CLINICAL
INVESTIGATION

Treatment of children with frequently relapsing steroid-sensitive nephrotic syndrome: recent trial results

Despite being an orphan disease idiopathic nephrotic syndrome in children is the most frequent glomerular disease in this age group. A total of 80–90% of children between 2 and 10 years of age respond to corticosteroids, but carry the risk of relapses that may even appear frequently (frequently relapsing nephrotic syndrome, [FRNS]). To avoid repeated courses of corticosteroids and associated drug toxicity in these patients manifold strategies for a corticosteroid-sparing treatment of FRNS exist, but evidence on their efficacy and safety is low. This article discusses the results of recent therapeutic trials on FRNS and their possible impact on existing guidelines. Since the prognosis of steroid-sensitive nephrotic syndrome toward renal function is generally good, not only the efficacy but also the toxicity of different treatment regimens is discussed.

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The incidence of idiopathic nephrotic syndrome (INS) is reported to be 2–7/100,000 children below 16 years of age [1] and has been reported to be 1.8 per 100,000 children below 16 years of age in Germany [2]. Despite of fulfilling the criteria of an orphan disease, INS is the most common glomerular disease in childhood. Nephrotic syndrome is clinically defined by urine protein excretion of ≥40 mg per m^2 body surface area (BSA) per hour (h) or urine protein/creatinine (Up/c) ratio ≥2 g/g (first or second morning urine) and serum albumin concentration ≤2.5 g/dl [3]. Edema are generally present, especially at first onset of the disease, as well as hyperlipidemia.

In order to assess the individual facets of the disease a classification using the following criteria is helpful:

• Etiology (primary disease: either idiopathic or genetic; secondary disease: for example, due to infections, autoimmune diseases, tumors, etc.);

• Age at onset (until third month of life [congenital nephrotic syndrome]; 4 months to 1 year [infantile nephrotic syndrome]; >1–10 years; 11–18 years);

• Histology (minimal change disease; focal segmental glomerulosclerosis [FSGS]; diffuse mesangial sclerosis; mesangial-proliferative glomerulonephritis; membranoproliferative glomerulonephritis; membranous nephropathy);

• Responsiveness to a defined treatment with corticosteroids (e.g., 60 mg/m^2 BSA per day [d] for 4 weeks).

This review focuses on idiopathic forms of the nephrotic syndrome that typically occur between 2 and 10 years of age. A total of 80–90% of these children respond to corticosteroids and show the histological pattern of minimal change disease in 80% of cases. The risk of relapse is high with 50–70% of patients experiencing relapse within 2 years after onset and 80–90% of patients experiencing relapse until the end of adolescence [4,5]. Treatment of those 30% of patients suffering from frequent relapses or steroid dependent nephrotic syndrome (SDNS) (Table 1) remains challenging.

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Table 1. Definition of nephrotic syndrome in children.	
Item	**Definition**
Nephrotic syndrome	Urine protein concentration of ≥40 mg/m² BSA per hour (urine collection for a minimum of 12 h) or Up/c ratio ≥2 g/g (first or second morning urine); and serum albumin concentration ≤2.5 g/dl
Complete remission	Reduction of urinary protein (concentration or excretion) in the first or second morning urine for 3 consecutive days to: dipstick negative or trace or Up/c ≤0.2 g/g or urine protein excretion of ≤4 mg/m² BSA per hour (urine collection for a minimum of 12 h)
SSNS	Remission within 28 days after beginning of standard prednisone therapy for first episode of idiopathic nephrotic syndrome in children (60 mg prednisone/m² BSA per day)
SRNS	No remission within 28 days after initiation of standard prednisone therapy for the first episode of idiopathic nephrotic syndrome in children
Relapse	Reappearance of proteinuria for 3 consecutive days:dipstick ≥ 100 mg/dl (first or second morning urine) or Up/c ratio ≥2 g/g (first or second morning urine) or urine protein excretion of ≥40 mg/m² BSA per hour (urine collection for a minimum of 12 h)
Infrequently relapsing nephrotic syndrome	Relapses occur 1- to 3-times in any 12 month period or one relapse within the first 6 months period after initial response
FRNS	Relapses occur four or more times in any 12 month period or two or more relapses within the first 6 months period after initial response
SDNS	Relapses occur during the alternate day prednisone treatment period or within 2 weeks after discontinuation of prednisone treatment
Secondary steroid-resistant nephrotic syndrome (late nonresponder)	No remission within 28 days after initiation of standard prednisone therapy for relapse of idiopathic nephrotic syndrome in children (60 mg/m² BSA/day)
BSA: Body surface area; FRNS: Frequently relapsing nephrotic syndrome; SDNS: Steroid-dependent nephrotic syndrome; SRNS: Steroid-resistant nephrotic syndrome; SSNS: Steroid-sensitive nephrotic syndrome; Up/c: Urine protein/creatinine ratio. Data taken from [3,4,6].	

