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Research Article

Pharmacological and Non-Pharmacological Approaches to the Treatment of Steroid-Sensitive Pediatric Nephrotic Syndrome: A Review

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Abstract

Nephrotic syndrome is a disease with a very variable prevalence in the pediatric population whose main treatment consists of corticosteroid therapy. However, long-term use of corticosteroids can lead to multiple complications, whether ocular, cardiovascular, osteoarticular or even related to obesity. The use of corticosteroid-sparing therapy is the best strategy to reduce exposure to steroids for long periods. In this context, levamisole proved to be a low-cost corticosteroid-sparing agent with a low rate of adverse events.

An integrative review of the main evidence available in the literature regarding the use of corticosteroid sparing agents in pediatric patients with frequent relapsing or corticosteroid dependent nephrotic syndrome was performed. Twenty-three studies were selected and evaluated using the Critical Apprasial Skills Program (CASP) and Grading of recommendations assessment, development, and evaluation (GRADE). Traditional and non-traditional therapies were described and reviewed for the treatment of cortico-sensitive nephrotic syndrome, including diet and vitamin and mineral supplementation**.**

In the integrative review, studies have shown that there is no reference steroid-sparing medication in the pediatric population. When necessary, corticosteroid-sparing therapy should be individualized and discussed with family members. The use of prednisone or prednisolone remains the initial treatment of choice for idiopathic nephrotic syndrome.

The choice of the best therapeutic strategy in NIS should consider clinical data, medication availability and be shared with the family, especially in the case of prolonged medication use.

Key words: corticosteroid sensitive nephrotic syndrome; childhood; levamisole, adolescents

1. Introduction

Nephrotic syndrome (NS) is defined by the triad proteinuria, hypoalbuminemia and edema. Many glomerular diseases can cause nephrotic syndrome, which varies according to the age at which the disease manifests. While genetic defects are more frequent in children under one year of age, primary or idiopathic NS (NIS) is more common between one and 10 years of age and results from intrinsic glomerular damage without a defined cause [1,2]. Secondary NS, more common in adolescents and adults, encompasses glomerular lesions that usually result from systemic diseases.

SNI in pediatrics, the focus of this review, has a very variable annual incidence, between 1.15 and 16.9 per 100,000 children, due to ethnic and regional differences [2]. Although the etiopathogenic mechanisms are complex and multifactorial, NIS is best defined as a podocytopathy. The structural and functional alterations of podocytes affect the permeability of the glomerular filtration barrier and give rise to massive proteinuria [2,3]. According to the type and degree of podocyte injury, NIS may present with different histopathological manifestations [2–4]. Minimal glomerular lesion NS (SNLM) is the most common form of pediatric NIS, but in recent decades an increase in the incidence of focal segmental glomerulosclerosis (FSGS) has been reported [2–5]. The mainstay of treatment for NIS is corticosteroid therapy, mainly prednisone or prednisolone, with protocols largely based on the International Study of Kidney Diseases in Children and on the recommendations of the International Association of Pediatric Nephrology [6–9].

Classification	Definition
Nephrotic syndrome	Edema, urinary protein/creatinine ratio > 200mg/mmol or more than 3+ on the urinary dipstick, hypoalbuminemia < 2.5g/L
Complete remission	Urinary protein/creatinine ratio < 20 mg/mmol or < 1+ on the urinary dipstick for at least 3 consecutive days
Early responder/corticosteroid sensitive (SNSC)	Achieves complete remission with 4 weeks of corticosteroid therapy
Early resistance/corticosteroid resistant	Failure to achieve complete remission after 8 weeks of corticosteroid therapy
(SNRC)	Urinary protein/creatinine ratio > 200mg/mmol or more than 3+ on urinary dipstick for 3 consecutive days after remission period
Relapse	More than 2 relapses after 6 months of initial treatment or more than 4 relapses within 12 months
Frequent recurrence	Two consecutive relapses during the period of corticosteroid therapy or after 14 days of cessation of corticosteroid therapy

Table 1: Classification of nephrotic syndrome according to KDIGO (10)

The vast majority of children with SNI will experience complete remission of the disease after treatment with corticosteroids. However, treatment modifications are often required due to complications or toxicity associated with prolonged use of corticosteroids [1,2,9,11]. Among the complications of NIS, many of them potentially related to treatment with corticosteroids, we can mention: the risk of bacterial infections, [12] hyperlipidemia, [12] the risk of thromboembolic events, [13] in addition to bone complications [14,15] and eyepieces [14,16,17]. It is important to emphasize that about 40% of untreated pediatric patients died, and half of the cases are related to infectious processes [14,18,19].

