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REVIEW

Difficult-to-treat idiopathic nephrotic syndrome: established drugs, open questions and future options

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Abstract The idiopathic nephrotic syndrome in childhood can be classified according to the International Study of Kidney Disease in Children (ISKDC) based on the response to steroids. Typically, steroid-sensitive nephrotic syndrome (SSNS) is characterised by minimal changes in disease (MCD) histology, whereas in steroid-resistant nephrotic syndrome (SRNS) focal segmental glomerulosclerosis (FSGS) is the most prevalent lesion. Patients with SSNS may develop frequent relapses and/or steroid dependency, which can be difficult to treat. New studies confirm the value of calcineurin inhibitors (CNIs) and mycophenolic acid in preventing relapses of SSNS. Rituximab also plays an important role, but many questions regarding initial dosing, repetitions of courses, and long-term side effects remain unclear. SRNS, especially when unresponsive to treatment, can lead to chronic kidney disease. In particular, treatment with CNIs has improved the prognosis and recent data indicate that treatment can even be discontinued in many patients with full remission. In CNI-unresponsive SRNS, rituximab is less effective than in SSNS and the role of other biologicals (such as ofatumumab, abatacept, and others) remains unclear. A significant proportion of children with FSGS have genetic causes and most patients do not respond to immunosuppression, although individual patients with partial and even complete response have been documented. Future studies should evaluate treatments leading to long-term remission without maintenance immunosuppression in SSNS; in both genetic and immune-mediated SRNS, novel options to decrease the number of treatment-unresponsive patients seem mandatory, as they are at a high risk of developing end-stage renal disease.

Keywords Steroid-sensitive nephrotic syndrome · Steroid-resistant nephrotic syndrome · FSGS · Immunosuppression biologicals · Rituximab · Ofatumumab

Introduction

Idiopathic nephrotic syndrome can be classified according to the International Study of Kidney Disease in Children (ISKDC) into steroid-sensitive nephrotic syndrome (SSNS) or steroid-resistant nephrotic syndrome (SRNS). The corresponding histological lesions are typically minimal change disease (MCD) and focal segmental glomerulosclerosis (FSGS). For many years, both disorders were thought to be immunological disorders, although in FSGS it is now known that a significant proportion of patients have single-gene causes of the nephrotic syndrome [1].

Treatment protocols for SSNS are still controversial: a 2007 analysis by the COCHRANE group concluded that in SSNS, extended steroid treatment for more than 3 months would result in lower risk of relapses, although this analysis included unpublished studies [2]. Recently, three randomised controlled studies could not find a benefit of prolonging steroid treatment for 6 months compared with 8 or 12 weeks [3–5]. Surprisingly, the rates of long-term remission (>2 years) comparing short versus long treatment in Dutch and Indian studies was only 20 vs 23% [3] and 17 vs 27% [4], which is considerably less than in historical series, raising the question of whether the natural history of SSNS has changed. Only in the study by Yoshikawa et al. [4] was the

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2-year remission rate 50% in the 8-week group vs 57% in the 6-month group, somewhat better than in historical studies, where the rate of long-term remission after 2 years was often around 40%.

As prolongation of steroid treatment does not seem to be a successful option, modification of the initial steroid treatment should be evaluated. Although the addition of cyclosporine A [5] did not improve long-term remission at 2 years, replacement of steroids with other drugs may be an important future option. Currently, a study using mycophenolate mofetil (www.INTENT.de) has been initiated and another study evaluating the use of levamisole at presentation is under way.

Alternative treatment of frequently relapsing and steroid-dependent SSNS: new data

Several steroid-sparing agents in the treatment of relapsing steroid-sensitive nephrotic syndrome are available. Levamisole has been evaluated in a randomised controlled study from the Netherlands and France and data are due to be published. In preliminary communications, a reduction of relapse rate of 20% compared with patients receiving placebo was documented; patients with frequently relapsing nephrotic syndrome had a superior response compared with patients with steroid dependency [6].

