Second Trial of Cyclosporin A-Induced Remission in Other Immunosuppressant Therapy-Resistant FSGS Patient

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= **Abstract** =

다른 면역 억제제에 듣지 않는 국소성 분절성 사구체 경화증 환자에서 Cyclosporin A 2차 치료에 의한 완해 경험

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Focal segmental glomerulosclerosis(FSGS) has been detected in approximately 10% of cases of idiopathic nephrotic syndrome in children, and exhibits a poor response to initial steroid therapy, as well as a higher rate of progression to chronic renal failure and relapse after kidney transplantation. We describe a case of an eleven year-old boy with steroid-resistant FSGS who exhibited a response to a second trial of cyclosporin A(CsA) therapy. At the age of 26 months, this patient was diagnosed with steroid-resistant FSGS. For 9 years, he had undergone a gauntlet of therapies to induce remission; oral steroids, cyclophosphamide, methylprednisolone(mehylPd) pulse therapy, CsA, and ibuprofen therapy. Although these therapies failed to induce remission, the patient's renal function remained in the normal range during the nine years of treatment. At the age of ten years, the patient's proteinuria decreased, and complete remission was attained with a second administration of CsA, coupled with a low dose of oral steroids. This patient continues to receive CsA without relapse. Therefore, our major concern involves the possibility of relapse after the discontinuation of CsA therapy. Our findings in this case suggest that, in cases of refractory FSGS, if renal insufficiency does not emerge, aggressive therapy for the amelioration of proteinuria should be continuously pursued. **(J Korean Soc Pediatr Nephrol 2005;9:83-90)**

Key Words : Steroid-resistant FSGS, Cyclosporin A, Remission, Renal insufficiency

Introduction

Focal segmental glomerulosclerosis(FSGS) is the second most frequent cause of idiopathic nephrotic syndrome in children[1]. The normal presentation involves persistent nephrotic syndrome, microscopic hematuria, hypertension,

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and renal insufficiency[2]. Although the rate of progression to end-stage renal disease(ESRD) associated with this condition is less than 15% when remission has been achieved, more than 50% of patients progress to ESRD within 5 to 10 years without remission[1, 2]. In steroid-resistant manifestations of FSGS, the induction of remission constitutes the most relevant factor with regard to whether the patient with progress to ESRD[2]. Therefore, in order to achieve remission, a variety of treatment agents, including cyclophosphamide, cyclosporine A(CsA), methylprednisolone(methylPd) pulse, and mycophenolate mofetil(MMF), have been attempted. However, the remission rates associated with this condition remain unacceptably low[1-11]. In this case, we encountered a patient who suffered from FSGS, and evidenced no response to any treatments, including oral steroids, methylPd pulse, cyclophosphamide, CsA; or ibuprofen for 9 years. However, this patient's disease did not progress to ESRD, and complete remission was achieved after a second administration of CsA.

Case report

A three-year old patient was initially admitted to our hospital for refractory proteinuria. He had been diagnosed with nephrotic syndrome at the age of 26 months at a local hospital, and had received oral prednisolone (60 mg/m^2/day) for five months. Despite the administration of prednisolone treatment, the patient's proteinuria persisted, and was aggravated by an upper respiratory tract infection, but improved in response to an increased oral prednisolone dosage. After five months of prednisolone therapy, oral cyclophosphamide was administered for eight weeks, meeting with no response. The patient was transferred to our hospital seventeen months after the initial diagnosis. At that time, we detected hypertension. Serum creatinine and albumin levels were 0.3 mg/dL and 2.7 g/dL, respectively, and the 24-hour urine total protein was 4,822 mg/24hr(urinary protein=340 mg/m^2/hr). Renal vein thrombosis was detected via renal ultrasound. A percutaneous renal biopsy specimen revealed FSGS with segmental sclerosis(36%). There was a significant component of interstitial fibrosis, with mild focal tubular atrophy, or loss(Fig. 1). The administration of oral captopril was initiated for hypertension, and heparin and warfarin therapy were pursued in order to treat the thrombosis. This regimen was followed for five months. One month after the patient's transfer, methylPd pulse therapy was initiated. Nine months later, methylPd pulse therapy was discontinued due to lack of response, and only oral