Several pharmacological and non-pharmacological strategies have been described and studied, especially with regard to therapeutic alternatives in cases of dependence or toxicity to corticosteroids [2,3,6,14]. However, it is not yet possible to define the best initial corticosteroid-sparing therapy. In this scenario, molecular biology may guide the individualization of therapy based on the best response for each patient, and may even propose the use of initial therapies other than corticosteroids. This review aims to describe the main current therapeutic strategies in the treatment of NIS in steroid-dependent patients, with frequent relapses or steroid toxicity.

2. Methods

This is an integrative review whose data collection was carried out between March 2019 and January 2021 following the methodology suggested by the literature, using a validated data collection instrument. The following health science descriptors (DECs) from the VHL portal (virtual health library) were used: steroid-sensitive nephrotic syndrome, children, childhood and treatment. Articles published in the last five years, in English and Portuguese, were accepted for this review. The search was carried out in the following PubMed and Virtual Health Library databases (Scielo, LILACS and MEDLINE). Article references were also included if they met the inclusion definition criteria. Initially, 266 articles were found, which were later selected, and 25 articles met the criteria for this review. These articles were evaluated using Critical Appraisal Skills Program (CASP). The level of evidence of the articles was evaluated using the Grading scale of Recommendations Assessment, Development and Evaluation (GRADE) which will be classified as A (High quality) articles with strong confidence that the true effect is close to the estimated effect; B (Moderate) when there is moderate confidence in the estimate of the effect, there is a possibility that the effect will be substantially different from the estimate; C (Low) the estimated confidence in the effect is limited and D (Very low) when there is little confidence in the effect estimate.

3. Results

Initially, 266 articles were selected by searching for descriptors in the databases. After the initial evaluation (abstracts and title) 200 articles were excluded. In this way, 66 articles were selected, of which 17 were excluded due to duplication and 26 after reading, due to incomplete data, inadequate research protocols, case reports and literature review. For the final analysis, 23 articles were selected, including 13 clinical trials and 10 observational articles (Figure 1). The selected articles were classified based on the GRADE classification (Table 2).

Figure 1: Diagram of selected articles on the treatment of cortico-sensitive nephrotic syndrome in children

Article title	Author	Journal/year of publication	Objective	Sample	Results/conclusion	GRADE
The Effect of a Gluten-Free Diet in Children with Difficult-to-Manage Nephrotic Syndrome.	Lemley et al (44).	Pediatrics 2016	To evaluate the effectiveness of a gluten-free diet in NS	2- 14 years N=8	Demonstrated impact of gluten-free diet in patients with difficult-to-manage nephrotic syndrome	C
Clinical course & management of childhood nephrotic syndrome in Germany: a large epidemiological ESPED study.	Franke et al (33)	BMC nephrology 2019	Demonstrate course and treatment of patients with NS in Germany	0-18 years N=326	Incidence of NS 43% of the population studied. 30% of patients experience some complication, with infectious complications being the most common.	B
A randomized clinical trial indicates that levamisole increases the time to relapse in children with steroid-sensitive idiopathic nephrotic syndrome	Gruppen et al (30	Kidney International 2015	Demonstrate the effectiveness of the use of levamisole in preventing relapses in SNSC	2-16 years N=99	Levamisole was effective in terms of time to relapse and number of relapses compared to placebo.	B
Extending initial prednisolone treatment in a randomized control trial from 3 to 6 months did not significantly influence the course of illness in children with steroid-sensitive nephrotic syndrome	Sinha et al (32)	Kidney International 2017	To assess the effectiveness of prolonging the initial use of corticosteroids for 6 months	1-12 years N=181	Prolonging corticosteroid therapy from 3 months to 6 months does not reduce the number of relapses and has the same effect in sustaining relapse at 1 year.	B

