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EDUCATIONAL REVIEW

New therapies in steroid-sensitive and steroid-resistant idiopathic nephrotic syndrome

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Abstract Although many children with idiopathic nephrotic syndrome (INS) respond initially to steroid therapy, repeated courses for patients with relapses often cause significant steroid toxicity. Patients with frequent relapses who develop steroid dependency thus require alternative treatment. The first such options have been considered to be cyclophosphamide or levamisole, although the latter is no longer available in many countries. There is also an increasing body of data indicating that mycophenolic acid (MPA) may be an alternative for these patients. Calcineurin inhibitors (cyclosporine A or tacrolimus) are usually effective and often used after cytotoxic treatment, but long-term treatment with these agents is necessary, raising concerns of a possible accumulation of side effects. Some patients show a tendency to relapse even on such maintenance regimens, and some even have a refractory course that creates a medical dilemma. For this situation, recent data indicate that monoclonal antibodies directed to B-cells (e.g. rituximab) may have some effect and that such drugs may also prove to be a therapeutic option in less complicated cases. Patients that do not respond to steroid treatment need genetic testing and a renal biopsy since focal segmental glomerulosclerosis (FSGS) may be present. Treatment options include pulse methylprednisolone, often in addition to calcineurin inhibitors, mainly in the form of cyclosporine, but tacrolimus has also come into recent favor. Some studies have found cytotoxic treatment, especially intravenous cyclophosphamide, to be effective in steroid resistant nephrotic syndrome, but it seems to be inferior to calcineurin inhibitors. MPA and rituximab have also been used in children with primary FSGS, but the response seems to be inferior to that in patients with steroid sensitive nephrotic syndrome. Taken together, INS in both steroid-sensitive and steroid-resistant patients is a potentially complicated disorder, and despite a wide arsenal of immunological interventions, some patients have a treatment refractory course. Prospective studies or at least standardized treatment for complicated cases is urgently needed.

Keywords Nephrotic syndrome · Steroid sensitive · Steroid resistant · Immunosuppression · Minimal change glomerulonephritis · Focal segmental glomerulosclerosis

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Introduction

In children, the term nephrotic syndrome describes the clinical triad of heavy proteinuria (>1 g/m^2/day or protein/ creatinine ratio >200 mg/mmol), hypoalbuminemia (<25 g/l), and the presence of generalized edema. Hypercholesterolemia was formerly included in the diagnostic criteria, although this is secondary to hypoalbuminemia. The most frequent cause of nephrotic syndrome is the so-called "idiopathic" nephrotic syndrome (INS), which predominantly includes two histological subtypes, namely, the minimal change nephrotic syndrome (MCNS) and focal segmental glomerulosclerosis (FSGS). Around 80% of pediatric cases show minimal change disease (MCD) based on the results of histological examination. Most of these children respond to steroids, as shown by the International Study of Kidney Diseases in Children (ISKDC); thus, a renal biopsy is no longer performed in children with steroid sensitive nephrotic syndrome (SSNS) [1].

Steroid resistant nephrotic syndrome (SRNS) is defined by the ISKDC as persisting proteinuria after a 4-week

course of oral prednisone (60 mg/m^2/day). A recent development in many centers has been standard treatment with a short course of intravenous methylpredinsolone in the case of steroid resistance [2] to exclude patients with delayed response ("late-responders"). Based on biopsy results the majority of patients with SRNS will either have FSGS, diffuse mesangial proliferation (DMS), or MCNS. Thus, most pediatric nephrologists would recommend a renal biopsy in patients with SRNS after confirmation of the clinical diagnosis, since this may have an impact on prognosis and on the choice of treatment.

In the past decade several genetic causes of SRNS have been identified (e.g. mutations in genes for podocin, WT1 but also APL1 variants and others), accounting for up to 30% of SRNS in children. The precise impact of these mutations on treatment outcome in these patients have not been established, although it should be noted that patients with genetic forms of SRNS have been included in all previous studies on SRNS, possibly with a significant negative impact on outcome. The pathogenesis of acquired SRNS is unclear, although an underlying immunological defect is suspected and is the rationale for the use of immunosuppressants or immunological interventions in this disorder.

The aim of this review is to summarize recent advances in the treatment of children with INS, both the steroid-sensitive and -resistant forms. The review includes a description of new therapies, such as mycophenolic acid (MPA) or rituximab, as well as new therapeutic aspects of drugs that have been used for a long time, such as steroids. In the first part, we focus on SSNS and in the second part, on SRNS. The optimal sequence of drugs, especially for the treatment of SSNS, is also discussed, but can not yet be definitively identified.