It should be kept in mind, that every relapse could potentially be complicated by thromboembolism, infection, severe edema, acute renal failure, psychological changes and disturbances in carbohydrate and lipid metabolism in the same way this can happen at the onset of the disease. Especially with repeated treatment courses of corticosteroids one has to consider the potential long-term risk of hypertension, obesity, striae, hirsutism, cataract, glaucoma, arterial hypertension, growth failure, osteopenia and avascular bone necrosis.

Manifold treatment options exist for patients with frequently relapsing nephrotic syndrome (FRNS). However, evidence on efficacy and safety is low due to a lack of randomized controlled trials (RCT). From the current point of view an exact characterization of the disease according to the above-mentioned criteria and the clinical course (e.g., differentiation between frequent relapses and corticosteroid dependent disease) is mandatory for future trials on this topic. This is of utmost importance, because the etiology and pathogenesis of the disease still remain unclear. The course of the disease is variable, and

the severity of the disease changes during childhood. The reason for this clinical variability is unknown. After all, the prognosis of steroid-sensitive nephrotic syndrome is generally benign and less than 30% of patients will expect a relapse in adulthood [7]. For that any treatment option for FRNS should primarily respect the principle of *nihil nocere*.

Analyzing recent trial results on FRNS this review addresses the following questions:

- What, if any, is the impact of initial treatment of INS on the development of FRNS?

- Suggested first-line treatment of FRNS are corticosteroids [8]. Corticosteroid-sparing agents are recommended to be used in patients, who have developed corticosteroid-related adverse events. How are corticosteroid-related adverse events assessed that qualify for an alternative treatment?

- Which attempts exist in prevention of relapses in FRNS?

- Many corticosteroid-sparing agents are considered in the guidelines [8], but there is no clear recommendation, because the available studies are heterogeneous. How can recent clinical trials on this topic contribute to a more detailed insight into the efficacy and safety of novel treatment regimens with the overall aim of an individualized treatment?

Impact of initial treatment

There is general agreement on the unique value of corticosteroids as first-line treatment of childhood INS to induce remission. Current recommendations merely vary in the length of initial treatment, that is eight (ISKDC) or 12 (GPN) weeks. Attempts to reduce the number of relapses and the risk to develop frequent relapses by prolonging initial treatment beyond 12 weeks showed some success, but this was attributed to an increased cumulative dose, rather than treatment duration [9]. Although the Cochrane Systematic Review from 2007 on this topic indicated, that both, total dose and total duration of prednisolone, may reduce the risk of relapse and of FRNS [10], a closer look at the included studies reveals that no analytical differentiation was made between total dose and total duration of prednisolone with exception of two studies [9,11]. Furthermore, power and reliability remain questionable since the number of included patients was low in all studies included. Anyway, there is some evidence that especially younger children might benefit from an intensified initial treatment either by increasing the cumulative corticosteroid dose for a prolonged period of time [11] or by adding cyclosporine (CsA) [12]. However, these findings result from posthoc subgroup analyses. Nonetheless they underline the heterogeneous clinical phenotype of the disease and the necessity to exactly define treatment groups in future trials.