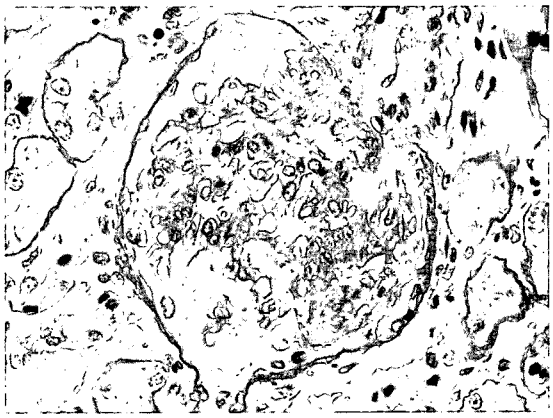

Fig. 1. Light microscopy view showing focal segmental glomerulosclerosis(H&E, ×400). The specimen shows a significant component of interstitial fibrosis, with mild focal tubular atrophy or loss.

prednisolone therapy was continued. The patient suffered from recurrent abdominal pain and edema, and the patient was intermittently infused with intravenous albumin.

Two months after the discontinuation of the methylPd, we initiated a combination therapy of CsA(4.3 mg/kg/d divided two) and low dose prednisolone. The pretreatment serum cholesterol level was 465 mg/dL. Trough whole-blood cyclosporine levels were maintained in the 45 to 70 ng/mL range. After the initiation of CsA therapy, the urinary protein-to-urinary creatinine(UP/UC) ratio decreased from 7.1 to 0.6, but remission still did not occur. Even after 13 months of CsA therapy, the patient did not go into remission. CsA therapy was discontinued due to persistent proteinuria and peritonitis, and only deflazacort administration was maintained. When the patient was six years old, ibuprofen therapy for the amelioration of proteinuria was attempted for three months after the discontinuation of deflazacort therapy, but this met with no response. Ibuprofen therapy was halted, and oral deflazacort therapy was reinitiated, but the proteinuria persisted. During these treatments, our patient suffered from complications, including cellulites(three times), pneumococcal meningitis, and spontaneous bacterial peritonitis(twice). At the age of seven, plasmapheresis was planned, but could not be conducted, due to poor vascular access. During four years, only oral deflazacort therapy was maintained, but proteinuria persisted.

When the patient was eleven years-old, a second run of CsA therapy(5.3 mg/kg/d) with deflazacort administration every other day, was initiated(Fig. 2). Pretreatment serum cholesterol level was 191 mg/dL, and the UP/UC ratio was 2.3. During treatment, trough whole-blood cyclosporine levels were maintained in the 37 to 112 ng/mL range. The UP/UC ratio decreased dramatically in

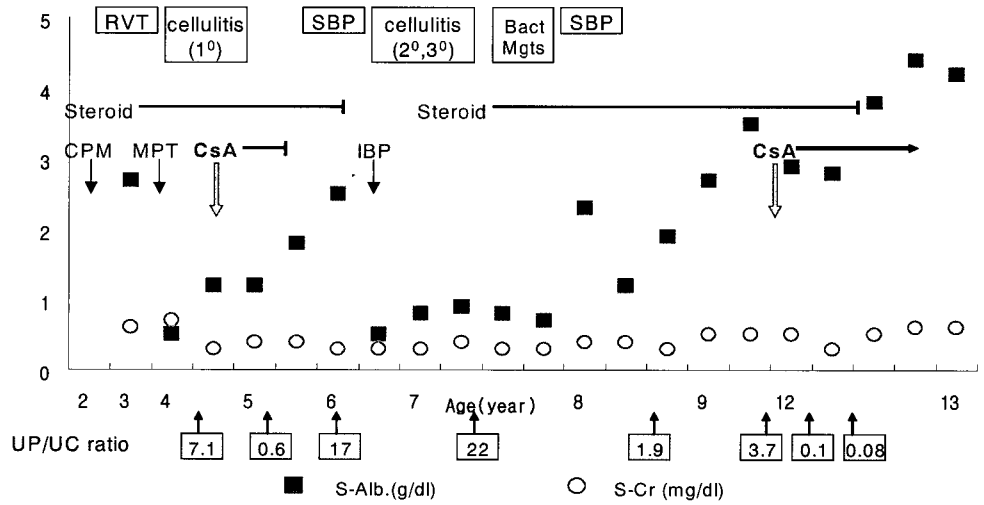

Fig. 2. Therapy and proteinuric response.
Abbreviation : UP/UC, urinary protein/urinary creatinine value; MPT, methylprednisolone pulse therapy; CPM, cyclophospamide; IBP, ibuprofen RVT, renal vein thrombosis; SBP, spontaneous bacterial peritonitis; Bact Mgts, bacterial meningitis.