Evaluation of mycophenolate mofetil or tacrolimus in children with steroid- sensitive but frequently relapsing or steroid dependent nephrotic syndrome	Wang J et al (34)	Asian Pacific Society of Nephrology 2016	Comparing the effectiveness of MMF vs TAC in reducing relapses and maintaining remission	0-7 years N= 72	There was no statistical difference in the maintenance of remission between the two groups, as well as in the reduction of relapses.	D
Use of a low-dose prednisolone regimen to treat a relapse of steroid-sensitive nephrotic syndrome in children	Raja K et al (23)	Pediatric Nephrology 2016	Demonstrate the effectiveness of treating NS relapse with low doses of prednisolone	3-17 years N= 15	Low-dose prednisolone (1mg/kg) was shown to be effective in achieving remission after relapse with improved quality of life.	C
The effect of vitamin D and calcium supplementation in pediatric steroid-sensitive nephrotic syndrome	Banerjee S et al (44)	Pediatric nephrology	Avaliar a eficácia da suplementação de cálcio e vitamina D na recidiva da SN	3-6 years N=43	The level of vitamin d was significantly lower in the group that had relapses, but this was not proven in the group that received treatment. There was no reduction in relapses in the group that received vitamin D	C
The effect of systemic corticosteroids on the innate and adaptive immune system in children with steroid responsive nephrotic syndrome	Baris He et al (25	Eur J Pediatr. 2016	To evaluate the effects of corticosteroid therapy on the immune system at the beginning of therapy and with prolonged use	1-18 years N=14	T cells are suppressed very early in patients with NS compared to late but persistent suppression of B cells even after discontinuation of treatment.	C
Evaluation of mycophenolate mofetil or tacrolimus in children with steroid sensitive but frequently relapsing or steroid-dependent nephrotic syndrome.	Wang J et al (34)	Nephrology 2016	Comparing the effectiveness of MMF vs TAC in reducing relapses and maintaining remission	1-18 years N= 72	Tacrolimus proved to be more beneficial than mycophenolate in terms of adverse events, being a promising drug for use as a replacement for calcineurin inhibitors.	C
Rituximab versus cyclophosphamide as first steroid-sparing agent in childhood frequently relapsing and steroid-dependent nephrotic syndrome	Kari JA et al (28)	pediatric nephrology 2020	To compare the efficacy and safety of rituximab versus cyclophosphamide as a first-line treatment	1-18 years N= 46	Both medications showed statistical significance in reducing corticosteroid therapy, patients using cyclophosphamide had more Hematological events and the Rituximab group had more events secondary to administration.	C

The safety and efficacy of mycophenolate mofetil in children and adolescents with steroid-dependent nephrotic syndrome: a single-centre study	Karunamoorthy S et al (36)	Clinical kidney jornal 2019	Demonstrate the efficacy and adverse event profile of MMF	1-18 years N= 87	The most commonly encountered adverse events were urinary tract infection, diarrhea and leukopenia, and the vast majority of patients had a satisfactory response to the use of mycophenolate.	C
Efficacy of Rituximab vs Tacrolimus in Pediatric Corticosteroid-Dependent Nephrotic Syndrome A Randomized Clinical Trial	Biswanath B et al (26)	JAMA 2018	To compare the efficacy of Rituximab versus tacrolimus in maintaining relapse-free time	3-16 years N=175	Rituximab was more effective in maintaining no recurrences for more than 12 months than tacrolimus (54 [90.0%] vs 38 [63.3%] children; P < .001; odds ratio, 5.21; 95%CI, 1.93-14.07).	B
Long term tapering versus standard prednisolone treatment for first episode of childhood nephrotic syndrome: phase III randomised controlled trial and economic evaluation	Webb N J et al (22)	BMJ 2019	To determine the effectiveness of extending corticosteroid therapy from 8 to 16 weeks in relation to relapses	1-14 years N=237	There was no statistical significance in the time to first relapse or the incidence of relapses between the groups. Noted improvement in quality of life reported for the extended therapy group	B
Results of the PROPINE randomized controlled study suggest tapering of prednisone treatment for relapses of steroid sensitive nephrotic syndrome is not necessary in children	Maxted Ap et al (40)	Pediatric Nephrology 2018	To compare the efficacy of low doses of Rituximab (375mg/m2) versus high doses (750mg/m2)	1-14 years N=60	Use of single and low dose Rituximab protocols does not affect the likelihood of relapse at 12 months	B
A global anti B cell strategy combining Obinutuzumab and daratumumab in severe pediatric nephrotic syndrome	Majeranowski A et al (49)	Pediatric Nephrology 2020	To assess the effectiveness of the combined strategy of obinutuzumab and daratumumab in SNCD	1-5 years N=14	The combination of Obinutuzumab and daratumumab induces B-cell depletion and remission in children with difficult-to-treat nephrotic syndrome	B
Histopathological Spectrum and Short-Term Outcome of Treatment with Cyclophosphamide in Relapsing Steroid-Sensitive Nephrotic Syndrome	Bajeer IA et al (27)	J Coll Physicians 2018	Describe the response to cyclophosphamide in relation to different histopathological lesions	4-7 years N=74	The use of cyclophosphamide and corticosteroids improves the outcome of patients with frequent relapsing nephrotic syndrome with minimal adverse effects	D

