ABSTRACT: Objective: To analyze and assess the treatment approaches for focal segmental glomerulosclerosis (FSGS) in adults.

Methods: We searched seven databases on literatures between 1993 and 2010 related to the therapy and prognosis of focal segmental glomerulosclerosis in adults. The literature research showed that all FSGS therapy aimed to reduce urine protein and protect renal function. According to the literature, FSGS patients usually should receive both immune and non-immune therapy. The immune therapy includes controlling blood pressure, blood fat and weight, while the non-immune therapy includes using hormonotherapy on mild or first-treated patients or taking hormone, immunosuppressant (cyclophosphamide, azathioprine and mycophenolate mofetil), Calcineurin inhibitors (cyclosporine and FK506), Rituximab and plasma exchange for seriously ill patients or patients who experience recurrence or depend on or resist hormone.

Results: As the etiology of FSGS in adults is diverse and complicated, a variety of therapeutic approaches have been developed and tested on small groups of FSGS patients. Each individual treatment has its own advantages and disadvantages. However, the remission rate for neither treatment is satisfactory. A better treatment should be developed and assessed with evidence-based large-scale and multi-center medical trials.

Conclusion: The current therapy approaches for adults FSGS have certain treatment effect. However, more work is required in developing a better new approach.

KEYWORDS: FSGS; treatment scheme; remission rate; prognosis
higher for male than for female [40]. In addition, research over the last two decades found out that the incidence of FSGS varies among different ethnic groups. For white population, the incidence of FSGS increases to 12%-25% from 4%-10% of primary nephritic syndrome in adults, becoming the second pathological type after primary nephritic syndrome in adults. Among black population, the incidence of FSGS accounts for 36%-80% and is the most common pathological type of primary nephritic syndrome especially the collapse type [32-34]. Yellow population has the lowest incidence of FSGS. In China, it is 3.2%-5.8% [35-37] of primary glomerular disease and didn’t change over the last decade. In Korea [38] and Singapore [39], the incidence of FSGS accounts for 4.6%-9.0% of primary glomerular disease.

Presently, it is speculated that podocyte damage is the key link in the occurrence of FSGS. All FSGS patients have urine protein, while 60% of them have nephritic syndrome and 50% of them have hematuria in various degrees. One third of FSGS patients show high blood pressure, insufficient renal function or damaged tubular function.

Prognosis standards include proteinuria quantity, the degree of interstitial fibrosis, the renal level and blood pressure. 80% patients with proteinuria won’t develop to the end-stage renal disease within 10 years. Patients with nephritic syndrome will get ESRD within 6-8 years while patients with proteinuria equaling to or more than 10g/d will get ESRD within 3 years mostly. More than half untreated nephritic syndrome patients would get ESRD within 5-10 years [40]; In 5 years, 52% of treated nephritic syndrome patients without remission will get ESRD, 17% of them get partial remission and 2% of them get complete remission [41]. Whether the proteinuria quantity remits or not is the golden standard used to determine the long-term survival and ESRD rate [42]. Patients with more than 20% interstitial fibrosis usually get unfavorable prognosis and their spontaneous remission rate is less than 6%. However, the treatment effect is closely related to race (the black population gets the lowest remission rate), age, inheritance, hormone doses and course of treatment [43].

Renal Pathology

At early stages, affected part of the capillary wall is cleared away and broken by collagen fibrosis form. Glomerular basement membrane shrinks and glomerular cell misses or is displaced by the foam cell, which shows excessive epithelial cell becoming the main component of cell although their quantity doesn’t increase. FSGS adult patients’ focal and segmental sclerosis always affects vascular pole, although the affected site changes. The early sclerosis may appear in the glomerulus situated in corticomedullary junction not in shallow cortex [3].

Symptom in the mid-late stage: the mesangial matrix increases mainly due to plasma protein deposition and a few mesangial cell proliferations. The affected area presents focal balloon adhesion or forms a dense fibrosclerosis, which refers to occlusion of glomerulus capillary loops and increase of extracellular matrix, including the abandoned capillary loops with glomerulus occlusion, extracellular mesangial matrix multiplication and vitrina formed by proteins exuded from the capillary, etc. In the biopsy tissue, involving glomerulus is visibly hardened partially, while the remaining glomerulus is basically normal, distributed in a focal segment. Diffused glomerulus sclerosis is taken on during this period.

