Strategies to treat nephrotic syndrome in children

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Abstract

Childhood nephrotic syndrome is often encountered in the field of pediatrics. However, its pathogenesis has not been fully clarified. For treatment, corticosteroids and immunosuppressive agents are effective, which has been demonstrated based on experience. However, the criteria for administration of corticosteroids have been established.

In 2005, guidelines regarding pharmaceutical strategy for idiopathic nephrotic syndrome in children were published by the Japanese Society for Pediatric Nephrology. However, the contents slightly differed from treatment methods employed in Japan and various countries; new evidence was also obtained after the guidelines were prepared.

In this study, we introduce current strategies to treat steroid-sensitive, frequently relapsing/steroid-dependent, and steroid-resistant nephrotic syndrome based on our experience.

Key words: nephrotic syndrome, steroids, immunosuppressants

Introduction

Nephrotic syndrome (NS) refers to a syndrome in which glomerular basement membrane disturbance results in the massive leakage of protein from blood into urine, causing hypoproteinemia and systemic edema. In Japan, approximately 1,300 children per year are registered as new-onset cases in the medical aid for specific chronic disease of children. The annual incidence is estimated to be 5/100,000 children; NS is an important disease in the field of pediatrics. Furthermore, idiopathic NS without underlying disease accounts for approximately 90% of children with NS.

Oral corticosteroids are administered as first-choice agents at the initial onset of idiopathic childhood NS. This treatment leads to remission in approximately 80% of children. The disease type is classified as steroid-sensitive NS. However, it recurs in 80% of responders. Approximately 50% of these children show frequently relapsing NS. In children with this type of NS, the incidences of adverse reactions to corticosteroids including obesity, growth disturbance, hypertension, diabetes, osteoporosis, and adrenal failure, are high. Furthermore, non-responders to steroid therapy are regarded as showing steroid-resistant NS. In most cases, this syndrome is likely to go renal failure.

Treatment guidelines for childhood NS ("Guidelines for Drug Therapy for Idiopathic Childhood Nephrotic Syndrome, Version 1.0") were prepared by the Japanese Society for Pediatric Nephrology in May 2005. However, despite this proposal, the majority of treatment methods depend on each institution in clinical practice. Furthermore, there are differences between treatment methods employed in other countries, as described in the Cochrane Reviews, and the above guidelines.

In this study, we introduce strategies to treat childhood NS based on our experience.

Definition of idiopathic NS (Table 1)

In diagnostic criteria for childhood NS, marked proteinuria is emphasized as the most
important finding. Decreases in the serum protein and albumin concentrations are essential for diagnosis. Although most children show edema/hyperlipidemia, these are referential items, and not essential. Other items are evaluated in accordance with the diagnostic criteria established by the Specific Disease/Nephrotic Syndrome Survey and Research Group, Ministry of Health, Labour and Welfare.

1. Steroid therapy for steroid-sensitive nephrotic syndrome (SSNS)

Usually, NS patients who respond to treatment with corticosteroid hormones, achieving complete remission, are regarded as having SSNS.

Treatment at the initial onset

For initial remission induction, as a rule, high-dose prednisolone is orally administered at an initial dose of 60 mg/m²/day (or 2 mg/kg/day) for 4 weeks (3 to 4 times a day). Usually, proteinuria subsides within 1 to 2 weeks. In the field of pediatrics, no administration period/dose-decreasing method has been established. However, international (or modified ISKDC method) and long-term gradual reduction systems are commonly employed. In the former, prednisolone is administered once in the morning every two days for 4 weeks at a maintenance dose of 40 mg/m²/day after the end of initial-dose administration. As the treatment period is shortened, this method is useful for evaluating sensitivity to steroids.

The Guidelines for Drug Therapy for Idiopathic Childhood Nephrotic Syndrome are shown in Table 2. Initially, 2 mg/kg/day of prednisolone is administered 3 times a day for 4 weeks (maximum: 80 mg). After initial massive-dose therapy, the dose is decreased to 1.3 mg/kg/day, and the alternate-day administration method is conducted. The administration period can be established based on each attending physician’s decision. However, short-term (4-week) therapy is recommended.

