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Case Report

Long-Term Azathioprine Therapy in Two Children with Steroid-Dependent Minimal-Change Nephrotic Syndrome

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TANAKA, H., ONODERA, N. and WAGA, S. *Long-Term Azathioprine Therapy in Two Children with Steroid-Dependent Minimal-Change Nephrotic Syndrome.* Tohoku J. Exp. Med., 1999, **187** (3), 273-278 —— Long-term azathioprine therapy as an alternative treatment to cyclophosphamide was done in 2 children with steroid-dependent minimal-change nephrotic syndrome (MCNS). They had already been treated with prednisolone, intravenous methyl-prednisolone pulse therapy, cyclophosphamide and mizoribine. Although cyclophosphamide had been proved to be effective in maintaining their remission, the cumulative dose of the agent limited another course of cyclophosphamide therapy. Since ciclosporine therapy is much expensive, a trial of azathioprine (2 mg/kg per day) was started, and the therapy resulted in inducing sustained remission and reducing prednisolone. The patients were well tolerated the long-term azathioprine therapy over a year. Although the efficacy of azathioprine in the management of childhood MCNS might be restricted, we therefore suggest that this agent should be reconsidered as an alternative treatment to cyclophosphamide. —— alternative treatment; azathioprine; childhood; long-term treatment; steroid-dependent minimal-change nephrotic syndrome

It has been reported that the long-term outcome of steroid-dependent minimal-change nephrotic syndrome (MCNS) of childhood is favorable (Kashtan et al. 1988; Takada et al. 1988). However, a significant proportion of children with MCNS experience frequent relapses, which impair the quality of life (Takada et al. 1988; Brodehl 1991; Neuhaus et al. 1994). Therefore, alternative immunosuppressive treatment to corticosteroids has been performed to prevent frequent relapses and to avoid steroid toxicity. Immunosuppressive drugs found to be effective in steroid-dependent MCNS of childhood are alkylating agents

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and ciclosporine (Brodehl 1991; Neuhaus et al. 1994; Gregory et al. 1996). However, alkylating agents, such as cyclophosphamide and chlorambucil have a significant potential toxicity, which concern mainly gonads and oncogenicity (Etteldolf et al. 1976). While, ciclosporine has been reported to be effective in most patients with steroid-dependent MCNS (Kitano et al. 1990; Brodehl 1991; Gregory et al. 1996). But these patients relapsed at ciclosporine tapering, thus necessitating prolonged therapy (Kitano et al. 1990; Neuhaus et al. 1994). Since chronic renal toxicity may be induced by the prolonged ciclosporine therapy (Habib and Niaudet 1994), the use of ciclosporine might be limited.

Azathioprine has been safely used in the treatment of rheumatoid arthritis (Fries et al. 1996) and chronic eczematoid rash (Dutz and Ho 1998) for a long time. Concerning MCNS, azathioprine has been found to be no obvious efficacy in inducing or maintaining remission in childhood MCNS (Abramowicz et al. 1970; Barratt et al. 1977; Neuhaus et al. 1994). Meanwhile, some adult patients with MCNS showed a favorable response to long-term azathioprine administration (Cade et al. 1986). We therefore conducted long-term azathioprine therapy in 2 children with steroid-dependent MCNS, and found that this agent to be of benefit in maintaining their remission and reducing prednisolone. Azathioprine therapy might be reconsidered in the selected patients with steroid-dependent MCNS of childhood.

Patients and Methods

Case 1

A 7-year-5-month-old boy with a 2-year history of nephrotic syndrome (NS) was hospitalized with the 7th relapse of NS. Although he had been treated with prednisolone, intravenous methyl-prednisolone pulse therapy (MPT), cyclophosphamide and an newly developed immunosuppressant, mizoribine (Bredinin®, Asahi-Kasei, Osaka), he developed a steroid-dependent frequent relapser. Renal biopsy revealed minor glomerular abnormalities with trace IgM depositions. Tubulointerstitial changes were not observed. He had been experienced frequent ralapses at the dosage of prednisolone around 10 mg per alternate day. Serum urea nitrogen and creatinine were within normal values.

After admission, the prednisolone therapy at a dosage of 30 mg (1 mg/kg) per day was conducted, and which resulted in a gradual subsidence of proteinuria. Then, the prednisolone dosage was tapered on a gradual basis. Since 2 times of 8-week course of cyclophosphamide (2 mg/kg per day) had been already done, and mizoribine had not been proved to be effective, azathioprine (2 mg/kg per day) combined with alternate day prednisolone (20 mg) was conducted at the age of 7-year-6-month. Thereafter, he was discharged and followed at outpatient clinic. Although the dosage of prednisolone decreased to 2.5 mg per alternate day, the remission of his NS was maintaining over 2 years. Clinical toxicity of the long-term azathioprine therapy was not observed.

Case 2

A 7-year-10-month-old boy with a 3-year history of NS was hospitalized because of the relapse of NS. He had been treated with prednisolone, MPT, cyclophosphamide and mizoribine. He had a steroid-dependent MCNS confirmed by renal biopsy, and experienced frequent relapses at a dosage of 30 mg (1.5 mg/kg) per alternate day of prednisolone. Although MPT and mizoribine had not been proved to maintain the remission, a 12-week course of cyclophosphamide (2 mg/kg per day) resulted in maintaining the remission and reducing prednisolone. At the time when the prednisolone dosage was 5 mg per alternate day, he had the 4th relapses of NS.