In adult, FSGS process can be accompanied with various degrees of balloon adhesions, foot cell hyperplasia, hypertrophy, vacuolar degeneration, hyalinization, segmental endothelial and mesangial cell proliferation, renal tubular epithelial cell injury, focal tubular atrophy, interstitial fibrosis, and the formation of foam cells and lesion of renal interstitial lymphoid and mononuclear cell infiltrates. The current FSGS diagnosis standard is based on the focal, segmental sclerosis of glomerulus accompanied by capillary foam cell adhesion and aggregation.

Pathological types: according to the recommendation from the FSGS working group of the international Renal Pathology Society in 2003, there are collapse type, tip, cell type, perihilar type and non specific type. Presently, there is no unanimous understanding on those classifications, which may include the same disease at different stages (such as perihilar type and non specific type), or different pathogenesis of different diseases (such as perihilar type and collapse type).

Immunofluorescence: FSGS is not classified in the immune-related disease section, but in focal or segmental sclerosis section (i.e. the lesion part). IgG, IgM, C3, and other immune response products and plasma proteins suffuse and deposit in the focal place of capillary loops or glomerular mesangial region in the form of particles or block mass, which can eventually injure mesangial matrix and mesangial cell when in a serious condition, and a few of which are also negative.

Ultrastructure: electron dense deposits are seen in the hardened parts and manifested as: mesangial matrix increase, capillary collapse, electron-dense deposits, the formation of large number of vacuoles within the cytoplasm of lesion site, disappearing of epithelial cell foot processes fusion, plasma exudation appeared beneath the endothelium, separation phenomenon in foot processes and glomerular basement membrane, as well as diffuse or focal, segmental foot processes degeneration in normal or involved glomerulus[4].

FSGS pathological features in adult patients: glomerulus present focal or segmental sclerosis; immune pathology: IgM

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DOI: 10.5780/jbm2012.13| Page 2
and (or) C3 suffuse and deposit in the focal place of capillary loops (or the hardened site) or glomerular mesangial region in the form of particles or block mass, and can also be negative; electron microscopy: comparatively extensive foot process fusion disappears, electronic dense deposit is seen in hardened parts.

Treatment of adult patients with FSGS

There have been a variety of treatments developed for adult patients with FSGS. All patients with FSGS should be treated with non-immune therapy in conjunction of immunotherapy. The non-immune therapy includes the control of blood pressure, lipids and weight while the immunotherapy includes hormones, hormone plus immunosuppressants (cyclophosphamide, azathioprine and mycophenolate mofetil) or calcineurin inhibitors (cyclosporine and FK506) and rituximab program, as well as plasma exchange for those seriously ill patients.

Non-immune treatment and its Curative effect

Currently there is no randomized controlled trial of non-immune treatment specially designed for FSGS, but it is generally believed that all FSGS patients should take the non-immune treatment, including control of blood pressure, lipids and weight, not matter whether they take the immunotherapy treatment. Praga et al [69] reported in 1995 that for FSGS patients with BMI>, weight loss (> 10% BMI) is also conductive to reduce proteinuria. In 1996 Maschio [70] et al reported for non-nephritic patients with FSGS, it is recommended to use ACEI / ARB agents to reduce proteinuria, delay glomerulosclerosis and control of blood pressure, though no randomized controlled trial had been carried out on this recommendation. In 2005, Deegens [71] et al retrospectively analyzed 104 patients who had been diagnosed with FSGS through renal biopsy. Among the 104 cases, 20 of them met the following conditions: ①, proteinuria> 3.5g / d, ②, proteinuria and hypertension> 1 year, ③, the size of normal kidneys, ④, no basis for kidney disease, ⑤, no family history; Three patients did not receive treatment; 17 patients received ACEI at different treatment time. During the average follow-up period of 9.4 years, 13 patients (65%) sustained remission of proteinuria. For patients with FSGS at nephrotic levels, non-immune therapy should be based on the use of immunotherapy.