Treatment strategies for frequently relapsing or steroid-dependent SSNS (Table 1)

Impact of initial steroid treatment

The impact of initial steroid treatment on the subsequent course, especially the reduction of relative risk for relapses has been discussed repeatedly, especially by the Cochrane group, which claims that prolongation of initial steroid treatment for more than 3 months may result in a decreased risk for relapses [3]. Unfortunately, several weakly powered and unpublished studies from different geographic regions are included in this analysis. No adequately controlled studies at the onset of the nephrotic syndrome have been performed in recent years. One recently published series by the Arbeitsgemeinschaft für Pädiatrische Nephrologie (APN, now GPN), in which cyclosporine was added to the initial 3-month course of steroids, indicated that intensification of immunosuppression at the onset does not lead to superior long-term remission rates for the whole cohort of patients with SSNS [4]. However, in a subanalysis, patients younger than 6 years had a significantly higher rate of sustained remission at 2 years. This result confirms observations by Hiraoka et al. [5], who showed that prolongation of steroid treatment was beneficial only for children who were younger than 3 years at diagnosis. One double-blind Dutch study that compared a 12-week steroid regimen to an extended 6-month steroid treatment according to the Hiraoka protocol is currently under way, and the first results are expected in 2012. Until then, it is likely that the initial approach to the treatment of SSNS at presentation will show considerable variability, as recently documented by a survey in the USA [6].

Frequent relapses and steroid dependency: impact of definitions

Patients with more than four relapses in one year or more than two following the first 6 months after the initial presentation are classified as frequent relapsers according to the ISKDC criteria [7]. Steroid dependence is defined by the APN by the occurrence of at least two relapses during treatment with alternate-day steroids or within 14 days after stopping this treatment [8]. Due to the different long-term outcomes of these both clinical presentations of SSNS and the consecutive different treatment modalities which are needed, a distinct differentiation between frequent relapsing and steroid-dependent nephrotic syndrome is necessary.

With respect to steroid dependency, it should be noted that the severity and degree of steroid dependency is highly dependent on the steroid protocol used. If patients receive a tapering course of prednisone (where the definition of steroid dependency is relapse at a dose of >0.5 mg/kg), the threshold (and degree of steroid toxicity) will be much lower than in those in whom treatment is finished at a alternate dose of 40 mg/m^2/day (corresponding to approx. 1.5 mg/kg). These different definitions may have had an impact on results of alternative treatment in SSNS.

Alternative treatments for frequent relapsers may not be necessary because these patients often have a relatively good prognosis. Patients with steroid dependency, however, represent a more serious problems, especially when relapses recur despite alternative treatment. These patients are often exposed to many drugs (often for an extended time), and relapses may continue into adulthood [9]; thus steroid-dependent nephrotic syndrome is not regarded as a benign condition, even though renal function is not compromised [10]. Consequently, treatment series which include frequent relapsers may have a better outcome than those in which steroid-dependent patients, especially those with heavy steroid dependence, are included. To date, many studies

include a mix of patients with frequent relapses and different degrees of steroid dependency.

Levamisole

Within the context of new treatment options, the role of levamisole is controversial, although it has been used in SSNS treatments for more than 20 years and is often recommended as a first option [3, 11]. The mode of action of levamisole is unclear, although an immune-modulatory effect has been claimed. The side effects of levamisole are usually mild and include neutropenia, rashes, cutaneous vasculitis, and gastrointestinal symptoms. The dose used is 2–2.5 mg/kg given on alternate days, with a maximum dose of 150 mg.

Availability has become a problem more recently [11], although it is available for a European double blind study (Elmisol) in which levamisole is compared to placebo for frequent relapsers. Data from this study are not yet available. One problem of the protocol is the extended treatment with prednisone which may obscure the beneficial, steroid-sparing effect of levamisole that has been shown by the study of the British Association for Pediatric Nephrology.

Alkylating agents (cyclophosphamide, chlorambucil)

Alkylating agents have been used in childhood nephrotic syndrome since the 1960s. These lead to a depletion of immune competent cells although the exact mechanisms of action in SSNS are not known. Side effects include bone marrow suppression with leukopenia, hemorrhagic cystitis and, among many others, gonadal toxicity. Additionally, hair loss or thinning is possible. The maximum dose currently recommended is 2 mg/kg/day for 12 weeks, i.e. a total of 168 mg/kg, which is lower than the gonadotoxic dose of 300 mg/kg. In some countries, an equivalent dose of 3 mg/kg is given for 8 weeks.