The most recent trial on the potential value of a prolonged initial treatment period by a Dutch group did not show any benefit toward risk of relapse or toward development of frequent relapses. In this prospective trial children with INS had been randomized to either 12 or 24 weeks of initial corticosteroid treatment without a difference in the cumulative corticosteroid dose [13]. In summary, the Dutch study supports the notion that there is no advantage in prolonging initial corticosteroid therapy in INS beyond 12 weeks and disproves some studies with limited methodological quality [14,15]. However, a reduction of the initial corticosteroid-associated toxicity might be achieved, when the corticosteroid dose is spread out to a longer period [11,13].

Two recent adequately powered studies emphasize that extending duration and total dose of prednisolone in initial treatment does not significantly influence the course of SSNS. Yoshikawa et al. demonstrate that initial prednisolone treatment of childhood nephritic syndrome for 2 months is not inferior to 6 months in terms of occurrence of FRNS but results in lower cumulative corticosteroid dose in the 2-year trial period [16]. In the study by Sinha et al. there was no difference in number, occurrence or frequency of relapses after 3 or 6 months initial treatment. Cumulative prednisolone dose, however, was increased by approximately 24% in the 6-months treatment group [17].

The ongoing study PREDNOS in the UK compares the standard therapy in the UK (60 mg prednisolone/m² BSA per day for 4 weeks followed by 40 mg/m² BSA on alternate days for 4 weeks) against an extended protocol with 4 weeks followed by 12 weeks prednisolone 60 mg/m² BSA per day (maximum 80 mg per day) on alternate days tapered by 10 mg/m² every 2 weeks [18]. The minimum follow-up is 24 months. The results of this study will help to finally answer the question, whether there is a benefit of a longer duration and a higher cumulative steroid dosage in the initial treatment of INS, assessed by the frequency of relapses as the primary study end point.

How are corticosteroid-related adverse effects assessed?

Corticosteroids are the backbone of the initial treatment of the nephrotic syndrome as well as of the treatment of relapses. Even though being effective, this treatment is associated with pronounced corticosteroid-associated toxicity due to high-dose prednisone administration over a prolonged period of time [4,5,8,11,13,19,20].

Major side effects comprise obesity, striae, hirsutism, cataract, glaucoma, arterial hypertension, disturbances of the carbohydrate and lipid metabolism, growth failure, osteopenia, avascular bone necrosis and psychological disturbances. Not all of these side effects are fully reversible after cessation of corticosteroid therapy. The KDIGO guideline from 2012 recommends corticosteroid-sparing agents to be prescribed for children with FRNS and SDNS, who develop corticosteroid-related adverse effects [8]. However, neither for short-term toxicity nor for long-term toxicity a validated corticosteroid-toxicity score exists. Therefore, the decision to introduce corticosteroid-sparing agents in patients with FRNS varies from center to center and from country to country [21]. In conclusion, there is a need to generate such a score to make therapeutic decisions verifiable. The difficulty undoubtedly is that corticosteroid-associated side effects appear with high interindividual variability and that there are objective, measurable side effects such as arterial hypertension, growth failure or obesity, some of which are potentially

temporary and limited to the treatment period (e.g., arterial hypertension), some of which may be not (e.g., obesity [22,23] or growth failure [19]) and some side effects are rather subjective, but incriminatory such as psychological disturbances.

All the above mentioned potential side effects of corticosteroid treatment should therefore be monitored for and documented routinely even in the long-term follow-up. By implication the decision to use corticosteroid-sparing agents in FRNS remains an individual one, and future studies will have to find arguments for alternative treatment options apart from repeated courses of corticosteroids in FRNS. In clinical practice the relative comfort and safety of some of the agents promising a corticosteroid-sparing approach certainly results in their early use in FRNS even before corticosteroid-associated adverse effects appear.

Which attempts do exist to prevent relapses in FRNS?

The number of relapses reflects the level of disease activity, and a high number of relapses are a risk factor for recurrence in adulthood [24]. It therefore seems prudent to look for strategies to avoid relapses even beyond the maintenance immunosuppressive/immunomodulatory treatment regimen. The overall aim is to minimize acute and chronic morbidity by the reduction of the cumulative dose of corticosteroids. A potential approach to reduce relapses is the observation that a significant number of children show distinct triggers for relapses including infections, in particular upper respiratory tract infections, allergic episodes, vaccinations or emotional stress.