Immunosuppressive therapy in children with primary nephrotic syndrome: single center experience, Karachi, Pakistan.	Moorani KN et al (11)	BMC nephrology 2018	To determine the response to steroids and alternative immunosuppressive agents in patients with NS	1-15 yearsN=176	Mortality from nephrotic syndrome found was 3% > levamisole and cyclophosphamide was effective in maintaining remission of SNCD and SNRF	C
Sixteen-week versus standard eight-week prednisolone therapy for childhood nephrotic syndrome: the PREDNOS RCT	Webb NJ et al (28)	Health Technol Assess 2019	To determine the effectiveness of extending the duration of corticosteroid therapy to 16 weeks	1-15 years N=237	There was no benefit in extending the time of use of corticosteroids by 16 weeks in relation to the relapse outcome. However, the course corticosteroid therapy for 16 weeks was cheaper and improved quality of life	B
Cyclophosphamide and rituximab in frequently relapsing/steroid-dependent nephrotic syndrome.	Webb H et al (29)	Pediatric Nephrology 2016	To compare the response to the use of Rituximab vs cyclophosphamide in patients with NS	1-15 years N=102	Rituximab was shown to be superior to cyclophosphamide in maintaining disease remission with fewer side effects, with only allergic reactions to the infusion of the medication having been described.	C
Cyclophosphamide in idiopathic nephrotic syndrome: Outcome and outlook	Berkane M et al (48)	Nephrol Ther. 2018	To determine the late outcome of cyclophosphamide and to assess factors related to sustained remission	1-7 years N=50	The use of oral cyclophosphamide is still an effective second-line treatment for nephrotic syndrome (frequent relapsing and steroid-dependent)	C
Discontinuation of maintenance therapy in frequently relapsing nephrotic syndrome	Vogd J et al (47)	Clin Nephrol. 2019	To describe the experience in patients after discontinuation of immunosuppressive therapy	2-18 years N= 24	There was no difference, in relation to relapses, in different forms of discontinuation of corticosteroid	C
Short courses of daily prednisolone during upper respiratory tract infections reduce relapse frequency in childhood nephrotic syndrome	Abeyagunawardena AS et al (31)	Pediatric Nephrology. 2017	To assess the effectiveness of short-term corticosteroid therapy during upper respiratory infection	2-18 years N=43	The use of low doses of corticosteroid therapy (0.5mg/kg/day) of corticosteroid therapy during episodes of upper respiratory infections may reduce the need for long courses of corticosteroid therapy, due to recurrence in this period, and consequent adverse events.	B

Table 2 : Comparative description between studies on the treatment of cortico-sensitive nephrotic syndrome in pediatrics, including results, conclusion and degree of evidence, author and year of publication.

4. Conventional Pharmacological Therapies

4.1 Corticosteroids

All the articles evaluated considered corticosteroid therapy as the initial therapy of choice in NS, and it induces remission in approximately 80% of patients. However, its main mechanism of action continues undefined. The recommended initial dose remains 60mg/m^2 /day for four to six weeks, followed by 40mg/m2 /day for two to five months with progressive dose reduction [11,20].

The optimal duration of steroid time to treat the initial episode of cortico-sensitive NS has become increasingly clear, and there is no benefit in extending the treatment beyond two to three months [21]. Webb et al compared the duration of prednisolone treatment and its cost in protocols of eight to 16 weeks of use. A total of 237 children who received 16 or eight weeks of corticosteroid therapy were randomized. The primary outcome analyzed was the time to first relapse at a minimum follow-up of 24 months. There was no significant difference regarding the primary outcome between the groups (p=0.28) or incidence of SNRF (extended course 60/114 (53%) vs standard course 55/109 (50%) p=0.75). There was also no difference in the evolution towards the need for a steroid-sparing agent between the groups (p=0.81) [22]. Sinha et al compared the duration of treatment for the first episode of NS, from three months to six months, and showed that there is no benefit in extending the initial therapy (21). Thus, the dose of 2mg/kg/day (60mg/m^2 /day) should be maintained for four to six weeks and when there is a satisfactory response, with complete remission for three days, the dose should be reduced to 40 mg/m^2/day every other day for at least four weeks, as suggested by Kidney disease Improving Global Outcomes (KDIGO) and the American Academy of Pediatrics [10,21–23] .