This emphasises that there needs to be a distinction between these two groups, especially because FRNS seems to have a better prognosis regarding long-term remission. Another recently published study demonstrated that daily levamisole resulted in better remission rates compared with historical controls, receiving alternated day levamisole, which has been used in most published series. Thus, higher doses of levamisole may be an option for improving remission rates in frequently relapsing nephrotic syndrome, especially as the rate of side effects was not increased in this series [7].

Mycophenolate mofetil (MMF) has received major attention in the treatment of relapsing steroid-sensitive nephrotic syndrome [8]. In a recently published randomised controlled cross-over study by Gellermann et al. from the GPN, cyclosporine A (CSA) was compared with MMF using a cross-over design. It was shown that remission rates after 1 year were superior with CSA (85% vs 64%), but renal function was significantly better with MMF. Importantly, a post-hoc analysis showed that patients with adequate MMF exposure (prodrug MPA > 50 μg/h/ml) remission rates improved and were comparable with those of CSA. Thus, pharmacokinetic surveillance seems important during MMF treatment, especially if relapses occur [9]. In another recently published randomised study, a superior response rate of the calcineurin inhibitor (CNI) tacrolimus compared with MMF was documented. The proportion of patients with a favourable outcome (defined as sustained remission or infrequent relapses) was significantly higher with tacrolimus (90.3%) compared with MMF (44.8%) [10].

Rituximab in steroid-sensitive nephrotic syndrome: open questions

Rituximab (RTX) has become an important treatment option in difficult-to-treat SSNS, especially in patients relapsing despite maintenance immunosuppression with CSA or MMF. Many reports and recent randomised studies are available and are discussed elsewhere [11–16]. However, several open questions regarding the use of RTX in SSNS remain. For instance, details of initial treatment, i.e. dose and number of infusions, have not been compared systematically in head-to-head studies. The most frequent dose used was 375 mg/m^2, but other studies used 750 mg/m^2 [11]. Retrospective studies suggested that one or two infusions revealed comparable results compared with three to four infusions, but again, this issue has not been addressed prospectively [11]; on the other hand, Japanese patients receiving only a single dose had a high rate of relapses after 1 year [17]. Some authors even suggested repeated pre-emptive RTX infusions when B-cells increase to extend B-cell depletion, but this has been abandoned recently owing to toxicity [18]. Although 63% of patients did not relapse with extended B-cell depletion, the rate of long-term remission >2 years (41%) was not superior to protocols not using this approach.

A reduction in initial dose (leading to similar remission rates) may be an attractive option in reducing costs and the risk of acute and long-term side effects. More immunological studies in optimising patient selection and remission rates are urgently needed, such as the study by Colluci et al., which showed that the number of memory B-cells (IgM and switched memory B-cells) is more relevant than the total number of B-cells (CD19 or CD20) in discriminating between relapsers and non-relapsers [19].

A second unresolved issue concerns discontinuation of maintenance immunosuppression. In most studies, maintenance immunosuppression was stopped successfully after administration of RTX, but studies from Japan suggested that continuing treatment with MMF led to superior remission rates [20]. The genetic background may be at least in part responsible for this variation in response. In a recent study from India [14], there was no difference in relapse rate between patients with pre-emptive MMF treatment and patients in whom MMF was stopped; this study, however, was uncontrolled. In view of the good response rate of RTX in difficult-to-treat SSNS, it may be intriguing to use RTX in less severe cases, e.g. before cyclophosphamide or CNIs. This option has been discussed [21], but no systematic data are available. Yet, only 12 out of 15 patients in the randomised study by Ravani et al. [22] had never received cyclophosphamide or CSA.

Disappointingly, relapse-free survival in this group was only 66% and 34% at 1 and 2 years respectively, and thus similar to cytotoxic treatment.