response to the CsA therapy, and remission was attained after 40 days of CsA therapy (UP/UC ratio=0.13). As the UP/UC ratio decreased, the deflazacort administration was discontinued after six months of the combination therapy. The CsA dosage was tapered off seven months after the initiation of therapy. The patient continues to receive CsA(3 mg/kg/d), and is without relapse for fifteen months, and his serum creatinine levels have been maintained within the normal range. The evaluation of tubular function showed the normal range. Because of adverse effect attributed to corticosteroid therapy, the patient was short(139 cm, <3th percentile) for his age and received growth hormone therapy.

Discussion

Recently, the yearly incidence of primary FSGS has risen from 4-10% in 1974 to 12-25% in 1993[2, 12]. Resistance to steroid therapy has been reported in around 70% of FSGS patients, and progression to ESRD has been reported in up to 60% of cases after 10 years[1, 3, 13-17]. Recent reports have shown that nephrotic patients entering remission did not progress to ESRD within a twelve-year period. However, in patients with no remission, serum creatinine levels almost doubled, while 50% of untreated nephritic patients progressed to ESRD[2]. Therefore, remission significantly altered the course of nephrotic FSGS patients[1, 2]. In our case, although the patient did not achieve remission for nine years and, therefore, ran a clear risk of progression to ESRD, his serum creatinine levels remained in the normal range. An upper respiratory tract infection aggravated the degree of proteinuria, and his proteinuria improved as the result of an increase in the dosage of oral steroids. The patient's clinical manifestations were somewhat similar to those associated with minimal change nephritic syndrome.

In steroid resistant manifestations of FSGS, cyclophosphamide, methylPd pulse therapy, CsA, MMF or plasmapheresis can all be attempted, but the remission rate is known to be quite low, as compared with steroid-dependent FSGS[1-11, 14, 18]. The recent International Study of Kidney Diseases in Children(ISKDC) report on the treatment of FSGS with alkylating agents(cyclophosphamide) reported complete remission in only 25% of patients, and no response whatsoever in 57%[8]. Remission rates of up to 60% have been noted in conjunction with the combination of high-dose intravenous steroids and alkylating agents[3, 8, 9, 14, 15]. The reported remission rate for FSGS when treated with methylPd ranges from 69% to 83% during the treatment period, but the reported persistent remission rate after the discontinuation of treatment is 23%[10].

CsA has proven to be effective in the management of nephrotic syndrome in children demonstrating both steroid-dependent or steroid-resistant disease courses[3-6, 16-25]. The reported remission rate for FSGS patients who are treated with CsA ranges from 20% to 90%[3-6, 19-28]. Children exhibiting the steroid-resistant FSGS form appear to be less likely to exhibit an initial response to CsA than children with steroid-dependent

FSGS, and the presence of FSGS has been strongly associated with CsA resistance[4, 6, 19-28]. Therefore, our patient had a greater possibility of exhibiting CsA resistance. In CsA therapy, two factors increase the percentage of remission in cases of steroid-resistant FSGS. The first is the combination of CsA and low-dose steroid therapy, and the other is increased CsA dosages in cases involving high serum cholesterol levels[3-5]. The combination of CsA and low-dose steroid therapy yields better results, and a recent report demonstrated that in steroid-resistant nephrotic syndrome patients who were treated with a combination of CsA and prednisone for 5 months, 42% achieved complete remission[3, 23]. Some reports have demonstrated that, in steroid-resistant FSGS patients treated only with CsA, remission occurred in 20-30%[2, 3]. Patients with very high pretreatment serum cholesterol levels require greater CsA dosages than the dosages used to achieve a response in our test case[3, 4]. Also, in patients with high pretreatment serum cholesterol levels, the administration of high dosages of CsA did not increase the incidence of side effects[3, 4]. In our patient, both the first and second CsA administration attempts were combined with low doses of steroids. Also, in association with pretreatment serum cholesterol levels, there were substantial differences between the initial and second trial(at the time of initial trial, 483 mg/dL, and at the time of second trial, 191 mg/dL). In both the initial and second trials, the CsA dosages were not significantly different. Therefore, we can surmise that the achievement of remission after a second CsA trial may be associated with low pretreatment serum cholesterol levels.