The effects of long-term corticosteroid use include growth disorders, excessive weight gain, cardiovascular and behavioral disorders, cataracts, glaucoma, osteopenia, bone avascular necrosis, and lipid disorders. However, not all therapy side effects will be reversible [24]. Infectious processes are very common during corticosteroid treatment. In 2016, Baris et al performed an immunological assessment using blood samples in patients with NS using 2mg/kg/day of prednisolone compared to patients who did not receive the treatment. Notably, untreated patients had absolute number of lymphocytes (p=0.01), absolute number of CD3+ (p=0.02) and CD8+ T cells (p=0.006) higher than the group using corticosteroids. Thus, it is important to consider immunocompromised patients using corticosteroids since the beginning of their treatment [25].

Regarding relapses, there are not enough studies to establish the most appropriate treatment, but most authors recommend a dose of 60mg/m^2 /day or 2mg/kg/day until the patient is in complete remission for at least three days. After remission, the dose should be reduced to 40mg/m^2 /day or 1.5mg/kg/day every other day for at least three months. It is also suggested that corticosteroid therapy be maintained at the lowest possible dose, on alternate days, and that it be able to maintain remission without side effects in patients with frequent relapses and in steroid-dependent patients. If the alternate-day dose is not able to maintain remission, the lowest possible daily dose should be maintained. The use of low doses of corticosteroids daily during episodes of upper respiratory infections is also recommended, even for patients using the medication on alternate days [11,22,23].

For patients with SNCD or SNRF who develop side effects related to long-term use of corticosteroids, even at low doses, the use of corticosteroid-sparing medications is indicated [21,23].

4.2 Corticosteroid-sparing therapies

4.2.1 Cyclophosphamide

Cyclophosphamide is the most commonly used corticosteroid-sparing agent. Its use in NS protocols dates from 1967, it is the first effective cytotoxic drug as a steroid-sparing agent. This drug proved to be

effective in the treatment of patients with frequent relapses. A single cycle of eight to 12 weeks is recommended at a dose of 2mg/kg/day, with a maximum accumulated dose of 168mg/kg, with the aim of reducing adverse events. It should be started only after complete remission with corticosteroid therapy. Studies have demonstrated the superiority of the intravenous route of administration in sustaining remission after six months, but not after 12-24 months, when compared to the oral dose of medication [26].

Cyclophosphamide has multiple adverse events including leukopenia, thrombocytopenia, alopecia, hemorrhagic cystitis, in addition to gonadal dysfunction and high long-term cancer risk. Gonadal toxicity associated with cyclophosphamide is well documented, affects more males and is dose dependent, justifying the recommendation of a single course of medication. Accumulated doses greater than 300 mg/kg are associated with azoospermia [27,28].

Compared with other steroid-sparing drugs, it was effective in sustaining long-term remission, including a satisfactory response for steroid-resistant patients. Webb et al compared the efficacy of cyclophosphamide in relation to rituximab in SNCD and SNRF patients, demonstrating a satisfactory response to treatment with an efficacy index very close to levamisole and cyclosporine, but with superiority to rituximab, including in corticosteroid-free time (12 months for rituximab and three months for cyclophosphamide) [29]. However, the results found may be related to the degree of immunosuppression received by these patients, in general, patients receive more immunosuppressants (of different classes) before the use of rituximab. Kari et al compared the use of rituximab in relation to *cyclophosphamide as* the first steroid-sparing agent in patients with SNCD and SNRF, and it is not possible to affirm the superiority of rituximab in relation to cyclophosphamide, although rituximab is a safe medication [28].

4.2.2 Levamisole

Also used as an anthelmintic agent, levamisole has been shown to be effective as a steroid-sparing drug. It is an imidazole derivative with immunomodulatory characteristics that acts by increasing the Th1 response and reducing the Th2 response (Figures 2 and 3), thus decreasing the transcription of cytokines and interleukin 18. Its use is restricted in Europe and the United States due to its adverse events. [11,30,31].

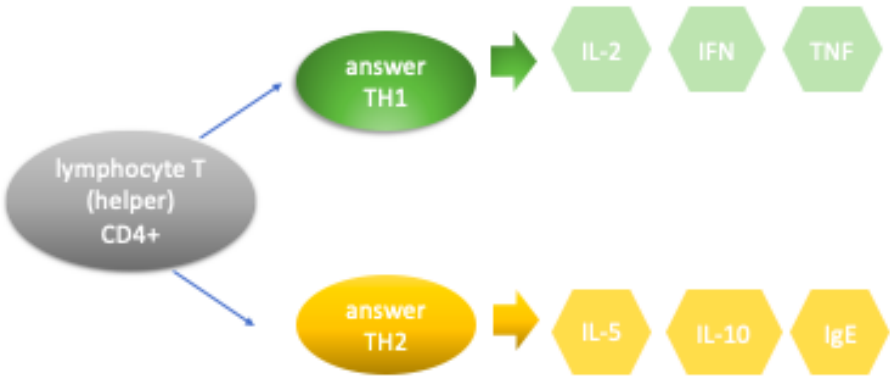

Figure 2 - Schematic drawing of the Th1 and Th2 response (Source: Pediatric Nephrology Unit – Santa Casa de Belo Horizonte Hospital – Minas Gerais - Brazil)