In the long-term gradual reduction method, prednisolone at the initial dose is administered for 4 weeks, as described in the international system. Subsequently, the dose is gradually decreased to 1 mg/kg/day at 2-week intervals, and, then, the administration method is switched to alternate-day administration for dose reduction. Treatment is completed 6 months after the start of prednisolone therapy. In the article “Corticosteroid therapy for nephrotic syndrome in children” in the Cochrane Reviews published
in 2007, it is described that, concerning the prevention of relapse within 1 to 2 years after the end of treatment, the frequency of relapse after long-term administration (3 to 7 months) was lower than after the ISKDC system most routinely employed. Furthermore, it was concluded that 6-month administration can reduce the risk of relapse without serious adverse effects. In the article “Treatment of idiopathic nephrotic syndrome in children”, which was published on UpToDate.com, long-term steroid therapy with gradual dose-reduction is also recommended. A consensus regarding this therapy has been established.

We have now employed this long-term gradual reduction system, and favorable results were obtained.

**Treatment at the time of relapse**

In most children with SSNS, the dose-reduction or discontinuation of steroids cause relapse. Concerning treatment at the time of relapse, several methods are used in the field of pediatrics. In the modified ISKDC method, prednisolone at 60 mg/m²/day is administered until 3 days after obtaining a urinary protein-negative finding, followed by subsequent alternate-day administration at 40 mg/m²/day for 4 weeks.

In the Guidelines for Drug Therapy for Idiopathic Childhood Nephrotic Syndrome, the standard ISKDC method to treat relapse (A) and an ISKDC-based dose-reduction system involving a 3-month period of treatment (B) are presented. In this study, either (A) or (B) was selected as a therapeutic strategy (Table 2). In long-term, low-dose, alternate-day therapy, prednisolone at 40 to 60 mg/m²/day is administered until a urinary protein-negative finding persists for 1 week. Subsequently, it is administered every two days for 6 weeks, and the dose is decreased to 15 mg/m²/day within the 6 subsequent weeks of alternate-day therapy. Administration at this dose is continued, and completed, with a post-relapse treatment period of 12 to 18 months. In the Cochrane review, it was concluded that, concerning treatment at the time of relapse, long-term alternate-day therapy also more markedly prevented relapse compared to

<table>
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<th>Table 2</th>
<th>Treatment at the initial onset in accordance with the Guidelines for Drug Therapy for Idiopathic Childhood Nephrotic Syndrome prepared by the Japanese Society for Pediatric Nephrology.</th>
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<td>Prednisolone</td>
<td>(1) 60 mg/m²/day (approximately 2.0 mg/kg/day), administered 3 times a day for 4 weeks (maximum: 80 mg/day). (2) 40 mg/m²/day (approximately 1.3 mg/kg/day), administered once in the morning every two days for 4 weeks (maximum: 80 mg/day). However, the dose-reduction method (2) is employed based on attending physicians' evaluation.</td>
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<td>Treatment at the time of relapse</td>
<td>Prednisolone (Either A or B is selected.) (A) (1) 60 mg/m²/day (approximately 2.0 mg/kg/day), administered 3 times a day until 3 days after the disappearance of proteinuria (maximum: 80 mg/day). (2) 40 mg/m²/day (approximately 1.3 mg/kg/day), administered once in the morning every two days for 4 weeks (maximum: 80 mg/day). (B) (1) 60 mg/m²/day (approximately 2.0 mg/kg/day), administered 3 times a day until 3 days after the disappearance of proteinuria or for 4 weeks at maximum (maximum: 80 mg/day). (2) 60 mg/m²/day (approximately 2.0 mg/kg/day), administered once in the morning every two days for 2 weeks (maximum: 80 mg/day). (3) 30 mg/m²/day (approximately 1.0 mg/kg/day), administered once in the morning every two days for 2 weeks (maximum: 40 mg/day). (4) 15 mg/m²/day (approximately 0.5 mg/kg/day), administered once in the morning every two days for 2 weeks (maximum: 20 mg/day). However, the dose-reduction methods (2) to (4) are employed based on attending physicians' evaluation. Long-term gradual reduction therapy is also selected, if necessary.</td>
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the standard method to treat relapse. In addition, the results suggest that the total dose of a steroid can be reduced due to a decrease in the frequency of relapse in children with frequently relapsing NS.3

We have also employed this system for treatment.

2. Immunosuppressive therapy for frequently relapsing/steroid-dependent nephrotic syndrome (FRNS/SDNS)

In approximately 30% of children with NS, the recurrence of 2 to 3 times a year or more frequently. It is classified as FRNS. Therapy with immunosuppressive agents is required in some cases.