Lastly, side effects of RTX need to be addressed. Although RTX is usually tolerated well, severe complications (including death) have been described [23, 24], usually in conjunction with other immunosuppressive treatment. Some acute side-effects may be more frequent than thought. Kamei et al. observed a high frequency of granulocytopenia after RTX, especially in young children [25]. Long-term follow-up studies on immune function have not been performed systematically, but the study from Colucci et al. [19] on memory B-cell function shows that some of the actions of RTX are long-lasting and may lead to long-term immune dysfunction.

Taken together, future studies regarding RTX use in SSNS are urgently needed to optimise response rates and evaluate and reduce the risk of side effects.

Steroid-resistant nephrotic syndrome/focal segmental glomerulosclerosis: genetic versus immune

The treatment and prognosis of SRNS has changed in recent decades; in addition, major advances in elucidating the pathogenesis of FSGS have been made and it is now clear many patients have single-gene mutations in structural proteins of the podocyte, such as podocin [1]. Although progression into end-stage kidney disease is frequent in these, the risk of recurrence after transplantation is low. Thus, genetic (familial) forms of FSGS should be distinguished from immunological (sporadic) forms, where response to immunosuppressive treatment is possible; however, recurrence after renal transplantation remains a risk. Although the exact mechanisms of immune dysfunction in immunological FSGS are unknown, recurrence after renal transplantation is thought to be due to production of a soluble permeability factor, e.g. by immune cells.

Immunological (sporadic) FSGS prognosis of immune-FSGS has improved considerably with the introduction of CNIs, especially CSA [8]. Remission rates of 40–80.7% have been reported, in part using concomitant high-dose steroid pulses. It should be noted, however, that no testing for mutations (podocin and others) was performed in old studies so that response rates in truly non-genetic cases may be even higher. CSA or tacrolimus are therefore the first-line treatment in SRNS, especially since studies assessing the use of cyclophosphamide and MMF in SRNS have been disappointing [26, 27].

Recent data have shown that response to CSA seems to occur rather rapidly after a median of 2 months [28], although some patients need up to 4 years to enter complete remission [29]. Thus, in patients with partial response—although there is no accepted definition of this group—CNI treatment should not be discontinued too early. Although most patients with SSNS become CSA-dependent and discontinuation is not possible, the study by Klaassen et al. showed a different pattern in SRNS. Discontinuation of CSA was possible in 79% of patients who entered complete remission and after a median follow-up of 9.7 years, no further relapses off treatment occurred in 11 out of 15 patients [29].

Rituximab in FSGS

In their first report in 2007, Bagga et al. had an excellent response (3 with complete remission, 2 with partial remission) to RTX in all 5 treated patients, including 3 with FSGS [30]. In a controlled study, Magnasco et al. enrolled 31 children, half of whom received RTX in addition to prednisone and CNIs. There was no change in proteinuria after RTX, although a remission of proteinuria was noted in 6 patients with delayed resistance (i.e. patients with secondary steroid resistance), indicating that this subgroup may respond differently [31]. Lastly, a follow-up study from Sinha confirmed that response to RTX is inferior in SRNS compared with SSNS; no response was seen in 70.7% of patients. There was a higher proportion with MCD that showed remission compared with FSGS ($p < 0.011$) [14]. In an interesting small series by Basu et al., 10 out of 15 patients achieved complete and 5 achieved partial remission when MMF was given after an initial lack of response to RTX; most patients had MCD. Whether this protocol increases remission rates after RTX needs to be confirmed by future studies, however [32]. Kamei et al. treated 10 patients with SRNS who were unresponsive to CNIs with RTX and pulse steroids and was able to achieve remission in 6 children [25]. Although this approach needs to be confirmed by a prospective, controlled study, it may be that a combination of RTX with other immunosuppressants (MMF, steroids or others) may be successful in some patients with SRNS.