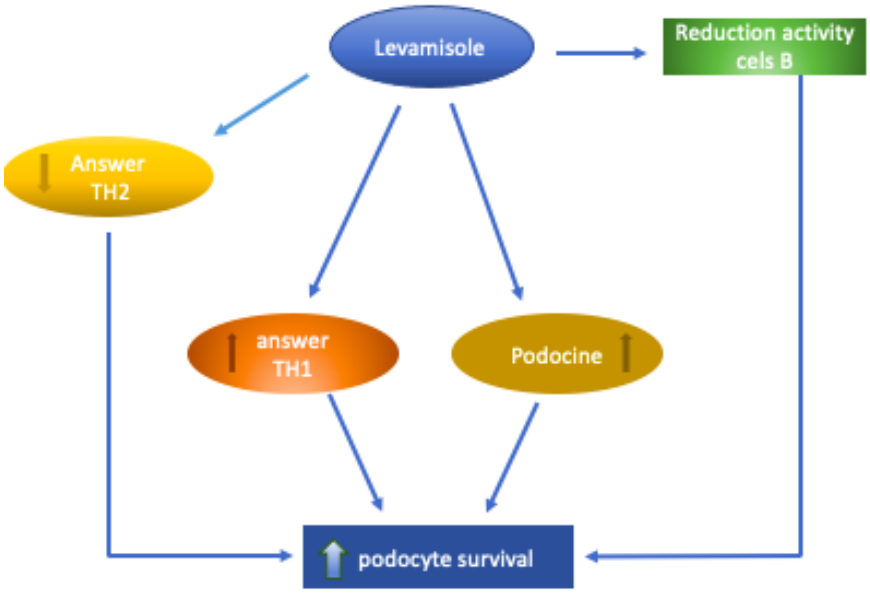

Figure 3 - Schematic drawing immunological effects of levamisole (Source: Pediatric Nephrology Unit – Santa Casa de Belo Horizonte Hospital – Minas Gerais - Brazil)

In general, it presents fewer adverse events when compared to mycophenolate, in addition to being better tolerated (30,32), both agents being effective in maintaining remission. Adverse events related to levamisole are minimal, with leukopenia and gastrointestinal discomfort being more common. Reports of vasculitis associated with the use of medication are rare [11,21,32]. It has been considered the least toxic and cost-effective steroid-sparing agent. However, it is not available for use as a steroid-sparing agent in a large number of countries [32].

The usual recommended dose is 2.5mg/kg/day (maximum 150mg) given every other day for at least 12 months with hematological follow-up every 12-16 weeks, when most children will relapse if levamisole is discontinued. There is evidence that prolonged use of levamisole for more than one year reduces the risk of relapses [11,30]. ANCA positivity is a common side effect of levamisole. Monitoring is required to determine side effects including ANCA positivity and treatment modified accordingly [33].

4.2.3 Cyclosporine

Cyclosporine is an effective calcineurin inhibitor in reducing the number of relapses in steroid-dependent patients and frequent relapses , and it has been recommended by KDIGO as the first line in the treatment of steroid-resistant patients [11,32]. The proteinuria-reducing action is explained primarily by the immunosuppressive action which, presumably, is directed at the glomerular permeability factor, and secondly by a non-immunological effect directed at glomerular permeability. However, cyclosporine may h ave important cosmetic effects such as hypertrichosis and gingival hypertrophy. In addition, there is a high risk of developing renal dysfunction. Kidney biopsies of patients on prolonged use of cyclosporine suggest tubulointerstitial injury in 30-40% of cases, in those patients using the medication for 12 months [20]. These agents increase the risk for diabetes, which is generally related to the dose used. The recommended dose is 4-5mg/kg/day divided twice that should be adjusted to a pre-dose serum level of 60-100ng/ml and two

hours post-dose of 300-700ng/ml, with use for a minimum of 12 months [26].

In a systematic review carried out by Larkins et al, cyclosporine compared to prednisone reduces the number of children who have relapses, and when compared to alkalizing agents (cyclophosphamide) there is no difference in relation to relapses in the first year, but alkalizing agents have greater benefit in the second year of use [26].