In the Guidelines for Drug Therapy for Idiopathic Childhood Nephrotic Syndrome, it is recommended that one of the following 3 agents should be selected as a strategy to treat FRNS, considering the efficacy and adverse effects:

1. Cyclosporine at 3 to 6 mg/kg/day (the dose is regulated while monitoring its blood concentration.)
2. Cyclophosphamide administered at 2 to 3 mg/kg/day for 8 to 12 weeks
3. Mizoribine at 4 mg/kg/day.

Immunosuppressive agents

1. Cyclosporine therapy

Cyclosporine inhibits calcineurin activity. It is often administered to patients who do not respond to cyclophosphamide, or in order to prevent the serious adverse effects of cyclophosphamide, such as gonadal disturbance and tumorigenesis. This agent is useful for the treatment of FRNS/SDNS. A clinical study reported that withdrawal from steroid therapy was possible in most patients. However, the discontinuation of cyclosporine therapy increases the risk of relapse.5 Adverse effects include hyperalkaline-phosphatasemia, hypertension, hypertrichosis, and gingival thickening. As serious adverse effects, chronic nephropathy (cyclosporine-induced nephropathy) and neurotoxicity (white matter encephalopathy) are raised; caution is required. Chronic nephropathy is hardly to evaluate based on the results of urinalysis or hematology. For its diagnosis, only renal biopsy is confidential method. This nephrotoxicity consists of arteriole and interstitial lesions. The discontinuation of cyclosporine for 6 months to 1 year significantly reduces arteriole lesions, inhibiting the deterioration of interstitial lesions. Long-term therapy with moderate-dose cyclosporine (trough value: approximately 100 ng/ml) (period: 2 years or more) was reported as a risk factor for interstitial lesions.6 According to a study conducted by the Japanese Study Group of Renal Disease in Children, when the trough value of cyclosporine was established as 80 to 100 ng/ml for 6 months after the start of administration and 60 to 80 ng/ml for the subsequent 18 months, remission could be maintained during 24-month cyclosporine therapy in about 50% of patients.7

We also consider that cyclosporine is a key immunosuppressive drug in the treatment of FRNS/SDNS. In our hospital, cyclosporine at 2.5 to 5 mg/kg/day is administered twice a day for 1 to 2 years, with a trough value of 50 to 120 ng/ml.9 When administering this agent for 2 years, renal biopsy is performed to evaluate the occurrence of chronic nephropathy related to long-term use. Furthermore, we start cyclosporine therapy after glomerular growth if possible, considering the association between early administration during childhood and the inhibition of immature glomerular differentiation.

II. Cyclophosphamide therapy

Cyclophosphamide, an alkylating agent, is useful for treating FRNS (2 to 3 mg/kg/day, 8 weeks).9 However, concerning its usefulness in the treatment of SDNS, administration at 2 mg/kg/day for 8 weeks is ineffective. The efficacy of cyclophosphamide therapy at 2 mg/kg/day for 12 weeks remains controversial. Adverse effects including as bone marrow suppression, liver dysfunction, hemorrhagic cystitis, gonadal disturbance (especially spermatogenic dysfunction in boys), and tumorigenesis must be considered. In particular, male gonadal disturbance is an important problem. When the cumulative dose exceeds 300 mg/kg, this agent frequently causes azoospermia or oligospermia. Therefore, the cumulative dose should be regulated at 200 to 300 mg/kg.10

In our hospital, 2.5 to 3.0 mg/kg/day of cyclophosphamide is administered once or twice a day for 10 to 12 weeks to treat SDNS. Gonadal disturbance, as an adverse effect, is serious; this agent should be carefully administered, considering the patients’ age. As the use of this agent is limited to once in a lifetime, it should be employed in young children prior to puberty.

III. Mizoribine therapy
Mizoribine is a metabolic antagonist that was developed in Japan. In a double-blind, placebo-controlled, multicenter trial, which was conducted by the Pediatric Mizoribine Study Group, mizoribine therapy at 4 mg/kg/day for 48 weeks was compared with placebo administration for 48 weeks to investigate its efficacy and safety in children with FRNS/SDNS. Among registered children overall, there was no significant difference in the recurrence rate between the mizoribine and placebo groups. However, among children aged 10 years or younger, the recurrence rate in the mizoribine group was significantly lower than in the placebo group. As an adverse effect, hyperuricemia was observed. In most children experiencing adverse effect, mizoribine could be continuously administered without discontinuation or dose-reduction. Therefore, mizoribine may be useful for minimizing adverse effects, although its efficacy is not marked.