The results of initial studies showing long-term remission rates in up to 67% of cases have not been confirmed in later studies; patient selection is one probable reason for the discrepancy in results [12]. Recent studies show that several prognostic factors are important, including degree of steroid dependency and young age, possibly because calculations using body weight may result in drug under-exposure in young children [13]. Alternatively, younger children may have an immature immune system that responds differently to cytotoxic treatment. Also, certain genetic polymorphisms, such as glutathione-tranferase, may predict a better response to cytotoxic treatment [14]. More recently, Kyrileis et al. [15] studied 93 children with SSNS and MCD from a biopsy registry with a median follow-up of 8 years (range 139 years). Again, only 35% of patients reached long-term remission at 2 years after cyclophosphamide treatment; however, 52 and 71% were off drugs at 6 and 15 years, respectively, after the start of cyclophosphamide therapy. More than 25% of these patients relapsed after the age of 18, indicating that cytotoxic treatment is often not completely satisfactory. Long-term gonadal toxicity, however, may be significant [16].

Intravenous cyclophosphamide has been used in both SRNS and SSNS therapeutic regimens. This mode of application may be less toxic than oral treatment, and a recent study showed some short term-benefit in SSNS, but no difference in long-term response [17]. The short-term response was superior, with a mean relapse free period of 360±88 days compared with 96±88 days after oral cyclophosphamide. However, fewer than 20% of patients remained in long-term remission after 2 years, although significantly more patients in the intravenous group were reported to have a milder course. The fact that the total number of doses differed in treatment groups raises the question of whether equivalent doses (maybe given at different time intervals) may further improve results in the intravenous group. Sharda et al. also reported a benefit in 50% of patients after intravenous cyclophosphamide, but they presented no exact outcome data [14]. Toxicity is reported to be less pronounced in the intravenous group so that further studies seem warranted. One major advantage of intravenous protocols is the improved adherence to treatment.

Chlorambucil is also an alkylating agent and is used at a dose of 0.15–0.2 mg/kg in a 12-week treatment regimen. It is usually not used as the first-line cytotoxic agent; rather, it is reserved for children with a complicated course who require a second course, such as following a relapse on cyclosporine. In this situation it has shown good results [18], but repeated courses of cytotoxic treatment should be avoided since toxicity accumulates [9, 16] and alternative treatments are available (see below).

In summary, cytotoxic treatment is still an option in SSNS, especially because of its relative low costs and wide availability. Long-term remission at 2 years can be expected in ≥30% steroid-dependent patients, and even higher rates may be expected in selected patients. While this remission rate is less than previously reported and desired, long-term remission rates of other treatment options are not really superior. Toxicity remains an important issue, and repeated courses should be avoided. The use of intravenous cyclophosphamide deserves further study, and efforts should be undertaken to identify prognostic factors for response.

Calcineurin inhibitors (cyclosporine A, tacrolimus)

Calcineurin inhibitors, especially cyclosporine, are frequently used to treat relapsing nephrotic syndrome. They have been used for more than 2 decades [19]. They inhibit

interleukin-2 (IL-2)-driven T-cell activation, and the dose of cyclosporine used for SSNS is usually 5 mg/kg in two divided doses (150 mg/m^2). No minimum trough level is usually recommended, although in patients relapsing on calcineurin inhibitors, some researchers recommend target trough levels in the range of those of renal transplant patients in the stable phase. For cyclosporine monitoring, C2 levels has also been used in SSNS [20].

Cylosporine

Several published series, including a Cochrane analysis [21], document the beneficial effect of cyclosporine. Initial [22] but also recent [23] studies have compared this drug to cytotoxic treatment. In these studies, cyclophosphamide seemed to induce long-term remission without further treatment in a larger proportion of patients than cyclosporine. Long-term treatment with cyclosporine is necessary (cyclosporine dependency); consequently, side effects may accumulate, especially nephrotoxicity, hypertension, and cosmetic effects (hypertrichosis and gum hyperplasia). Recent studies have focused on this issue in particular. Kengne-Wafo et al. [24] found that a third of their patients had mild to moderate histological changes, as evidenced on biopsy, especially when treated long term and in combination with angiotensin-converting enzyme (ACE) inhibitors or angiotensin receptor blockers. Fujinaga et al. also demonstrated nephrotoxicity [25], especially in younger children who needed treatment for more than 5 years. In order to decrease this risk, a dose reduction is often performed in order to determine the individual threshold dose when proteinuria does occur.