Immune therapy options and efficacy

1. Glucocorticoid treatment and its efficacy

Glucocorticoid, the classic drug to treat FSGS, is the top choice, but its usage was subjected to restrictions on the degree of medical science development and the level of human’s awareness of this disease. Short course of Glucocorticoid therapy was applied to treat FSGS in early days but the effect was not satisfactory. In 1988, Meyrier, etc. [5] reported that among the 153 cases of FSGS patients treated with the hormone therapy during the period of 1961-1986, the hormone dose and the course of treatment were inconsistent. 24 patients (15.6%) had the symptom completely relieved, while 31 patients (20.02%) had it partially relieved and 98 patients (64.20%) had no relief at all. Although the response rate was low, it was observed that the prognosis of the fully relieved group was much better than that for the other two groups. As previously reported in 1980, the complete remission rate in FSGS was less than 20%. Because FSGS was considered to be steroid-resistant at the remission stage, there was a misunderstanding among physicians and they were reluctant to use hormone therapy to treat FSGS. In 1987 Pei [44] et al reported, among 55 patients with FSGS, 18 patients were treated with 0.3-2mg / (kg • d) prednisone ± cytotoxic therapy. 24 weeks after the treatment, 7 cases (38.89%) presented complete remission. In the following 5 years, 17 cases (96%) showed complete remission. For those with no response to the treatment, 8 cases (45%) progressed to ESRD. This verified the importance of dose and duration of treatment in FSGS. Because higher hormone dose and extended treatment course were tried to improve efficacy after 1980 (see Table 1), complete remission rate went up to more than 30% as reported in 1988. Based on the retrospective analysis of reports after 1990, under the same or similar hormone dose, the remission rate was 5%-30% when the treatment was less than 8 weeks, with the highest complete remission rate at 13%. If the treatment was extended to 24-54 weeks, the complete remission rate was 30%-47%, with the highest complete remission rate at 71%. This showed that the long course of treatment is more effective than the short course of treatment. In 1995 Korbet [45] analyzed the hormone therapy efficacy of FSGS treatment around 1980 and found out that with less than 8 week treatment, the complete remission rate was less than 20%. When treatment went over 20 weeks, complete remission rate was more than 30%. In the same year, Rydel [46] analyzed retrospectively 81 cases of FSGS (60 patients with nephritic syndrome). Among those 81 cases, 30 (37.04%) received 60mg / d prednisone for 8 week and then the dose was reduced gradually and 50% of the patients responded to the treatment. In the case of the same dosage, hormone response time and non-response time were 10.8 weeks and 6 weeks respectively. In 1993 Glassock [47] proposed a FSGS hormone therapy schedule: in the strengthening phase, 1mg / (kg • d) prednisone (up to 80mg / d) was applied for 8-16 weeks; in the maintenance phase, 0.5mg / (kg • d) prednisone was applied for 6-8 weeks; in the reduction phase, the duration from gradual reduction to discontinuation should be at least 8 weeks. The whole course was 22-32
weeks. In 2000 Burgess [48] observed 17 cases of FSGS patients with nephritic syndrome. Their average age was 35 years old. Those patients had 24h proteinuria (5.3 ± 3.9) g / d and serum creatinine 1.8mg/dl. Among the 11 cases receiving hormone therapy, 3 patients (27.27%) presented complete remission at the average amount of hormone reaching (0.6 ± 0.4) mg / (kg • d), and the remission time was 21.6 ± 13.6 weeks, and 4 patients (36.36%) showed partial remission. The total course of treatment was 33.2 ± 15.6 weeks. 5-year kidney survival rate was 86%. For those six patients who did not receive hormone therapy, 5-year kidney survival rate was only 65%. Burgess believed that it was supposed to extend the strengthening treatment of 1mg / (kg • d) or 60mg / d prednisone for 24 weeks to determine whether it is "hormone resistant".

As more and more treatment cases have been reported, a classic hormone therapeutic approach for FSGS has been proposed as: in the strengthening phases: 1mg / (kg • d) or 40-60mg / d prednisone (up to 80mg / d) was applied for 8-12 weeks; in the maintenance phase: 0.5mg / (kg • d) or 60mg / (kg • d) or 60mg / (kg • d) prednisone was applied for 6-8 weeks; the reduction period should be at least 8 weeks; the whole course was 22-28 weeks. It’s worthy noting that if the intensive treatment period was less than 8 weeks, the complete remission rate would be less than 20%. However, if this intensive treatment period raised to 16-24 week, the complete remission rate would increase to more than 30%. A 25 - 36 week treatment would make all patients relieved.