Studies from Saudi Arabia, Sri Lanka and India suggest that the use of a 5–7 days course of daily prednisone therapy at the time of an upper respiratory tract infection lowers the rate of relapses in children with FRNS [25–27]. Accordingly, the KDIGO guideline [8] suggests, though with low quality of evidence, daily prednisone be given during episodes of upper respiratory tract and other infections to reduce the risk for relapse in children with FR and SD SSNS already on alternate-day prednisone.

There is an ongoing RCT from the UK (PREDNOS 2), which assesses the efficacy of a 6 day course of daily prednisolone starting at the time of onset of an upper respiratory tract infection to avoid relapses in FRNS (primary end point) [28]. It is of note that this study includes subjects, who do not receive long-term immunomodulatory therapy as well as those who do, including also those on prednisolone up to 15 mg/m^2 on alternate days. In April 2014, 80/300 children with FRNS have been recruited so far.

Which agents should be used in children with FRNS to maintain remission?

Worldwide, the most common first-line treatment for FRNS is corticosteroids. The use of low-dose daily or alternate day maintenance prednisone during relapse-free periods to avoid relapses is based on observational studies rather than RCT data [29,30]. This approach is therefore suggested only with low quality of evidence [3,8].

Within the last decade no well-designed prospective clinical trial was performed in this field of interest. Alternative treatment options beyond corticosteroids to maintain remission in FRNS are alkylating agents (cyclophosphamide, chlorambucil), levamisole, mycophenolate mofetil (MMF), calcineurin inhibitors (CNI) (CsA, tacrolimus), mizoribine and rituximab (Figure 1).

However, published data has not allowed to establish any distinct recommendation in favor of one of these agents yet. For example, timing and use of cyclophosphamide in comparison to CNI remain unsolved according to published RCTs. Both RCTs from the nineties, comparing CsA and alkylating agents, revealed similar relapse rates during treatment [31,32]. One has to consider, however, that a comparison between alkylating agents and CNIs is conceptually problematic, because CNIs have to be administered long-term to maintain the therapeutic effect, while alkylating agents, administered for 8–12 weeks, have a long-lasting effect due to their biologic interaction with DNA cross-linking and death of target cell populations [8].

Alkylating agents: cyclophosphamide & chlorambucil

There have been no trials toward alkylating agents recently. Meanwhile, data about the associated toxicity has led to a decreased use of alkylating agents. Chlorambucil and cyclophosphamide are equally effective in reducing the risk of relapse in FRNS, but toxicity of chlorambucil seems slightly higher regarding suppression of spermatogenesis [33,34]. Reduced gonadal function after use of cyclophosphamide without a clear safety threshold has been demonstrated [35].