Genetic (familial) forms of FSGS

Although this has not yet been addressed prospectively, retrospective series have indicated that most patients with infantile and genetic FSGS do not achieve remission with cyclosporine [28]. In this study, children with infantile nephrotic syndrome, e.g. due to WT1 and nephrin mutations, were included. On the other hand, a single-centre study indicated that complete response may occur in individual patients with genetic FSGS so that—in view of the poor prognosis—a trial of CNIs seems justified, especially because the genetic analysis usually requires some time. This is supported by studies that documented a podocyte-stabilising effect of cyclosporine [33].

More recently published data indicate that other immunosuppressants such RTX also seem to interact with regulatory elements of the cytoskeleton [34]. Fornoni et al. found that RTX may bind directly on sphingomyelin phosphodiesterase acid-like 3b protein (SMPDL3b); it is part of the phospholipid membrane. Thus, RTX may also have an effect at the cellular level and prevent SMPDL3b down-regulation in podocytes.

The first option in non-genetic SRNS is CNIs. However, in genetic forms of SRNS, Büscher et al. demonstrated that most patients with SRNS did not benefit from CSA. None of the patients in the retrospective study with a genetic form of SRNS showed a complete response to CSA, but 2 patients with WT1 mutation showed partial remission. In contrast, 17 out of 31 patients (55%) without mutations achieved CR. The rate of response to CSA was significantly better without mutations in podocyte genes (68% vs 17%, $p < 0.005$) [28]. In another recent multicentre study, Büscher et al. were able to document a rate of 2% with complete and 16% with partial remission in hereditary forms of SRNS [35]. Thus, they confirmed observations by Klaassen et al. showing that a complete or partial response is possible and thus a trial of CNIs in genetic forms of FSGS may be justified, especially as it usually takes some time before the results of testing are available [29]. Currently, no controlled data are available as to how long CNI treatment in genetic forms of SRNS should be continued, but in the series by Büscher et al. and Klaessen et al., most patients with complete remission responded after a median of 2 months. Thus, this period seems to be a minimum. It is currently unknown, whether patients with distinct mutation, e.g. in WT1 or NPHS2, show a differential response.

New biologicals and other options

As treatment-resistant FSGS carries a high risk of progressing to end-stage renal disease (ESRD), attempts to achieve remission with other biological drugs are important. As response to RTX, a non-humanised anti-CD20 antibody is less frequent in FSGS use of a humanised anti-CD20 antibody, ofatumumab may be more beneficial. Basu administered ofatumumab to 2 patients with MCD and 3 patients with FSGS. All received multiple medications before this intervention, including two courses of RTX. After ofatumumab, improvement of proteinuria and an increase in the serum albumin levels from 1.2 g/dl to 3.1 g/dl within 6 weeks was noted. Hypoalbuminemia resolved after the third dose and remission was achieved after six doses. No serious side effects were reported [36]. These preliminary data suggest that ofatumumab might be an alternative drug in RTX-resistant SRNS, but more RCTs are clearly necessary and have been initiated recently [37]. Furthermore, ofatumumab may also be an alternative anti-CD20 agent if RTX is not tolerated (Table 1) [38].

Anti-IL 2 antibodies

In 2015, a pilot case–control study with 5 patients who were resistant to all available treatments, including RTX, was designed by Bonanni et al., because IL2 blockade increases Treg lymphocytes; up-regulation of Treg immunity improves nephrotic syndrome in animal models. Unfortunately, in their study, Bonanni did not ameliorate proteinuria and in all 5 children kidney disease had progressed after 2 years [39].

Fresolimumab

Trachtman et al. investigated the TGF-ß antibody fresolimumab in 16 patients aged ≥18 years with primary FSGS. Initially, fresolimumab was safe and well tolerated; however, one patient was diagnosed with a primitive neuroectodermal tumour 2 years post-treatment. Although overall assessment suggested no significant change in proteinuria, reduction of proteinuria was observed in 3 African–American patients with no dose-related differences, suggesting that further studies might be justified [40].