Tacrolimus

Tacrolimus is also a calcineurin inhibitor and is also used in children with SSNS, especially in the USA and Canada; however, the results of only a few studies have been published. Initial series used tacrolimus in patients refractory to cyclosporine A (CSA) [26] and found no superiority (nor inferiority) to CSA [27]. In terms of side effects, the risk of diabetes may be increased in children with SSNS, possibly due to repeated steroid treatment [28]. Individual patients are treated with tacrolimus instead of cyclosporine to reduce cosmetic side effects; however, systematic data are lacking. In theory, tacrolimus should have similar treatment results in SSNS as cyclosporine, since the mode of action is almost identical.

In summary, calcineurin inhibitors (both cyclosporine and tacrolimus) are important and effective drugs in the treatment of relapsing and especially steroid-dependant SSNS. The necessity of long-term treatment (calcineurin dependency) is an important disadvantage and may result in long-term side effects. Therefore, surveillance renal biopsies are important while the patient is on long-term calcineurin treatment.

Mycophenolic acid

Mycophenolic acid inhibits T- and B-cell proliferation and has been introduced in recent years for the treatment of SSNS. The doses used range from 12 mg/kg/day to the typical does used in renal transplantation (1200 mg/ m^2). A reduction of relapse rate has been documented by several small studies from various regions [29, 30]. A larger series from the USA [31] showed an improved relapse rate during MPA treatment relative to those reported by these smaller studies; however, the patients in the U.S. study were still on maintenance steroids. Interestingly, eight of 32 patients remained in remission on maintenance steroids after stopping MPA, while other patients required re-institution of MPA treatment. MPA seems to work less well in severely affected patients [32], although a head-to-head study with cyclosporine is pending. The major advantage of MPA is its decreased nephrotoxic potential, and in some studies it has been possible to switch from CSA to MPA [33]. On the other hand, a recent study by Dorresteijn et al. showed a higher incidence of relapses on MPA than on CSA [34], with a decreased nephrotoxicity documented in patients on MPA compared to CSA. The relapse rate on MPA was nominally higher, without reaching statistical significance, but this may be related to the small number of patients included in the study (12 per group). One issue that needs to be addressed is the value of therapeutic drug monitoring in improving the outcome of MPA treatment in SSNS. Preliminary data raise the question of whether underexposure may result in relapses [35]. To date, the side effects of mycophenolate may be underreported: for example, de Mello et al. [36] report severe gastrointestinal complications in some of their patients and the death of one of these patients, but they do not mention this side effect in the abstract.

Mizoribin is another inosine monophosphate dehydrogenase inhibitor, which has been studied in Japan [37]. However, the Cochrane database concluded that mizoribin has no effect [38], and for this reason and because the mode of action is similar to the more widely used MPA, mizoribine will not be discussed further in this review.

Rituximab

Several data indicate that both T- and B-cell immunity is altered in SSNS [39]. Therefore, anti-B-cell treatment with rituximab, a B-cell depleting antibody, may be an option in the arsenal of immunosuppressive drugs. Several case reports are now available, as well as larger series from

France, Japan, and an international registry [40–42]. It seems that the majority, if not all, patients with SSNS showed some benefit; however, the approach and strategies before and after rituximab treatment have not yet been clearly delineated. It should be noted that relapse rates following rituximab treatment may depend on the recovery of B-cells during the long-term course and not on the initial degree of B-cell depletion. On the other hand, patients reaching long-term remission after rituximab therapy increase their B-cell count, indicating that other factors must be present.

To date, rituximab has been used in the treatment of refractory patients (severe steroid dependency and maintenance immunosuppression with cyclosporine or other drugs). In some, but not all, patients, maintenance immunosuppression was discontinued. One large series of 22 patients included a number of patients that were not steroid responsive according to the ISKDC definition [40]. The patients in this study received two to four infusions of 375 mg/m^2 of rituximab, including seven patients that were nephrotic at the time of treatment; three of these latter patients achieved a full remission. The study group was able to show that maintenance immunosuppression that included steroids could be reduced in most patients (86%) following rituximab treatment. Relapses after rituximab were related to the degree of B-cell depletion; however, some patients did not relapse despite high CD19 counts. A recent study from Japan found that a single dose of rituximab was able to initiate steroid-free remission in all patients. However, 75% of patients relapsed, and only three had sustained remission for more than 1 year [41]. In an unpublished German registry of 27 patients treated with rituximab, the duration of remission was not different between patients receiving one or two versus three or four infusions of rituximab. A recent international registry reported a superior initial response of steroid-sensitive (82%) versus steroid-resistant patients (44%) [42]. The same result was obtained by Gulati et al., who documented very good response in SSNS during a 12-month follow-up [43].