A distinct differentiation of FRNS and SDNS is mandatory for the interpretation of trial results. Cyclophosphamide shows higher efficacy in FRNS than in SDNS [36]. Recent data confirm that poor outcome regarding relapses is associated with young age, male sex and FSGS [37,38]. Additionally, in patients with SDNS requiring high dosage of corticosteroids to maintain remission cyclophosphamide is less effective [39]. A retrospective analysis in France has shown better efficacy of cyclophosphamide in children with SDNS
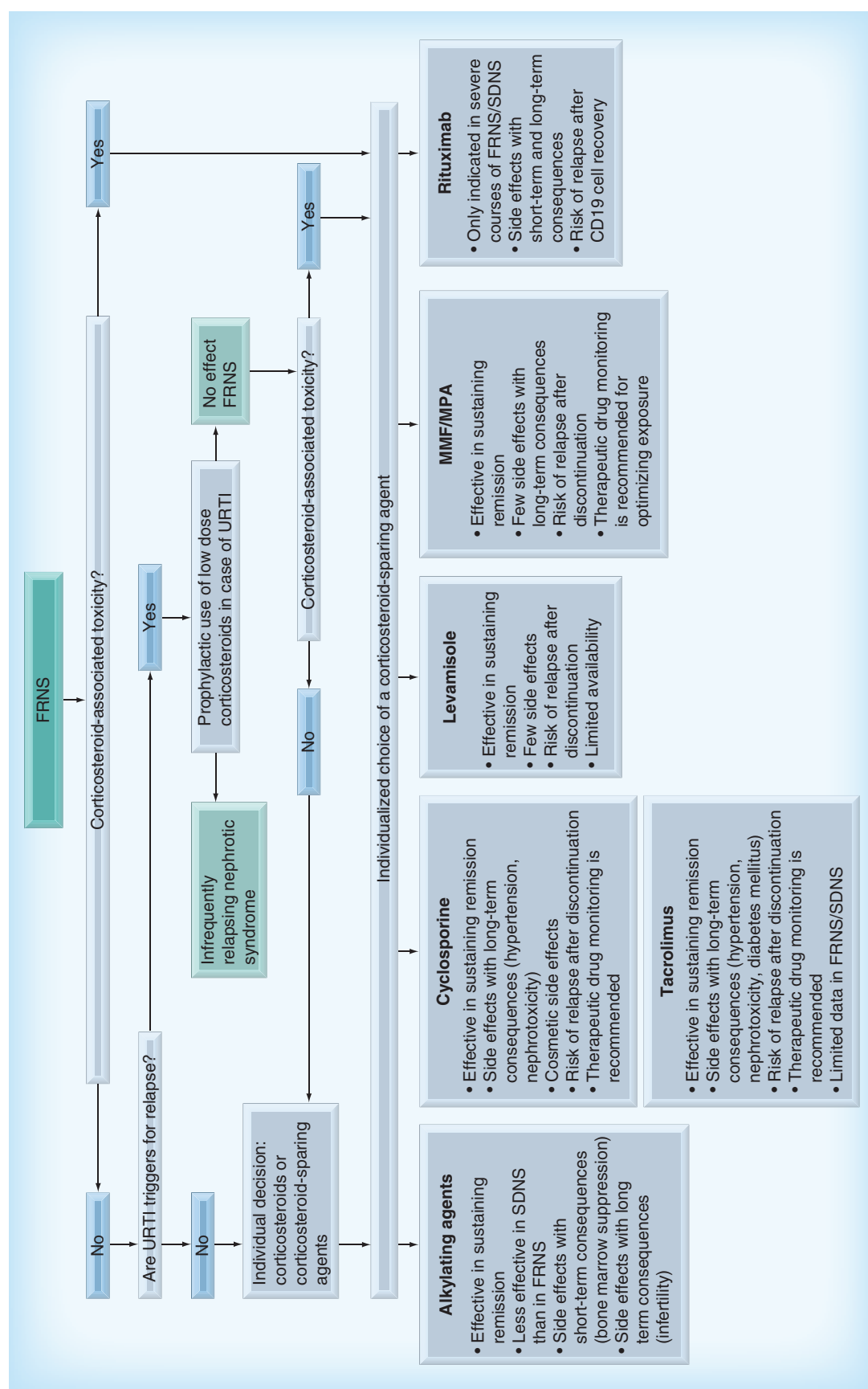
Figure 1. Summary of treatment options in frequently relapsing nephrotic syndrome. In children suffering from FRNS the presence of corticosteroid associated toxicity should be considered regularly. In case of corticosteroid associated toxicity alternative immunomodulatory therapy should be discussed.
If recurrent URTI is an individual trigger for relapses for relapses of SSNS, prophylactic use of low dose corticosteroids in case of URTI may help to prevent relapses. In FRNS alkylating agents, calcineurin inhibitors, levamisole, MMF/MPA and rituximab significantly reduce the risk of relapse. Due to a lack of head-to-head trials a clear recommendation for corticosteroid-sparing agents in FRNS is not possible. Characteristics of each substance are ticked in the particular box.
FRNS: Frequently relapsing nephrotic syndrome; MMF: Mycophenolate mofetil; MPA: Mycophenolic acid; SDNS: Steroid-dependent nephrotic syndrome; URTI: Upper respiratory tract infection.