Abatacept

Abatacept is a fusion molecule composed of the Fc region of IgG1 and CTLA-4-Ig (cytotoxic T-lymphocyte-associated protein 4). It is a co-stimulatory inhibitor that targets B7–1 (CD80) and CD86 disrupting T-cell activation. In experimental models, B7–1 mediates podocyte injury and proteinuria by disrupting the binding of talin to ß1-integrin; this could be blocked by administering abatacept. Yu et al. treated 5 patients with FSGS, including 4 with recurrence after renal transplantation. B7–1 staining of podocytes in kidney biopsy specimens was positive and after abatacept all 5 patients achieved remission. The authors concluded that abatacept may be a treatment option for B7–1-positive FSGS [41]. This optimistic first report could not be confirmed by others, however. In a study of 9 patients with recurrent FSGS, none responded to abatacept, neither were the authors able to stain for B7–1 in these and other renal biopsies; thus, further studies are clearly needed [42].

ACTH

Adrenocorticotropic hormone was used for treatment of nephrotic syndrome long before prednisolone and other drugs were available; a recent review of the older literature nicely demonstrates the therapeutic effects of ACTH in MCD [43]. However, it is less clear whether ACTH has an effect on SRNS/FSGS. In a meta-analysis of 18 articles by Kittanamongkolchai et al., 23% of patients were reported to have achieved remission within 2 years; non-response in the first year was 50%. In the studies analysed, a wide variation in

Table 1 Biologicals and other treatment modalities in focal segmental glomerulosclerosis (FSGS)

Drug	Study	*n*	Dose	Outcome	Adverse events	Comment
Cyclosporine	[8]	Review	5 mg/kg in 2 divided doses	Long-term treatment necessary	Nephrotoxicity, hypertension, cosmetic effects (hypertrichosis, gum hyperplasia)	Surveillance renal biopsy
	[28]	91	Not reported	17% with genetic CNS/SRNS respond to CSA vs 68% without mutations respond to CSA	ESRD	
	[29]	36	150 mg/m^2/day in 2 doses 4/9 patients with mutations: 2 CR and 2 PR	All patients with FSGS achieved PR, 7/23 achieved CR compared with patients with MCNS (12/13 patients)—in 15/19 discontinuation was possible (6 FSGS), 7 patients had NR (6 FSGS)	Cosmetic side effects (4 patients changed to tacrolimus)	
	[35]	231	CSA doses were titrated to achieve blood levels between 80 and 150 ng/ml	Genetic forms: 2% achieved CR, 16% PR nongenetic SRNS benefits (60% CR, 18% PR)—median time to CR was 2.5 months, 82% responded within the first 6 months of treatment	Not reported	
RTX	[30]	5	375 mg/m^2 weekly for 4 weeks	4 had CR (after 6 months 1 had a relapse), 1 had PR	Not reported	
	[31]	31	375 mg/m^2 iv in 2 doses	No reduction of PN after 3 months (CD20 count was still undetectable)	Bronchospasm, hypotension in 1 patient	
	[14]	193	375 mg/m^2 weekly for 2–4 doses	7/58 had CR and 10/58 PR, no response in 70.7%—remission with FSGS 8/41 vs MCNS 9/17	Urticaria, fever, chills, throat pain, hypertension	
	[32]	24	2 doses iv 375 mg/m^2 weekly at 3 months: second course of RTX plus MMF (1,200 mg/m^2 per day in 2 divided doses) to all patients with PR and patients with relapses after CR	11/24 FSGS—5/11 achieved CR or PR after 6 months, after 24 months: only children with MCD remained in remission	Dizziness, mild dyspnoea	
	[25]	10	375 mg/m^2 1–4 doses plus MP (30 mg/kg/day iv for 3 consecutive days once every 2 to 4 weeks repeatedly until CR	7/10 achieved CR—3 of them had subsequent relapses, 1 achieved PR—mild renal insufficiency	18 symptoms were observed, but no serious adverse events	
	[22]	30	1 × 375 mg/m^2	Relapse-free survival was 66% at 1 year and only 34% at 2 years	Mild nausea and/or skin rash	Only children with uncomplicated disease
Ofatumumab	[36]	5	Initial: 300 mg/1.73 m^2 body-surface, followed by 2,000 mg weekly for 5 infusions	Only 1 had a relapse after 2 months	1 transient infusion reaction	
	[37]	140 protocol	1,500 mg/1.73 m^2 diluted in 1 L normal saline, at a rate of 12 ml/h in the first 30 min up to a maximum of 200 ml/h	Primary endpoint: relapse or need of steroids secondary endpoint: relapse-free period, relapse rate per year, amount of steroid required to maintain CR or PR, test circulating cell populations	Minimal risk of side effects	
	[38]	2 case reports	750 mg/1.73 m^2	Ofatumumab superior to RTX	Mild allergic reaction	