In our review, regarding the effective blood concentration of mizoribine as 3 μg/ml, it is difficult to maintain this blood concentration in children aged over 10 years, since a dose of 150 mg/day is covered by health insurance. Currently, we consider that mizoribine therapy should be selected in children aged 10 years or younger or weighing less than 30 kg.

IV. Therapy with mycophenolate mofetil
Mycophenolate mofetil (MMF) is a purine metabolism antagonist, as are azathioprine and mizoribine. This prodrug is converted into mycophenolic acid (MPA) in vivo, showing pharmacological actions. In a prospective study involving 19 patients with SDNS, this agent significantly reduced the frequency of relapse compared to steroids. It is known that the incidence of adverse effects is lower than those related to other immunosuppressive agents. However, frequent adverse effects include digestive symptoms such as abdominal pain, nausea, and diarrhea.

We also administered MMF to 11 children, and it maintained remission and decrease the doses of steroids. This agent could be relatively safely administered. Therefore, it may replace cyclosporine.

V. Tacrolimus therapy
Tacrolimus inhibits calcineurin activity, as reported for cyclosporine. It selectively suppresses the transcription of IL-2 and other cytokines in T lymphocytes. Sinha et al. performed therapy with this agent or cyclosporine by dividing 20 patients with severe SDNS into 2 groups, and indicated that there was no advantage of this agent other than cosmetic adverse effects, although the two agents prevented relapse.

We have also employed this agent to treat severe SDNS.

VI. Rituximab therapy
Rituximab is a chimera-type monoclonal antibody against the differential antigen CD20, which appears on the B-cell surface. It is classified as a biological preparation rather than an immunosuppressive agent. A study reported that, when rituximab was administered to 22 patients with severe SDNS, remission was achieved in 3 of 7 showing NS. In addition, the doses of immunosuppressive agents could be decreased in 19, suggesting the efficacy of this agent. For rituximab therapy, the risk of serious adverse effects such as hypotension, vascular edema, ARDS, fatal arrhythmia, cardiogenic shock, and pancytopenia must be considered.

In the autumn of 2008, a “multicenter, cooperative, double-blind, placebo-controlled, randomized, comparative study of rituximab for refractory childhood nephrotic syndrome” was initiated as a treatment promotion research business in Japan, and is currently being conducted.

In the article “Non-corticosteroid therapy for nephrotic syndrome in children” published in the Cochrane Reviews in 2008, it was concluded that the 8-week administration of cyclophosphamide or chlorambucil, and long-term therapy with cyclosporine or levamisole significantly decreased the recurrence rate compared to single therapy with steroids in patients with FRNS. In addition, it is described that the efficacy of each regimen should be compared in the future. Currently, chlorambucil and levamisole are difficult to obtain in Japan. On UpToDate.com, it is recommended that cyclophosphamide be administered for 12 weeks. On the other hand, the administration methods for 3 immunosuppressive agents are described in the Guidelines for Drug Therapy for Idiopathic Childhood Nephrotic Syndrome. However, no appropriate administration standards regarding the timing and choice of these agents have been established.

In this study, we propose long-term strategies to treat FRNS/SDNS with immunosuppressive agents, considering the age (Figure 1). Based on the results of our previous findings, we consider that mizoribine therapy, showing the lowest incidence of adverse effects among immunosup-
Fig. 1 Treatment strategy for frequently relapsing, steroid-dependent nephrotic syndrome.

Pressor agents, should be initially employed in children with FRNS/SDNS aged 10 years or younger or weighing less than 30 kg. Secondly, cyclophosphamide therapy should be performed only once in children prior to puberty (before the appearance of secondary sexual characteristics), considering that the risk of gonadal disturbance is low.

As growth disorder must be considered the most important problem during puberty, cyclosporine therapy, which is the most useful for treating FRNS/SDNS, facilitating long-term administration, should be selected. During this period, glomerular growth is completed, and no immature glomerulus may be present.

Recent studies have reported that a drug resistance phenomenon in which a dose higher than the standard dose is required to maintain remission, gradually leading to the drug’s unresponsiveness, “tachyphylaxis”, may occur during the administration of various immunosuppressive agents including cyclosporine. Therefore, double effects, obtaining the maximum efficacy of each agent and minimizing its adverse effects, can be achieved by switching a first-choice to another immunosuppressive agent with a different action mechanism before the appearance of drug resistance. For this reason, a metabolic antagonist, MMF, should be selected following the administration of a calcineurin activity-inhibiting agent, cyclosporine. If the high-dose administration of mizoribine with a similar action mechanism is possible, it may become a treatment option.