During the maintenance phase, treatment is focused on reducing recurrence and stopping the progressing into ESRD. In 1994, Nagai et al [16] used 1.0-1.6mg/kg prednisone (maximum 100mg) every other day to treat a group of 60+ year-old FSGS patients with complications during the maintenance period. The cure rate was 44% and there was neither recurrence appearing in the relived cases nor ESRD occurring in the following 148 weeks. For those who did not choose this treatment or for the un-remission patients, the incidence of relapse or progressing into ESRD was 47%. This research showed the good efficacy of this schedule and long-term prognosis. In 2000 Matalon [49] and other reported that using hormone every day or every other day for 24 weeks would led to the similar remission rates, but using hormone every day would significantly reduce side effects. In 2004 Chun [15] pointed out that it was proposed to use every-other-day therapy to treat FSGS patients with complications during the maintenance period [15].

It is proposed to consider "hormone resistance" [13] when it is ineffective to use hormone therapy of 1mg / (kg • d) of prednisone or equivalent doses for 12-16 weeks. However, we should also pay attention to the side effects of long-term use of hormone, which include infections, sodium retention, osteoporosis, cataracts, steroid diabetes, and high blood pressure.

2. Treatment options and efficacy of the immunosuppressant

2.1 Treatment options and efficacy of cyclophosphamide

Cyclophosphamide is immunosuppressive agent, which can quickly convert into the active metabolite phosphoric acid amide nitrogen mustard in human body. The majority of the active metabolites cross-link with DNA, and the rest cross-link with RNA, affecting cell transcription and translation. Cyclophosphamidum can affect both proliferative cells and quiescent cells, reduce the T lymphocyte and B lymphocyte level, and affect both cell-mediated immunity and humoral immunity.

In 1988 Meyrie [5] observed FSGS patients’ response to hormonotherapy, and could prognose the therapeutic effect of hormone plus immunosuppressive agents. Among the cases responding to hormonotherapy of hormones combined immunosuppressive agents, the ratio for complete remission, partial remission and the invalid were 50%, 25% and 25% respectively. For patients with no response to hormone therapy, those ratios were 10%, 10% and 80%

In 1991 Banfi [51] retrospectively analyzed the therapy of low-dose hormone in combination with cyclophosphamide and chlorambucil or azathioprine. In the following 75 ± 51 months, the rates for remission, stable disease and progression to ESRD were 60%, 10% and 30% respectively. In 2004 Martinelli, et al [52] divided 54 relapsing or hormone-resistant FSGS patients into 2 groups. Group A received the therapy of 1-2 mg / (kg • d) prednisone with 2-3 mg / (kg • d) cyclophosphamide or 0.1-0.2 mg / (kg • d) chlorambucil. The dose of prednisone was reduced 4-6 weeks after the treatment. The whole treatment course was 20-24 weeks. Cyclophosphamide or chlorambucil was used for 12 weeks. Group B received prednisone alone (with the same dose as for group A). In the following 86 months, the complete and partial remission rates in group A were 26.7% and 20% respectively, while those rates in group B were 20.4% and 14.8% respectively. Remission rates of repeated relapse and hormone resistance in group A were 70% and 33.3% respectively. Side effects in both groups were mild and similar. In 2001 Passerini [50] used hormone plus cyclophosphamide to treat repeatedly relapsing, hormone dependent or resistant FSGS patients. This new therapy helped reduce proteinuria and protect renal function, but side effects resulted from the long-term usage had also been reported.

Cyclophosphamide has dose-related side effects. Light side effects include mild hair loss, nausea and vomiting, while severe side effects are bone marrow suppression,
hemorrhagic bladder, transitional cell carcinoma and gonadal toxicity. When using Cyclophosphamide, patients need hydration and using mesna. Regular monitoring of blood count, liver function and urine is also required.

2.2 Treatment options and efficacy of azathioprine

Azathioprine is converted to active metabolite 6-mercaptopurine in the cell, interfering purine de novo synthesis combines with DNA and restraining DNA and RNA synthesis. Azathioprine also plays a critical role in reducing the generation of T and B lymphocytes and neutrophil migration, and inhibiting antibody production, NK cell activity, and endothelial cell proliferation. Presently, there is little information concerning azathioprine and its effectiveness in treating FSGS.