>7.5 years of age [40]. In summary, cyclophosphamide may be an effective second-line treatment in a selected cohort of patients especially in SDNS, but should be used reluctantly especially in adolescents because of its gonadal toxicity. In this respect the KDIGO guideline suggests that second courses of alkylating agents are not to be given [8].

Cyclosporine

Since the first reports on the efficacy of CsA in children with FRNS and SDNS, CsA has been established in corticosteroid-sparing treatment of INS in children [41]. Prolonged courses of CsA reduce the risk of relapse in children with FRNS compared with corticosteroids alone [33], as well as compared with alkylating agents [31,32], but children with FRNS or SDNS are at high risk of relapse after discontinuation, particularly those who experienced relapse during CsA treatment [42]. CsA administration by itself is a significant predictor of relapse in adulthood [37,43,44]. The length of treatment with CsA remains controversial, but most centers try to taper the medication after 1–3 relapse-free years.

In order to reduce the known adverse effects of CsA including hypertension, and acute and chronic CNI-induced nephrotoxicity, the focus on recent investigations on CsA in FRNS has been on identifying risk factors for CsA-associated nephrotoxicity (CsAN) and on optimizing therapeutic drug monitoring. In addition to regular monitoring of glomerular filtration rate, levels of uric acid should be measured in these patients, because hyperuricemia is an independent risk factor for hypertension [45]. The sustained remission rate was significantly higher in children with trough levels of 60–80 ng/ml than in children on a fixed dose of 2.5 mg/kg per day [46]. On the other hand CsA exposure with CsA-C_2 values >600 ng/ml [47] or high median CsA trough levels [45] are associated with the risk of CsAN. The incidence of CsAN increases the younger the patient is at start of therapy and the longer the duration is [48]. Performing therapeutic drug monitoring in children with FRNS one has to consider that CsA exposure is lower in remission than during relapse [49] due to hyperlipidemia and consecutive lipid binding of CsA. The functional relevance of this finding toward efficacy and toxicity, however, is unclear. Comparably to renal transplant recipients also younger children with relapsing nephrotic syndrome require a higher dosage of CsA to achieve the same exposure as adolescents, because the intestinal absorption area is smaller and the metabolic turnover is faster [50].

In summary, CsA is an effective agent to maintain remission in children with FRNS. Therapeutic drug monitoring should be performed to optimize efficacy

and to minimize toxicity. Treatment duration should be restricted to less than 3 years to avoid CsAN, of which duration of CsA therapy >3 years is an independent risk factor [47,48].

Tacrolimus

There is limited observational data, but no RCTs using tacrolimus in FRNS or SDNS. Most data published contribute to the role of tacrolimus in SRNS. However, the available data on FRNS show tacrolimus to be comparable to CsA in sustaining remission but with a better adverse effect profile, in particular in terms of cosmetic side effects such as hypertrichosis and gum hyperplasia [51,52]. Whether tacrolimus should be generally recommended in patients with FRNS, at least in those with cosmetic side effects attributed to CsA, cannot be finally answered from the recent data. Tacrolimus-associated adverse effects such as diabetes mellitus and increased exposure in case of diarrhea have been described in children with nephrotic syndrome [53–55]. According to experiences in children with SDNS and SRNS it may be possible to sustain remission with low-dose tacrolimus also in patients with FRNS [56].

Mycophenolate mofetil/mycophenolic acid

First observational studies demonstrating the efficacy of MMF to reduce the risk of relapse in SDNS and FRNS have been accompanied by its growing popularity due to the favorable adverse effect profile, especially with regard to the lack of nephrotoxicity [57–65]. Because of the paucity of RCT, KDIGO only suggests MMF, which is a prodrug of the active moiety mycophenolic acid (MPA), as second-line medication in FRNS with low evidence of quality [8].