Individual patients reach long-term remission, while others relapse after 9–12 months [44]. Other unsolved issues are dose and re-treatment with rituximab when relapses do occur. The selection of patients also needs to be addressed since rituximab is currently used as a rescue medication, especially since the long-term side effects are unclear at this stage. The first patients treated with rituximab tolerated this drug well, but one patient with SSNS who was treated with rituximab died due to pulmonary complications [45, 46]. Also, patients with progressive multifocal leukoencephalopathy (PML) have been reported after rituximab to have lupus nephritis and other disorders so that potential risks have to be balanced against the potential benefits.

In summary, rituximab seems to be an effective new option in the treatment of relapsing SSNS and has been reserved for complicated cases to date. Future studies should define patient characteristics and entry criteria for its use in SSNS, and these studies also need to address the effective dose and long-term risk profile. As yet it is unclear how many patients reach long-term remission after being treated with this drug or become rituximab-dependent.

Other biologicals used in SSNS

Calcineurin inhibitors work via the IL-2 pathway, blocking the IL-2 receptor on CD4+ cells with monoclonal antibodies, such as basiliximab. This may be one approach to reduce further relapses in SSNS. One recent case report [47] and one a abstract [48] suggest a response; however, other case reports do not indicate a benefit [49]. No controlled data or larger series on other biologicals are available. There is one report of successful anti-tumor necrosis factor (TNF) treatment in SSNS [50].

Vincristine

The response of relapsing SSNS to intravenous vincristine has been reported and was recently confirmed by Kausmann et al. [51], who treated patients relapsing despite cytotoxic or calcineurin treatment. These researchers used a dose of 1–1.5 mg/m^2 that was given weekly for 4 weeks, followed by monthly courses for 6 months; side effects were only minimal. With respect to the effect of vincristine, the authors were able to show a decrease in relapse frequency with vincristine treatment, with a reduction from four (12-month period preceding treatment) to 1.5 (12-month period following treatment) (p=0.004) relapses per year. The median sustained remission was 5 months, but one frequently relapsing patient remains in remission 4 years after vincristine therapy. The authors suggested that vincristine allowed steroid- and cyclosporine-sparing, contributed to long-term remission in some patients, and was especially valuable in children with poor compliance with oral medication.

Krsihnan et al. also published positive results with the use of vincristine [52]. In summary, vincristine may be a valuable option in individual patients with relapsing SSNS, and future controlled studies need to carefully evaluate the role of this drug.

Treatment of steroid resistant nephrotic syndrome

As illustrated by a survey from the USA some years ago, the treatment of SRNS is still somewhat controversial [53]. The ideal treatment leads to complete remission; however, partial responders also seem to have a better prognosis than children

not responding to treatment [54]. Patients with SRNS who do not respond to interventions are still at a high risk for end-stage renal disease (ESRD). As mentioned above, an initial mutation screen for relevant genetic causes (Podocin, Nephrin, WT1) for SRNS is recommended, especially in very young children and in parts of the world where consanguinity is high. It should be noted that results are often not available quickly, often necessitating that treatment be initiated before results are available. Recent data show that patients with genetic forms have a significantly poorer response to calcineurin treatment so that genetic testing will probably have a clinical impact in the future [55].

Definition of steroid resistant nephrotic syndrome

To date, steroid resistance is most frequently defined according to the ISKDC, i.e. as persisting proteinuria despite 4 weeks of oral prednisolone therapy. However, some patients show a response to pulse (or prolonged oral steroids) which may be due to a severe steroid dependence or "late response", indicating an overlap between steroid-sensitive and -resistant patients. Even if such patients respond, they often relapse early and require alternative treatment, such as with cyclosporine.

A further problem arises from the different definitions of partial response in SRNS, with some researchers regarding a reduction of proteinuria to be a prerequisite, while others would be happy with a rise of serum albumin >25 g/l. These issues need to be addressed and an international classification is needed, also as a marker of interventions.

In addition, patients from different geographic regions may show variable response to treatment. As will be shown, response to treatment may have genetic causes, and thus conclusions from treatment studies must not be generalized [56]. To make the situation even more complicated, some studies have analyzed the treatment effect of one drug in a mixed cohort of steroid-sensitive and -resistant patients [23, 36, 57] or in patients with secondary steroid resistance. Lastly, some overlap is also related to renal histology results in SRNS, i.e. MCNS or FSGS. The renal biopsy may be a non-representative biopsy, and nephrologists vary in their definition of histopathological staging. FSGS and MCNS have to be viewed as histological lesions that may be caused by many different causes. All of these issues may have an impact on treatment studies, and international efforts are urgently needed to clarify some of these points in order to optimize further studies.