The two primary concerns with CsA therapy have included its potential for nephrotoxicity(reported to occur in 17% to 60% of patients), and a tendency toward relapse after the discontinuation of CsA[3, 4, 6, 19-23, 25-29]. The incidences of nephrotoxicity and hypertension occurred with significantly higher frequency in patients with FSGS[4]. The three primary predictive factors associated with CsA nephrotoxicity include: the presence of renal insufficiency prior to treatment, dosage greater than 5.5 mg/kg/day, and the percentage of glomeruli-exhibiting FSGS lesions up on the initial renal biopsy[4]. The development of renal fibrosis in CsA nephrotoxicity was not coupled with a parallel increase in serum creatinine levels, and some authors have recommended that repeat renal biopsies should be conducted after 1or 2 years after the inception of CsA treatment, in order to verify tolerance, regardless of the serum creatinine levels[4]. In our patients, we detected no renal insufficiencies prior to treatment, and the CsA dosage used was not greater than 5.5 mg/kg/d. However, our patient continues to receive oral CsA therapy for 15 months. If the duration of CsA therapy must be prolonged, renal biopsy should be considered. Chishti et al. proposed that treatment with a single daily low dose of CsA(5 mg/kg/d) should be administered to steroid-resistant FSGS patients, in order to circumvent the side effects associated with long-term use[3]. In their study population, the response rate was 69%

in the steroid-resistant group, and none of the patients experienced nephrotoxicity[3].In our case, during the initial and second CsA attempts, low-dose CsA(4.3-5.3 mg/kg/d divided two) was used, but there were no side effects.

Many children who respond to CsA eventually become dependent on the drug, and exhibit a tendency toward relapse if the therapy is discontinued, or the dosage is reduced[4, 6, 21-23]. The mechanism underlying this relapse is as follows : CsA therapy suppresses cytokine production, and the discontinuation of therapy results in a rebound in the level, with a resultant increase in the severity of the glomerular injury[4, 6]. A recent report has shown that the presence of FSGS appears to cause an increase in the risk of secondary CsA resistance, and some of these children manifest a rapid progression to ESRD[6,8]. MMF therapy has been demonstrated to reduce the extent to which proteinuria occurs in FSGS, even when other therapies have failed, or a tapering in the CsA therapy has been planned[11, 21, 30]. Therefore, in our patient, if relapse occurs after the cessation of CsA therapy, MMF initiation should be considered.

Despite persistent proteinuria for 9 years, our patient did not progress to ESRD, and achieved complete remission in response to the second CsA trial. We suggest that, in cases involving steroid-resistant FSGS with no concomitant renal insufficiency, immunosuppressant treatment should be attempted, in order to prevent the progression of primary disease, as well as proteinuria-induced tubulointerstitial damage. Our patient continues to receive oral CsA therapy, and the primary concerns now include CsA-induced nephrotoxicity and relapse after the discontinuation of CsA[6]. Our patient achieved remission, and a second renal biopsy has not yet been done, but should be considered in order to evaluate the severity to which glomerulosclerosis, tubulointerstitial fibrosis and CsA induced nephrotoxicity have occurred if renal function deterioration is manifested[1, 7]. If the patient evidences a relapse after the cessation of CsA, readministration of CsA or MMF initiation should be considered. Furthermore, a long-term follow-up is clearly necessary in this case.

한 글 요 약

국소성 분절성 사구체 경화증은 소아 특발성 신증후군 환아의 약 10%를 차지하는데 초기 스테로이드 치료에 잘 반응하지 않고 만성 신부전으로 진행하는 경우가 많으며 신이식 후의 재발률도 높은 것으로 알려져 있다. 저자들은 생후 26개월에 스테로이드 저항성 국소성 분절성 사구체 경화증으로 진단 받고 9년 동안 경구 스테로이드, cyclophosphamide, methylprednisolone pulse therapy, cyclosporin A, ibuprofen을 포함한 치료를 받았으나 관해가 오지 않고 신기능은 정상으로 유지되던 10세 남아에게 두번째로 cyclosporin A를 저용량의 경구 스테로이드와 병용하여 투여한 결과 완전 관해에 이른 증례를 경험하였기에 문헌 고찰과 함께 보고하는 바이다. 또한 불응성 국소성 분절성 사구체 경화증에서 신기능이 유지된다면 단백뇨를 줄이기 위한 적극적인 치료가 지속적으로 필요할 수 있음을 알리는 바이다.

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