Table 1 (continued)

Drug	Study	*n*	Dose	Outcome	Adverse events	Comment
Anti-IL2 antibody	[39]	5	6 monthly cycles of low-dose IL2 (1×106 U/m^2 first month, 1.5×106 U/m^{2}following month)	Did not lower PN, did not affect renal function, but modifies the level of circulating Tregs	Acute asthma attack	
Fresolimumab (phase 1 study)	[40]	16	0.3–4 mg/kg	No significant reduction of PN 3 African–American with reduction of PN	Peripheral oedema, nasopharyngitis, 1 patient was diagnosed with a histologically confirmed primitive neuro-ectodermal tumour 2 years post-treatment	
Abatacept	[41]	5	1–3 doses of 10 mg/kg	B7–1 immunostaining of kidney-biopsy specimens identified subgroup of patients with proteinuric kidney diseases with benefit from Abatacept	Not reported	
	[42]	9	10 mg/kg	Abatacept or belatacept did not induce PN remission	Not reported	Only patients with recurrence of FSGS after treatment
ACTH	[43]	Review (419)	Short-term: 20–160 mg/day for approximately 12 days	Resolution of oedema, but temporary (1 month), PN completely resolved in only 54% patients, reduction of PN in 71% of patients	Hyperadrenocorticism, freckling	ISKDC: a similar response rate was seen in patients treated with prednisone for 1–2 weeks (short-term)—useful for patients who are not able to tolerate oral steroid treatment
			Long-term: 100–200 mg/day repeated weekly for up to 24 months—comparison of dosage is problematic			
	[44]	Review (270)	Synthetic: 0.25–3.3 mg/week	The degree of PN was inversely related to the cumulative dose of ACTH—the evidence for efficacy of ACTH in FSGS is limited, patients responded to both forms of ACTH equally	Oedema, insomnia, mood swings	
			Natural: 80–224 units/week			
	[45]	44 adults (15 FSGS)	80 units twice weekly	86.7% (13/15) showed ≥30% PN reduction, 60% (9/15) showed ≥50% PN reduction	Increased swelling, weight gain, hypertension, hyperglycaemia	
Adalimumab/galactose	[46]	21	Adalimumab: 24 mg/m^2 sc for 26 weeks	None achieved 50% reduction of proteinuria	Oedema, fatigue, infection	
			Galactose: 0.2 g/kg per dose orally twice a day dissolved in 15–30 ml of water	3/7 manifested at least a 50% decline in PN		

CR complete remission, *PR* partial remission, *NR* non-response, *PN* proteinuria, *CSA* cyclosporine A, *RTX* rituximab, *MMF* mycophenolate mofetil, *MP* methyl prednisolone, *Sc* subcutaneously, *iv* intravenous, *ACTH* adrenocorticotropic hormone, *CNS* congenital nephrotic syndrome, *SRNS* steroid-resistant nephrotic syndrome, *MCD* minimal change disease, *MCNS* minimal change nephrotic syndrome, *ESRD* end-stage renal disease, *ISKDC* International Study of Kidney Disease in Children

treatment duration ranging from 2 to 48 out of 56 months was noted. Sixty-eight percent were treated with natural ACTH (80–224 units/week) and 32% received synthetic ACTH (0.25–3.3 mg/week). A head-to-head comparison between the two does not exist. There is also no direct comparison with oral steroids and side-effects may be relevant (e.g. oedema and insomnia) [44].