Steroids and methylprednisolone pulses in SRNS, especially FSGS

There is accumulating evidence that intensified steroid treatment, such as high-dose intravenous (pulse) steroids (methylprednisolone), are beneficial in the treatment of acquired SRNS, despite resistance to oral prednisone [2]. The results of the so-called "Mendoza" regimen of intravenous methyprednisolone pulses are often cited [58], but it should not be forgotten that these patients were not only treated with three pulses of 30 mg/kg methylprednisolone at the beginning of the therapy but that they also received oral cyclophosphamide and alternate-day steroids. This is called a M-P/triple therapy protocol, and reported remission rates of 66% may have been a consequence of this combined treatment. Other recent studies have also used pulse steroids, mostly in combination with alkylating agents or calcineurin inhibitors [59–61]. Although some patients respond to pulse steroids, long-term problems may still occur, as indicated by Shenoy et al., who demonstrated in their study that responders often required alternative treatment and still had a risk of developing chronic kidney disease (CKD) [61]; on the other hand, some non-responders also had a benign long-term course.

Unfortunately, pulse steroid treatments have never been prospectively compared head-to-head with oral steroids. There is also some discussion on the recommended methylprednisolone dose (10–30 mg/kg) and the duration of treatment. Future studies must address the optimal methylprednisolone dose, duration of treatment, and combination treatment with other drugs (e.g. immunosuppressive and antiproteinuric) in patients with SRNS.

Calcineurin inhibitors (cyclosporine, tacrolimus)

At the present time, most pediatric nephrologists would use calcineurin inhibitors, especially cyclosporine, as adjunctive treatment in SRNS. In addition to its immunological effects, cyclosporine also exerts hemodynamic effects [62] and induces stabilization of the podocyte [63, 64]; both of these effects may contribute to the reduction of proteinuria. The dose of cyclosporine in SRNS is 5 mg/kg/day (or 150 mg/m^2) given in two doses; however, the dose is often increased in non-responders. Ingulli et al. reported that increased doses may have an impact on the reduction of proteinuria, but toxicity is significant [65]. The concomitant use of steroids is relevant in terms of side effects. Response to cyclosporine occurs within months in most patients, although some patients need to be treated for longer periods, even years.

The beneficial effects of cyclosporine in SRNS alone [66] or in combination with prednisolone or after induction treatment with methylprednisolone have been reported. A recent study by Ehrich et al. [59] reported excellent results for children receiving pulse steroids plus cyclosporine versus oral prednisolone plus CSA: significantly fewer patients developed CKD. In the study by Hamasaki et al. also, patients with SRNS achieved excellent remission rates

of 82.1 and 85.7% in both MCNS and FSGS, respectively, although the FSGS arm was relatively underpowered [67]. Recent data show that patients with genetic forms of SRNS have a significantly poorer response to CSA compared to those with no mutation [55].

Tacrolimus

Tacrolimus may serve as alternative calcineurin inhibitor in SRNS. Segarra et al. treated adult patients with SRNS with tacrolimus and recorded a 68% reduction of proteinuria; 40% of patients even reached full remission [68]. Duncan et al. [69] and Westhoff et al. [70] also showed a beneficial effect in SRNS. In a recent adult study from China, the complete or partial remission rates were 64.7 and 17.6%, respectively [71]. A beneficial effect of tacrolimus was reported for 94% of 13 children with SRNS having a variety of underlying disorders and pre-treatments [72]. Gulati et al. from India documented excellent remission rates in 18 of 19 patients [73], as did Butani et al. in 15 of 16 patients [74]. In a recent study, Roberti et al. [75] were able to induce partial and complete remission with tacrolimus in 81% of children with SRNS due to different histologies. The response in FSGS was inferior, however, and only one of ten patients showed complete remission and another four only had a partial remission. A recent head-to-head study compared cyclosporine and tacrolimus plus low-dose alternate-day steroids and reported an equal response; however, fewer patients in the tacrolimus group experienced relapses and cosmetic side effects [76]. No systematic data on the side effects of tacrolimus in steroid-resistant nephrotic patients, such as the incidence of diabetes, are published.