MMF has been compared with CsA in FRNS in two studies [64,65]. In a small number of patients the comparative study by Dorresteijn *et al.* did not show a significant difference in the number of relapses at 12 months, although CsA had a clear tendency toward a better outcome [66]. In the same study the glomerular filtration rate was significant better in patients on MMF compared with those on CsA [66]. The recent crossover prospective randomized trial of The German Society for Pediatric Nephrology (GPN) revealed a favorable effect of CsA toward number of relapses and duration of remission in the first year of observation, but no longer in the second year [67]. Again kidney function was significantly better in patients on MMF than in those on CsA. It is noteworthy that the efficacy of MMF was dependent on the degree of MPA exposure. In children with an estimated MPA-AUC$_{0-12}$ above 50 mg × h/l the efficacy of MMF was comparable to that of CsA. The importance of therapeutic drug monitoring of MPA in FRNS had already been shown

earlier in a smaller cohort of patients by analyzing full 12 h pharmacokinetic profiles [68]. Receiver operating characteristic curve analysis revealed a MPA exposure (MPA-AUC$_{0–12}$) of >64 mg × h/l as cut-off for the discrimination of patients without relapse from those who relapsed with a sensitivity of 100% and a specificity of 89% without any relevant MPA-related toxicity.

Also in SDNS MMF has the potential to reduce the prednisone maintenance dose and to sustain remission without chronic steroid therapy, as has been demonstrated by a Bayesian Phase II trial [69]. However, efficacy might depend on disease severity as discussed by a Japanese study showing CsA to be more effective for sustaining remission than MMF in severe SDNS after a single infusion of rituximab [70].

In conclusion, MMF is a valuable second-line therapy in FRNS without the burden of nephrotoxicity provided that MPA exposure is sufficient. Target values for adequate MPA exposure under MMF monotherapy for nephrotic syndrome are somewhat higher than in pediatric renal transplant recipients under combined immunosuppressive therapy. Further prospective studies comparing CNI and MMF/MPA including also pharmacodynamic and pharmacogenetic data would be helpful to review these medications.

Mizoribine

Mizoribine (MZR) is an imidazole nucleoside, which was first isolated from the mold *Eupenicillium brefeldianum* and inhibits lymphocyte proliferation via blocking inosine monophosphate dehydrogenase like MPA [71]. MZR, trade name Bredinin®, is only available in China, Japan and South Korea and nearly all experience with MZR in FRNS and SDNS comes from Japan. In studies on renal transplant recipients MZR and MMF are considered almost equivalent in terms of efficacy and safety, despite MZR shows the unique side effect of a significantly elevated uric acid serum level [72,73]. Incidence of adverse reactions due to MZR in patients with nephrotic syndrome (n = 240) was described in only 15.8% [72]. In detail the side effects of MZR are: leukopenia (0.83%), anemia (0.42%), pneumonia (0.42%), rash (2.08%), epilation (1,67%), increased uric acid serum concentrations (2.5%), cephalgia (1.67%), anorexia (0.83%), vomiting (0.42%), diarrhea (0.42%), stomatitis (0.42%) and abnormal hepatic function (2.29%) [71]. There is some evidence from observational studies that MZR pulse therapy is effective in decreasing the frequency of relapse and may prevent treatment with CsA [74,75]. A small Phase II trial suggested an association of dose and efficacy [76]. In a double-blind, placebo-controlled trial MZR did not significantly decrease the relapse rate in FRNS and prolonged the remission period only in a subgroup of patients below the age of 10 years (post-hoc analysis) [77]. The KDIGO guideline does not suggest using MZR as a corticosteroid-sparing agent in FRNS [8].

Levamisole

Levamisole, a synthetic imidazothiazole derivative, is used as an immunomodulatory agent. Former studies, summarized in meta-analyses, show heterogeneous results but conclude levamisole to be more effective than prednisone or placebo in reduction of relapses [33]. However, studies are rather heterogeneous regarding included population (FRNS, SDNS or both without differentiation), time period of administration of levamisole (4, 6 or 12 months), dosage (once per month, alternate day dosing) or in mode of publication (full papers versus abstracts) [78–83]. The efficacy of levamisole seems to be comparable to that of cyclophosphamide regarding prevention of relapses after 24 months [33]. Consequently KDIGO recommends levamisole as corticosteroid-sparing agent with the same grading as cyclophosphamide [8].