In 1986, Cade[62] et al reported that all 5 FSGS patients who resisted to or depended on hormone got remittance after one to three years treatment with 2-2.5mg/(kg.d) azathioprine and there was no recurrence over the next three to fifteen year follow-up visit. In 2006, Goumenos et al [63] made retrospective analysis on 51 cases of primary FSGS patients. Group A (control group) with 26 patients were applied symptomatic treatment. The other 25 patients were divided into B group, C group and D group. Group B (enough sugar cortical hormone group) were treated for 64 weeks with 1 mg/(kg.d) prednison. Group C (azathioprine combined hormone group) were treated for 72 weeks with 0.5 mg/(kg.d) prednison and 2mg/(kg.d) azathioprine. Group D (Cyclosporine combined hormone group) were treated for 100 weeks with 0.5 mg/(kg.d) prednison and 3mg/(kg.d) cyclosporine; During the therapy session, the amount of hormone used were lowered gradually and the follow-up visit lasted 5 years. After one year, the remission rates for group B,C,D were 62.5%, 80% and 85.7% respectively. After five years, the serum creatinine multiplication of group B, C and D decreased significantly compared with group A. Therefore, azathioprine combined with sugar cortical hormone can lower the amount of hormone needed during the treatment and could be used during the maintenance phase of the treatment. The side effects of azathioprine include gastrointestinal tract, bone marrow transplantation and infection. Therefore, it is necessary to monitor blood and liver function regularly during the treatment.

2.3 Treatment options and efficacy of Mycophenolate mofetil

Mycophenolate mofetil is the inhibitor of inositol monophosphate dehydrogenase (IMPDH) and the key enzyme for guanine nucleotide de novo synthesis. Lymphocyte proliferation depends on de novo synthesis and IMPDH inhibition can lead to depletion of intracellular guanine. Therefore, MMF can be used to selectively inhibit the multiplication of T lymphocytes and B lymphocytes, not other types cell proliferation. Clinical trials have shown that MMF was reflected in the effectiveness of hormone and cyclophosphamide(or cyclosporine) during maintenance phase treatment[59].

In 2004, Cattran[60] et al observed 18 FSGS patients with hormone resistance. 14 of them (75% of the total) resisted to cyclophosphamide or cyclosporine; After 24 weeks prednisone and mycophenolate mofetil treatment, 8 patients (44.44% of the total) got complete remission and 4 of them (22.22% of the total) got continued easing after stopping taking medicine for one year, 10 of them (55.55% of the total) had not eased. During the treatment, all patients’ renal function was stable and 3 patients (16.67%) progressed into ESRD during the follow-up period. During the whole treatment cycle, no patient had showed serious side effects. However, the recurrence was common.

In 2007, Segarra[61]et al observed 22 FSGS patients with 15 male and 7 female the average age at 39, and the average serum creatinine is 1.6mg/dl. The initial treatment for those 22 patients included 24 weeks combined cyclophosphamide (5 patients), tacrolimus (4 patients) and cyclosporine (13 patients) respectively, after washout period, patients with glomerular filtration rate (GFR) greater than 60ml/min choose 2g/d Mycophenolate Mofetil (MMF) and with GFR less than 60ml/min choose 1.5g/d, after 48 weeks treatment and taking twice a day, 2 patients accounting for 9.09% got complete remission and 10 patients accounting for 45% got partial remission during 21 weeks. During the whole treatment cycle, the down slope of GFR and Scr had not changed. The adverse reactions were mild, occurring in digestive system and blood system. Those side effects would gradually ease after the dosage was lowered and the medication was stopped. After the treatment, the blood should be monitored weekly.

3.Treatment options and efficacy of immunophillin modulator

Immunophillin is a group of protein that can combine series immunosuppressive agents including P cyclosporine, tacrolimus (calcineurin inhibitors) and sirolimus (rapamycin).