Alkylation agents

The role of cytotoxic treatment in SRNS is unclear because several publications indicate a response in some patients with SRNS. The overlap of SSNS and SRNS (or MCNS and FSGS) may be one reason, while others may related to geographic and genetic causes. The series by Rennert et al. [77], Gulati and Kher [78], Al Sallum [79], and Abeyagunawardena et al. [80] indicate a role for cytotoxic treatment in SRNS, and many of these studies used intravenous cyclophosphamide. In contrast, studies from the ISKDC [81] showed no benefit, similar to the results of a recent randomized study which showed no benefit of intravenous cyclophosphamide when compared to cyclosporine [60], although some individual patients in the cytotoxic arm entered remission. However, well-designed, adequately powered studies are lacking. Due to the toxicity and the available alternatives of cytotoxic treatment, many would not regard this drug as a first choice in SRNS. On the other hand, cyclophosphamide is widely available and relatively inexpensive, which are two important assets, particularly for developing countries.

Mycophenoloic acid

Experience with MPA in SRNS is limited, although data from an increasing number of studies are becoming available. Cattran et al. reported a reduction of proteinuria in 48% of adult patients [82]; in contrast, in a pediatric series only one of five children with SRNS responded [35]. El-Reshaid et al. claimed a benefit of MPA in SRNS, but it is difficult to attribute treatment response to a specific intervention in this study [83]. A number of other small studies report a beneficial effect [84], while others do not [85]. A differential response to MPA was noted in a recent South American series, with 20.6% of patients receiving MPA after cyclosporine and 27.8% of patients receiving only MPA reaching full remission. One patient in this study died due to pancreatitis [36]. In summary, MPA may be successful for some patients with SRNS, but more data are necessary. The overall response rate in SRNS seems to be inferior to than of calcineurin inhibitors. MPA may possibly be effective in patients who achieved remission with calcineurin inhibitor in order to taper this treatment, thus reducing toxicity [86].

Rituximab

The first reports on rituximab in SRNS relate to its use in recurring FSGS after renal transplantation when not all patients with this complication respond [87]. The response to rituximab in primary idiopathic FSGS or SRNS is variable: some individuals with a benefit have been reported from India [88], while other series report a less convincing response [89]. The international registry reports a benefit of only 44% in patients with SRNS. In the series by Gulati et al. [43], response to rituximab was worse than in a previous series, with only 27.1% reaching full remission and 21.1% having partial remission. These studies illustrate the importance of further studies and registries in order to be able to make a concise recommendation of whether to use or not use rituximab in SRNS. As with many novel treatments, one should be aware of reporting bias.

Other treatment options in SRNS: ACE inhibitors/angiotensin II receptor blockers, galactose, mTOR inhibitors

Only sparse information is available on the use of other treatment options, although some of these are used widely, such as ACE inhibitors or angiotensin II receptor blockers

Table 1 Treatment options for steroid sensitive nephrotic syndrome

Drug	Advantage	Problem	Comment
Levamisole	Low toxicity	Less effective in severe cases of steroid dependency Availability	First option for less severe cases
Cyclophosphamide (chlormabucil)	Short course may induce long-term remission	Long-term toxicity, especially infertility	Seems to be more effective in older and female patients, no repeated courses
Mycophenolic acid (MPA)	No nephrotoxicity	MPA dependency, less effective than calcineurin inhibitors Proportion of patients that reach long-term remission is unclear	Alternative to calcineurin inhibitors. Therapeutic drug monitoring may have no impact on steroid resistance
Cyclosporine	Effective in severe steroid-dependency	Cyclosporine dependency Side effects	Tapering to low doses possible
Tacrolimus	Effective in severe steroid-dependency	Tacrolimus dependency Long-term side effects unclear	Tapering to low doses possible
Rituximab	Effective in severe steroid-dependency	Long-term side effects are unknown	Proportion of patients with drug-free long-term remission unknown

(ARBs) in anti-proteinuric treatment, which are used by 97% of physicians in the USA for SRNS [6]. No data are currently available on the impact of this intervention on long-term prognosis in SRNS, although the combination of ACE inhibition and calcineurin inhibitors may increase nephrotoxicity [24]. The role of anti-proteinuric treatment in SRNS must be further studied, especially in its genetic forms. It must be mentioned, however, that a treatment with ACE inhibitors or ARBs can alter the volume state of patients with NS and may also alter renal function due to their effect on renal perfusion, especially when combined with calcineurin inhibitors.

Galactose has recently been shown to improve outcome in experimental models of FSGS [90]. However, only one report in humans is available [91], although a prospective study has been initiated.