After admission, the prednisolone therapy at a dose of 40 mg (1.5 mg/kg) per day combined with mizoribine was started, and resulted in a rapid subsidence of proteinuria. However, the reducing dosage of prednisolone (1 mg/kg per alternate day) induced another relapse. Then, azathioprine (2 mg/kg per day) was replaced mizoribine. Thereafter, the remission of his NS sustained over a year under the combination therapy of azathioprine and low-dose prednisolone (2.5 mg per alternate day). Clinical toxicity of the therapy was not observed.

Results

In the 2 children, the dosage of prednisolone could be decreased after the therapy to 2.5 mg per alternate day, which were less than half of the dosage administered before azathioprine therapy. As shown in Table 1, relapses did not occur during the observation period. No clinical toxicity of azathioprine therapy was observed.

Table 1. *Clinical character of the 2 patients with steroid-dependent minimal-change nephrotic syndrome*

No.	Sex	Age at onset (years)	Duration of illness before AZP (months)	Age AZP started (years)	Relapses (times)	Prior therapy	Observation period after AZP (months)	Relapses after AZP (times)	Efficacy of AZP therapy
1	M	5	24	7	7	PSL, MPT, CPA, MZB	24	0	Reduction of PSL
2	M	4	45	8	5	PSL, MPT, CPA, MZB	12	0	Reduction of PSL

AZP, azathioprine; CPA, cyclophosphamide; MPT, methyl-prednisolone pulse therapy; MZB, mizoribine; PSL, prednisolone.

Discussion

The efficacy of alkylating agents, such as chlorambucil and cyclophosphamide has been established in inducing and maintaining remission of childhood MCNS

(Kashtan et al. 1988; Brodehl 1991; Neuhaus et al. 1994). However, these alkylating agents have a potential toxicity concerning gonads and oncogenicity. Therefore the use of these drugs, especially in pubertal boys, is limited at the point of upper cumulative dose (Etteldolf et al. 1976). Furthermore, chlorambucil is not routinely available in Japan. In the present cases, cyclophosphamide had been used and proved to be of benefit in sustained remission. However, they had experienced another relapses after cessation of cyclophosphamide therapy. Recently, mizoribine, a newly developed immunosuppressant in Japan, has been reported to be of benefit and low clinical toxicity in the selected children with steroid-dependent MCNS (Hamasaki et al. 1997). But this agent failed to show comparable benefits in the treatment of present cases.

Meanwhile, ciclosporine has been reported to be effective in childhood steroid-dependent MCNS (Brodehl 1991; Gregory et al. 1996). But the effect of ciclosporine in maintaining remission of NS is ciclosporine dependent (Kitano et al. 1990). Thus, prolonged ciclosporine treatment should be required in frequent relapsing steroid-dependent MCNS of childhood, and such prolonged therapy may increase the frequency of nephrotoxicity (Habib and Niaudet 1994), although it was not always confirmed. Furthermore, the cost of long-term ciclosporine therapy is more expensive than the other immunosuppressants.

Therefore, these backgrounds required us to commence azathioprine as an alternative treatment to cyclophoshamide in the present cases, and the therapy proved to be of benefit in inducing sustained remission and reducing prednisolone. Since controlled trials of azathioprine in the treatment of childhood MCNS have not been proved the effectiveness (Abramowicz et al. 1970; Barratt et al. 1977), this agent is not usually used as an alternative treatment to alkylating agents. Recently, there are a few published reports to describe efficacy of long-term azathioprine administration in patients with MCNS (Cade et al. 1986; Kamil et al. 1993), although the agent occasionally applies to several chronic glomerulonephritis (Tareyeva et al. 1980).

The MCNS patients described here showed a favorable response to the long-term azathioprine therapy. They had already been received over a 12-week course of cyclophosphamide treatment before azathioprine. Although a probable explanation for the efficacy of azathioprine in our patients remains speculative, preceding cyclophosphamide might affect susceptibility to succeeding azathioprine. The prolonged azathioprine therapy over a year may be of benefit in the patients as in the previous report (Cade et al. 1986). Attempts to judge the therapeutic effectiveness of azathioprine in this paper, however, may not be confirmed, since it is well known that many children with steroid-dependent MCNS will improve with time (Takada et al. 1988). And the efficacy of azathioprine in our observation was based on only 2 cases. Accordingly, it is difficult to draw the conclusion. Further study is needed.

To date, newly developed immnunosuppressants, such as ciclosprine and

mizoribine have been proved to be of benefit in the management of childhood MCNS (Brodehl 1991; Gregory et al. 1996; Hamasaki et al. 1997). However, the cost of long-term therapy of these new agents are much expensive. Although the efficacy of azathioprine may be restricted in the treatment of MCNS, we therefore suggest that this agent should be reconsidered as an alternative treatment to alkylating agents or ciclosporine in the selected children with steroid-dependent MCNS.

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