In summary, further studies are needed, with concrete and standardised protocols [45].

Adalimumab and galactose

Trachtman et al. evaluated treatment of FSGS using the TNF-α-inhibiting antibody adalimumab and galactose. Adalimumab reduces the autoimmune response to TNF-α and is used successfully in various auto-immune disorders such as rheumatoid arthritis. However, none of the patients with FSGS assigned to adalimumab achieved a 50% reduction in proteinuria; thus, this treatment does not seem to be a promising agent for further studies in this cohort. In the same study, 2 out of 7 patients with FSGS had a 50% reduction in proteinuria after galactose, confirming previous case reports; the authors concluded that further studies using galactose should be performed and, for example, patients with earlier disease stages should be treated [46].

Non-immunological alternative treatment in idiopathic nephrotic syndrome

Non-immunological alternative treatment options have not been addressed systematically, but anecdotal reports are available, for example, on dietary interventions in SSNS. In a recent study, 5 patients on a gluten-free diet were able to achieve long-term remission [47], but these interventions clearly require controlled studies. For instance, 40 years ago a report on a milk–protein-free diet in SSNS was reported by Sandberg et al. [48], but this observation could not be confirmed later.

Experimental studies have shown that stimulation of the calcium-sensing receptor is capable of increasing podocyte stability and thus cinacalcet (or vitamin D) may be an option for improving proteinuria in nephrotic syndrome. Data on cinacalcet are not yet available, but a recent meta-analysis in IgA nephropathy suggested an effect of vitamin D supplementation [49]. In children with MCD vitamin D deficiency has been reported [50], but many questions remain open, for example, the impact of renal losses of vitamin D-binding globulin during relapse. Also, no controlled data are available that confirm a reduction of relapse rates using vitamin D supplementation. It seems that these non-toxic and non-immunological treatment strategies warrant further studies in MCD, but especially FSGS.

Conclusion

Recent studies have confirmed the important role of CNIs and MMF in the treatment of relapsing steroid-sensitive nephrotic syndrome. Although the latter seems to be less effective, side effects are fewer and with adequate pharmacokinetic monitoring, clinical response may improve remission rates. RTX is of major importance in multiple drug-dependent SSNS, but many questions regarding the dosing, repetition and long-term side effects remain unanswered. Future studies are needed to assess the anecdotal positive experience and compare it with alternative treatment with a gluten-free diet and vitamin D. The ultimate goal in the treatment of SSNS is to achieve a cure, i.e. that patients remain in long-term remission for ongoing or future treatments.

Most steroid-resistant NS patients with mutations in podocyte or other genes seem resistant to immunosuppressive treatment. Yet, because individual patients show partial or even complete response, a trial, preferably with CNIs, seems justified, especially because these drugs have been shown a podocyte-stabilising effect. CNIs are the first-line treatment in non-genetic (immunological) FSGS, leading to a complete response in many, but not all patients. These new biologicals may improve remission rates; RTX may be effective, but results are less favourable than in SSNS. More studies are needed, as reporting bias should be considered and a variety of alternative agents have been unsuccessful in controlled studies. Nevertheless, in every additional patient with SRNS responding to treatment, end-stage renal disease will likely be prevented and should be regarded as a success.

Compliance with ethical standards

Conflicts of interest The authors declare that they have no conflicts of interest.

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