A further option is the use of mTOR inhibitors. Some reports have indicated side effects [92], while others claim a response in some adult patients [93]. It is possible that a low dose is superior to high exposure [94]. Data on children are not yet available. Again, publication bias needs to be considered. It should be noted that in patients with FSGS after renal transplantation the use of mTOR-inhibitors has been associated with the recurrence of nephrotic syndrome [95]

Lastly, a beneficial effect on renal damage and podocyte injury has recently been documented in animal models [96]. Although these findings have not yet been translated into

Table 2 Treatment options for steroid-resistant nephrotic syndrome

Drug	Advantage	Problem	Comment
Steroids	Widely available Effective when used as pulse therapy	Toxicity Lack of studies relating to optimal dose and duration	Combination with maintenance treatment (see below)
Cyclophosphamide	Cheap	Long-term toxicity, especially infertility	Intravenous cyclophosphamide seems superior
	Widely available	Less effective than	
	Some patients benefit	other options	
		Optimal dose in SRNS unclear	
Mycophenolic acid	No Nephrotoxicity	Few data in SRNS	Alternative to or combination with calcineurin inhibitors
Cyclosporine	Effective	Long-term side-effects	Tapering to low doses seems possible
Tacrolimus	Effective	Long-term side-effects unclear	Tapering to low doses seems possible
Rituximab	Less effective than in steroid sensitive NS	Long-term side-effects are unknown	Option for treatment refractory patients, especially with recurrence of FSGS after transplantation

SRNS, Steroid resistant nephrotic syndrome; FSGS, Focal segmental glomerulosclerosis

clinical practice, they do indicate that there is hope for other promising treatments in SRNS.

Summary

In summary and to draw this review to a conclusion, new treatment options are available for SSNS and SRNS (Tables 1 and 2). In steroid-dependant SSNS, many patients relapse despite a wide arsenal of highly potent drugs; the induction of a cure, i.e. treatment-free remission, should be the ultimate goal of all interventions in this patient group. It seems that in many cases steroid dependency has been replaced by dependency on levamisole, MPA, calcineurin inhibitor, and rituximab. Thus, drugs should be introduced in a stepwise approach. In SRNS, the prognosis has improved, with much of this progress being due to the development of new and effective treatment options, especially calcineurin inhibitors. Steroids also seem to play an important role in SRNS. The optimal treatment of patients with genetic causes of FSGS is as yet unclear.

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Questions

Answers appear following the reference list.

Each statement is either correct or false.

1. The idiopathic nephrotic syndrome
(a) is rarely associated with response to steroids
(b) always responds to steroid treatment
(c) the majority of patients with minimal change disease respond to steroids
(d) pulse methylprednisolone is now used in many instances for children with steroid resistance
(e) clinical definitions are identical world-wide

2. Children with steroid resistant nephrotic syndrome
(a) should receive a kidney biopsy
(b) should be investigated for podocin mutations
(c) should be treated with cyclophosphamide initially
(d) have a low risk of end-stage renal disease, even if unresponsive to treatment
(e) are at risk of recurrence after renal transplantation

3. According to recent data, the rate of long-term remission after a 12-week course of cyclophosphamide in steroid sensitive nephrotic syndrome is
(a) Approx. 80–100%
(b) Approx. 70–80%
(c) Approx. 50–60%
(d) Approx. 45–55%
(e) Approx. 25–35%

4. Calcineurin inhibitors
(a) are effective drugs in severe steroid dependency
(b) seem to be superior as first choice in steroid resistant nephrotic syndrome compared to cytotoxic treatment
(c) may cause nephrotoxicity
(d) lead to long-term remission in steroid sensitive nephrotic syndrome even when treatment is discontinued
(e) have similar cosmetic side effects

5. Rituximab is currently used in individual patients with the idiopathic nephrotic syndrome (SSNS and SRNS). Rituximab
(a) depletes B- and T-cells
(b) does not have any documented side effects
(c) response is better in SSNS than in SRNS
(d) should be administered 4 times initially in all patients, as shown by randomized studies
(e) has been used also for patients with recurrence of FSGS after renal transplantation

6. The treatment of steroid-sensitive nephrotic syndrome with mycophenolic acid (MPA)
(a) may lead to a steroid-sparing effect
(b) has been evaluated in randomized controlled studies
(c) carries the risk of nephrotoxicity
(d) typical side effects include diarrhea
(e) the role of therapeutic drug monitoring in nephrotic syndrome remains to be established

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Answers

1.
(a) false
(b) false
(c) correct
(d) correct
(e) false
2.
(a) correct
(b) correct
(c) false
(d) false
(e) correct
3.
(a) false
(b) false
(c) false
(d) false
(e) correct
4.
(a) correct
(b) correct
(c) correct
(d) false
(e) false
5.
(a) false
(b) false
(c) correct
(d) false
(e) correct
6.
(a) correct
(b) false
(c) false
(d) correct
(e) correct