As a subsequent regimen, we consider that the additional administration of cyclosporine or tacrolimus (calcineurin activity-inhibiting agent) therapy is appropriate.

In patients with refractory NS, which is impossible to control, rituximab may be selected.

3. Treatment for steroid-resistant nephrotic syndrome (SRNS)

Patients in whom remission is not achieved despite steroid therapy at a maximum dose for 4 to 8 weeks are regarded as having SRNS. The condition leads to renal failure in 30 to 40% of patients 10 years after onset. The histological type is classified into 3: minimal change, focal segmental glomerulosclerosis (FSGS), and diffuse mesangial proliferation. In particular, FSGS shows an unfavorable prognosis, accounting for approximately 20% of etiologic factors for renal failure in children.

In the Guidelines for Drug Therapy for Idiopathic Childhood Nephrotic Syndrome, it is recommended that alternate-day prednisolone therapy at 1 mg/kg (once in the morning) should be combined with the following regimens in patients with SRNS:

1. Cyclosporine therapy: Cyclosporine at 3 to 7 mg/kg/day is administered. The dose is regulated based on the following trough values: 100 to 150 ng/ml (3 months), 80 to 100 ng/ml (3 months to 1 year), and 60 to 80 ng/ml (1 year or more).

2. Massive-dose steroid intravenous injection therapy: Methylprednisolone at 20 to 30 mg/kg/bolus (maximum: 1 g) is intravenously administered 3 times (1 course). A total of 1 to 10 courses are performed. However, the administration of prednisolone is discontinued during methylprednisolone therapy.

Regimens (1), (2), or (1)+(2) should be selected.

II. Pulse methylprednisolone therapy

When remission is not obtained despite initial-dose oral steroid therapy for 4 weeks or more, pulse methylprednisolone therapy (15 to 30 mg/kg/bolus (maximum: 1 g), 3 boluses per course) is employed. Mendoza et al. performed intravenous methylprednisolone administration (total: 30 times) and oral prednisolone therapy to treat steroid-resistant FSGS. When there was no response, they combined this regimen with an alkylating agent, and reported that complete remission was achieved in 12 (53%) of 23 patients, with a mean follow-up of 46 months. As adverse effects, arrhythmia, hypertension, shock, pancreatitis, and accelerated blood coagulation must be considered.

The efficacy of pulse methylprednisolone therapy for SRNS has not universally been demon-
strated. We also consider that this therapy should be employed once. However, it is ineffective for patients with marked sclerosis. Kidney function is impaired in some patients; this therapy should be carefully performed.

II. Cyclosporine therapy

A study retrospectively examined the results of long-term massive-dose cyclosporine administration, and indicated that the incidence of renal failure was significantly lower than in historical controls. Cyclosporine has been shown to antagonize/inhibit P-glycoprotein induced by a multidrug-resistance gene (MDR-1).

In our hospital, cyclosporine is combined with maintenance-dose prednisolone for the first year, considering that cyclosporine enhances steroid actions.

III. LDL apheresis therapy

In Japan, low-density-lipoprotein (LDL) apheresis therapy to relieve concomitant hyperlipidemia has been carried out as a treatment for refractory, steroid-resistant. FSGS.

We have also encountered steroid- and cyclosporine-resistant patients in whom LDL apheresis therapy resulted in the amelioration of steroid/cyclosporine sensitivity. When patients do not respond to cyclosporine, this therapy should be examined.

IV. MMF therapy

We administered MMF to steroid- and cyclosporine-resistant NS patients. Complete remission was achieved without adverse effects, and the doses of steroids could be decreased, suggesting the usefulness of MMF therapy as a treatment option for SRNS.

V. Rituximab therapy

According to a study internationally published, this agent was administered 4 times to 5 children with SRNS who showed resistance to various immunosuppressive agents. In 3 of these, remission was achieved, and incomplete remission in 2. The doses of steroids and immunosuppressive agents could be decreased. The prognosis of SRNS is unfavorable; rituximab therapy may become a treatment option in the future.

In the Cochrane Reviews of 2006, the efficacy of cyclosporine and effects of angiotensin-converting enzyme inhibitors on proteinuria were emphasized. However, no evidence-based treatment has been established, while a study reported that there was no correlation between the results of initial renal biopsy and the final outcome.

Thus, we introduced our current strategies to treat NS in children. However, the development of new potential agents and research on the etiology of NS with advances in medicine may alter the present protocol in the future.
References


