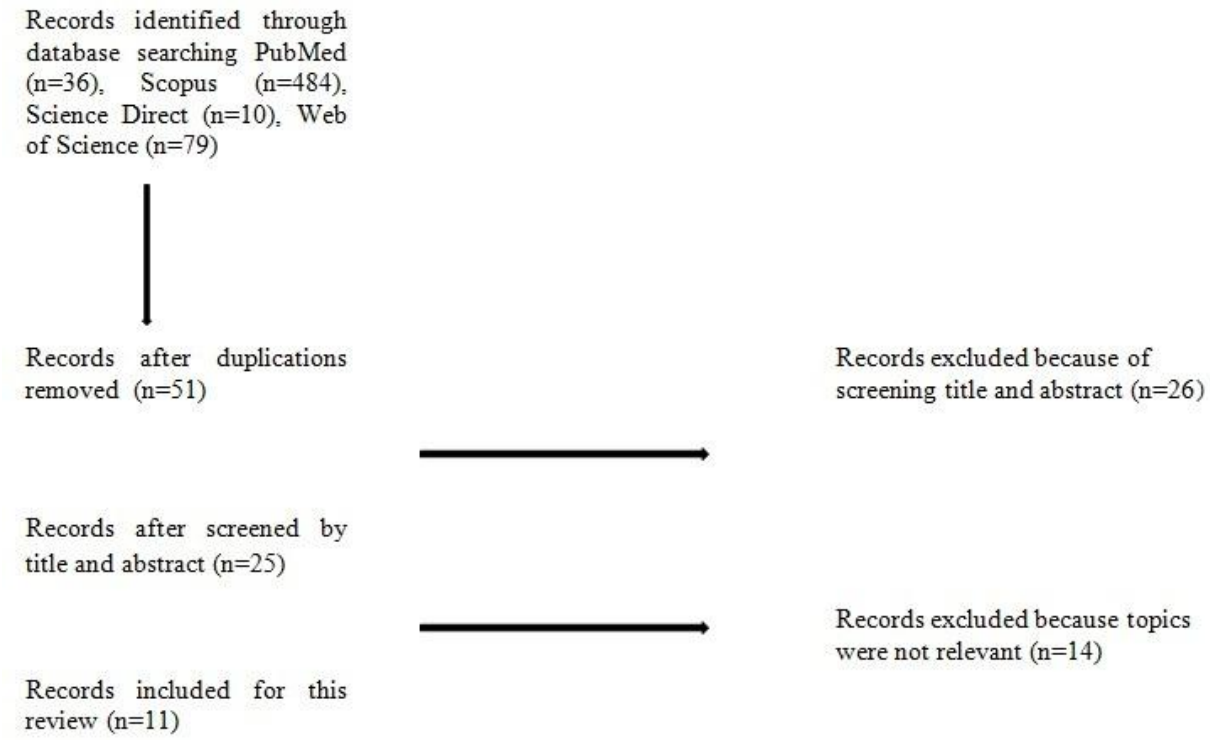

Figure 1: Flowchart of the study selection process

6. Results

table1 shows papers' characteristics and studies outcome 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 rates.Almost all studies revealed that Ofatumumab is a promising agent in refractory nephrotic syndrome treatment in children and could also be a potential drug that limits the use of corticosteroid and immunosuppressant. 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)(6)(11). Gastrointestinal complications such as nausea, vomiting and abdominal pain reported in some studies (1,13.16).

Table 1: General characteristics and Outcome of trials included in this systematic review

Ref. No.	Authors Name	Year	Country	Study design	Frequency	Age (Year)	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 NS with an allergy to rituximab.
7	Bonanni, A	2017	Italy	case report	1	14	1	nephrotic syndrome dependent on prednisolone plus cyclosporin 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 artichle	37	11.1	21	MCD =3 FSGS =14 IgM Nephropathy= 1	12	Not reported	1-Infusion reactions(Fever=1, Rash=7, Dyspnoea=3) 2-Early adverse events (≤3 months): Infections = 4 3-Late adverse events (>3 months): Infections =4, Neurological manifestation=1	Data from the artichle supports the use of anti-CD20 to maintain steroid-free remission of idiopathic nephrotic syndrom

12	shuichiro	2017	japan	Case report	1	5	1	MCD	8	1	Infusion reaction not seen	single infusion of lowdose 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
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.

*Abreviations: 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

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 was shown to be more effective and to have a better tolerance in pediatric SRNS in case of an allergic reaction to rituximab (10), however, in studies discussed in this systematic review ,with the use of Ofatumumab side effects such as rash (1,11) and allergic reactions (6,15) was observed too.

In another study carried out on Ofatumumab for childhood nephrotic syndrome 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 nephrotic syndrome treatment and recurrent post-transplant FSGS was incentive. They also realized that the desensitization protocol described might be helpful to address hypersensitivity reactions common in the use of Ofatumumab and suggested that prospective studies with larger sample sizes would be required to determine the safety of this therapeutic agent as well as its efficacy (5).

Manuel Podestà reported a case of a young male patient with NS refractory to steroids and cyclosporine which Rituximab (375mg/m2) achieved remission of the first episode and six relapses of nephrotic syndrome (NS). The seventh infusion was complicated by delayed serumsickness, which resolved with steroids. On subsequent relapse, Ofatumumab (300mg) achieved remission of the NS, without significant side effects. This patient received 3 times of Ofatumumab overally in approximately four years interval and one year after second injection he experienced a viral enteritis with high-grade fever and finally with 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, 15, 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 plas- mapheresis is reported to induce remission in 60% of patients (17,18). In patients with either SRNS or recurrent FSGS after kidney transplantation, who failed to respond to rituximab, the administration of Ofatumumab resulted in either partial or complete remission (18). It is well described that even a partial remission of nephrotic syn- drome improves long-term outcomes in patients with FSGS (19).

8. Conclusion

In conclusion, our systematic review showed that Ofatumumab may be an effective drug in refractory nephrotic syndrome treatment in children and could bring down the use of steroids and immunosuppressants. However, acknowledging the limitations of the study due to the size and nature of the studies included. Further large randomized trials are suggested.

Ethical Considerations

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

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Conflict of interest: None declared.

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