4.2.4 Tacrolimus

Tacrolimus has a similar response to cyclosporine, it acts by inhibiting calcineurin and, consequently, the production of cytokines by the CD4 lymphocyte, resulting in a decrease in the production of interleukin 2 and interferon-gamma. The recommended initial dose is 0.1mg/kg/day in two daily doses, and serum levels should be maintained between five and eight ng/ml pre-dose for a minimum period of 12 months, as directed by KDIGO [34–36]. In general, it is recommended as a replacement for cyclosporine when the cosmetic effects are excessive, but maintain the risk of adverse events such as nephrotoxicity and diabetes [36]. It must be administered for a minimum period of two years. The vast majority of studies, including serum levels, were carried out with post-kidney transplant patients. Basu et al in 2018 compared the response to the use of tacrolimus in relation to the response to rituximab in patients with steroid-dependent nephrotic syndrome, demonstrating that tacrolimus is effective in reducing relapses but inferior in relation to the reduction of weight gain, growth and normalization of the cholesterol, when compared to rituximab [36].

4.2.5 Mycophenolate

Mycophenolate is a potent inhibitor of inosine monophosphate dehydrogenase, being selective, potent and reversibly binding [32,37]. It is capable of inhibiting the synthesis of purines and, consequently, the synthesis and activation of lymphocytes. It was described as a corticosteroid-sparing medication in 1999 and is currently also used in patients with CDSN. It is effective in maintaining remission in patients with CDSN and RFSN in more than 50% of cases with low adverse events [24]. It has similar efficacy to levamisole, cyclosporine and tacrolimus in reducing the number of relapses, with less cosmetic effects and without generating nephrotoxicity like cyclosporine [26]. It should be used at a dose of 1200mg/m^2/day in two daily doses for at least 12 months of use, according to the KDIGO protocol [34,35]. The most common adverse events are gastrointestinal and hematological events such as leukopenia [35].

In a retrospective study, Karunamoorthy et al described the response to the use of mycophenolate in 87 pediatric patients, most of them with RFNS. As a result, they observed prolonged remission with the use of mycophenolate and low doses of corticosteroids in two-thirds of the cases evaluated, with an average treatment period of two years [37]. Wang et al compared the use of mycophenolate *versus* tacrolimus, demonstrating that both medications are effective in preventing relapses and in maintaining relapse-free time in patients with CDNS and RFNS [35]. Infection was the most common adverse event found and comparable in both groups [35,37].

4.2.6 Rituximab

Rituximab is a monoclonal antibody that inhibits CD20 and, consequently, the proliferation of B cells and their differentiation. Initially, rituximab was used to treat cases of lymphoma and a variety of autoimmune diseases, such as autoimmune anemia and related ANCA vasculitis. It has been shown to be the most promising corticosteroid-sparing medication available on the market, having been described for this use since 2004 [38–40]. The vast majority of studies have shown efficacy in inducing remission in patients with NS steroid-dependent [28]. However, the appropriate dose and duration of treatment still need to be better defined, as well as the risk of adverse events with its long-term use. The most commonly recommended dose is two infusions of 750mg/m^2 on day one and day 15 [28,40]

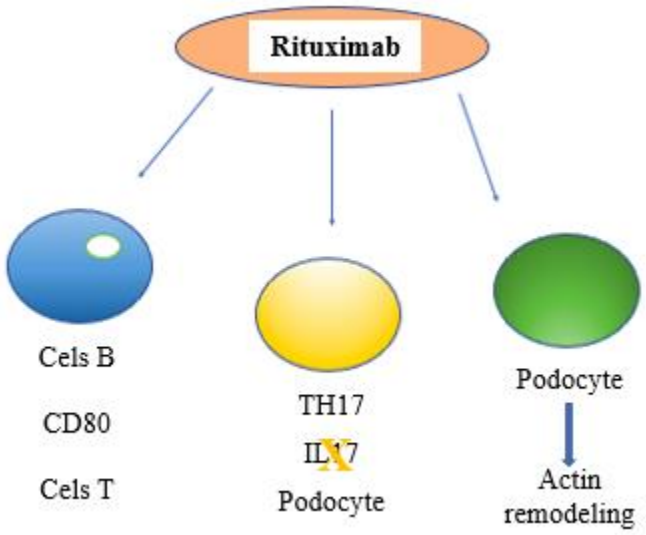

Figure 3 - Proposed mechanism of rituximab action (Source: Pediatric Nephrology Unit – Santa Casa de Belo Horizonte Hospital – Minas Gerais - Brazil)

Multiple published studies suggest that the response to the use of rituximab varies according to the clinical characteristics of each patient. This indicates that the association with molecular tests may predict which patients may present a satisfactory response to the use of medication [28,40].