The most recent trial was small and retrospective in character [84]. Notably it not only showed levamisole to be an effective corticosteroid-sparing agent but also demonstrated a long-lasting effect 12 months after withdrawal. Others report that most children relapse after discontinuation of levamisole [8]. There is an ongoing trial supported by the European Society for Paediatric Nephrology (ISRCTN23853712) on the role of levamisole in FRNS that is awaited to be published [85].

Adverse effects of levamisole are uncommon and include mild leukopenia, gastrointestinal upsets and cutaneous vasculitis. Generally levamisole is administered as a liquid that has the disadvantage of a bitter taste and is not available in every country. The development of an oral solid dosage form of levamisole suitable for the pediatric population should be followed by new trials in this field [86].

Comparison of MMF versus levamisole in children with FRNS/SDNS revealed MMF to be more effective than levamisole in maintaining remission (i.e., reduced number of relapses and longer duration of relapse-free interval) [87]. In patients with SDNS MMF is more effective than levamisole in reducing cumulative steroid dose.

Rituximab

Rituximab is suggested only for children with SDNS, who continue to have frequent relapses despite optimal combination of corticosteroids and corticosteroid-sparing agents and/or who have serious adverse effects of therapy [8]. In a RCT of an Italian group rituximab has shown to be effective to

lower the dose of maintenance CsA and prednisone in corticosteroid- and CsA-dependent patients in short term [88]. The same group confirmed these data in long-term in an uncontrolled trial [89]. There are cases series and retrospective observations that show comparable results [90–92]. One has to consider the risk of serious, but rare side effects such as lung fibrosis and viral myocardi-tis with the use of rituximab [93,94]. Further controlled studies are needed to address optimal patient selection, dose and safety of rituximab. The optimal therapeutic protocol seems to consist of repeated single infusions at the time of CD19-cell recovery [92,95]. However, a closer approach to the number of doses necessary for efficacy has to be proven in further comparative studies.

Recent studies published over the last 2 years illustrate the efficacy and safety of rituximab in children with com-plex courses of nephrotic syndrome by sustaining remis-sion and reducing the dose of corticosteroids and other maintenance immunosuppressants [96–99]. Especially the potential to lower the exposure to corticosteroids and consecutively halt the steroid-associated growth deficit [98] argue for further evaluation of this agent.

Conclusion & future perspective

Recent clinical trials in children with FRNS are sparse. Because the etiology and pathogenesis of the nephrotic syndrome in childhood remain unclear, it is difficult to identify causal treatment approaches. Future trials should therefore not only focus on optimizing efficacy and minimizing toxicity of new treatment protocols, but also revive the search for a more precise under-standing of the etiology and pathogenesis of nephrotic syndrome, as well as potential triggers for recurrent relapses, which are due to a transient dysfunction of the glomerular filtration barrier.

Besides the discussed cytokine imbalances and permeability factors in nephrotic syndrome further research in epigenetic phenomena such as altered histone methylation [100] and in the role of podocyte cytoskeleton alterations [101] may help to find new therapeutic approaches.

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Executive summary

- In frequently relapsing nephrotic syndrome (FRNS) prolonged prednisone treatment, daily prednisone during infections, alkylating agents, calcineurin inhibitors, levamisole, mycophenolate mofetil/mycophenolic acid and rituximab significantly reduce the risk of relapse.
- Repeated and long-term use of corticosteroids in FRNS bears the risk of incriminatory adverse effects.
- Due to a lack of head-to-head trials a clear recommendation for corticosteroid-sparing agents in FRNS is not possible.
- Not only efficacy, but also short- and long-term side effects have to be considered in choosing steroid-sparing agents in FRNS.
- Mycophenolate mofetil/mycophenolic acid is effective in sustaining remission in children with FRNS or steroid-dependent nephrotic syndrome, when dosage is optimized by therapeutic drug monitoring.
- An oral solid dosage form of levamisole suitable for the pediatric population could be promising for new comparative studies.
- Rituximab may be an effective third-line option in patients with complex courses of nephrotic syndrome. Risk of side effects has to be considered.
- Future scientific work in the field should revive the search for etiology and pathogenesis of idiopathic nephrotic syndrome.

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