Currently, its use is recommended only for patients who fail to maintain remission with appropriate use of the combination of corticosteroid therapy and corticosteroid-sparing medications, or who experience adverse effects from these medications. Basu et al compared the efficacy of rituximab in relation to tacrolimus as a way of establishing rituximab as a first-line steroid sparing agent [36]. One hundred and twenty patients were randomized and 117 completed one-year follow-up. For children with CDSN, rituximab appeared to be more effective than tacrolimus in maintaining remission. Although rituximab and tacrolimus treatments were relatively well tolerated, the number of infections in the tacrolimus group was relatively higher [36].

In relation to cyclophosphamide, in the study carried out by Webb et al (2016), rituximab (protocol with two doses of 750mg/m^2) proved to be effective in inducing prolonged remission and had fewer side effects than cyclophosphamide [29]. Regarding the ideal dose, Maxted et al compared a single dose of 375mg/m^2 with the usual dose used (1.5g/m^2) and demonstrated a similar outcome in suppressing CD19+ cells and maintaining remission in pediatric patients with CSND and RFSN at six months but less effective at 12 months. In 24 months, the low dose regimen was lower than the dose of 750mg/m^2 in two doses [40].

4.2.7 Ofatumumab

This medication has recently been licensed for use in humans and has shown efficacy in killing B cells. It is an antibody that recognizes the membrane epitope of the human CD20 molecule and whose structure allows for a closer antigen-antibody binding on the cell membrane of B cells [41]. A study demonstrated the potential effect of this drug in six patients with ISN who were resistant to other medications, and all patients showed normalization of proteinuria [38,42]. However, the result was only confirmed in patients with normal renal function, which could predict that ofatamumab would respond only in children with normal renal function [38,42].

4.3 Unconventional Therapies

4.3.1 Gluten-free diet

There is little evidence to support the use of a gluten-free diet in the treatment of patients with NS. The largest pediatric cohort was performed by Lemley et al with eight steroid-sensitive patients with frequent relapses or steroid-dependent patients, and the authors demonstrated a favorable impact of diet in reducing the number of disease relapses [43]. The gluten-free diet has the advantage of being easily accessible and does not present renal toxicity, but it has not yet been possible to establish the mechanism of action of such an intervention. However, gluten may be involved with inflammatory mediators responsible for increasing glomerular vascular permeability, and a diet that excludes this element may have a direct effect on podocyte structure [43]. Thus, better evidence is needed to establish the effectiveness of the intervention. With the advent of biomarkers, it may be possible to predict which patients will benefit from this measure [43].

4.3.2 Calcium and Vitamin D Supplementation

Low levels of 25-hydoxy-cholecalciferol occur in SNI and its main therapy, corticosteroid therapy, is related to the reduction of bone mineral density. In addition, patients with NS have a loss of vitamin D binding protein along with albumin. There is also an association between hypovitaminosis D and infections and inflammatory processes [44].

Although calcium and vitamin D supplementation improve the serum level of vitamin D, there was no efficacy in reducing relapses during the follow-up of patients using these medications [44]. As an adverse event to the use of vitamin D supplementation, the occurrence of hypercalciuria was noted. Banerjee et al there demonstrated an occurrence of 52% of hypercalciuria in patients treated with vitamin D compared to 18% of patients in the control group, which suggests caution in the use of this therapeutic strategy [44].

4.3.3 Zinc supplementation

Zinc supplementation as an adjunctive therapy in the treatment of INS does not have its mechanism of action clarified. However, zinc deficiency appears to be associated with reduced TH1 and TH2 cytokine activity increasing the risk of infections. In 2016, Bhatt et al published a review article in which they evaluated data from children aged between one and 18 years. In the articles analyzed in the systematic review, the dose used was between 10-20mg/day of zinc and the duration of treatment was between 6-12 months. Compared to placebo, the use of zinc reduced the frequency of relapses and reduced episodes of infection. However, the articles analyzed presented evidence of low quality, requiring prospective studies to define the real role of zinc supplementation, as well as the initial dose [45].

5. Conclusions

Considering that there is still no strong evidence on the choice of steroid-sparing medication, the decision of this choice must be individualized, always considering the risks of adverse events and the costs of these medications. This decision must also be shared with the children's family members so that they understand the need to use the medication and can make the correct use of it.

Regarding non-pharmacological therapies (diet and vitamin and mineral supplementation) it is not possible, to date, to recommend their routine use. With the advent of molecular medicine and the availability of molecular tests on a large scale, individualized and appropriate therapy for each patient may become a reality.

6. References

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