3.1 Treatment options and efficacy of Cyclosporine

By inhibiting calcineurin (Cn), cyclosporine plays an important role on immunosuppression. Cn is the key molecule for T lymphocyte activation and signal channel. By suppressing calcineurin activation, cyclosporine lowers IL-2 and r-interferon secreted by T lymphocyte, IL-1 secreted by
monocytes, macrophages, other Pro-inflammatory cytokine gene expression and Ca2+-dependent T cell activation.

Under the treatment of hormone or hormone combined cyclophosphamide, FSGS remission rate remains below 50%. This therapeutic approach is effective on patients with repeated recurrence or hormone dependence. It improves the remission rate, decreases urine protein and protects renal function [53-55]. However, after the dosage was reduced or the medication was stopped, high recurrence rate was observed. In addition, possible side effects, such as kidney toxicity and neurotoxicity were brought with long-term usage.

In 1986, a case of cyclosporine treating nephrotic syndrome was reported for the first time. Hormone combined cyclosporine is effective on recurrence patients who were sensitive to hormone. The symptom for most patients eased during the first a few months of treatment. 75% of patients had recurrence 8 weeks after the medication was stopped [5].

In 1993, Ponticelli et al [9] reported 14 FSGS patients who were treated with 5mg/ (kg*d) cyclosporine for 24 weeks, twice a day. 8 of them (57.14%) got complete or partial remission in the first 4 weeks and 6 of them (42.86%) failed to respond. After 48 week therapy, 5 of them (36%) got complete and partial remission and 9 of them (64.29%) got kidney damage. In conclusion, longer treatment course does help improve the remission rate but also increases the risk of kidney damage and neurotoxicity.

In 1994, Auriche et al reported 14 FSGS patients who were treated with 5.54 ± 0.81mg/ (kg*d) cyclosporine. Renal biopsy was done at 19.6-15.2 months. 9 patients(64%) developed ESRD and the treatment was stopped [20]. In 1995, French kidney disease consortium reported 46 FSGS patients treated with hormone combined cyclosporine. 11 of them (23.91%) had the symptom eased and 35 (76.1%) didn't show any response. Patients who resisted to hormone and cyclosporine showed weak response.

In 1999, Catrân et al [54] divided 49 hormone resistant FSGS patients into two groups randomly. Group A included 26 patients treated with 0.15mg/ (kg*d) prednisone combined 3.5mg/ (kg*d) cyclosporine and group B included 23 patients treated with 0.15mg/ (kg*d) prednisone combined placebo. All patients took prednisone once a day and had treatment stopped after 8 weeks. Then, they took cyclosporine twice a day and had the treatment stopped after 4 weeks. They took 26 weeks treatment in average 200 weeks follow-up visit. In the 26th week, the remission rate of group A was 70% and that for group B was 4%. In group A, 40% patients relapsed in the 40 weeks, 20% patients relapsed in the 40 weeks and the rest had no recurrence. The doubling of serum creatinine in group A is 25% and 50% in group B. Although it exists high recurrence rate after stopping cyclosporine, during the long-time follow-up visit, adopting cyclosporine can protect renal function better than placebo, which is meaningful to patients who may develop into ESRD.

The reports varied in the dosage and the frequency for FSGS patients to be treated with cyclosporine. Catrân et al [54] reported 3.5mg/ (kg*d) cyclosporine, Ponticelli [9] et al reported 5mg/ (kg*d) cyclosporine and Cochrance used 3.5-5 mg/ (kg*d) cyclosporine. However, Collaborative study group of Sandimmun in Nephrotic Syndrome identified that average 4.8mg/ (kg*d) cyclosporine led to remission or ineffectiveness while less than 2.5mg/ (kg*d) cyclosporine could maintain remission. Most patients need at least 24 weeks treatment with cyclosporine. Therefore, the follow-up period for the effect of cyclosporine should be at least 6 months [56].

Except kidney toxicity and neurotoxicity, the side effects caused by cyclosporine also include hypertension, gingival hyperplasia and acne.

3.2 Treatment options and efficacy of Tacrolimus

The mechanism and common side effects are the same to cyclosporine.

When patients present hormone resistance or dependence, instead of cyclosporine, FK506 combined with hormone treats FSGS patients who shows intractable nephrotic syndrome. In 2002, Segarra et al [58] chose 25 FSGS patients who resist to hormone and cyclosporine and treated these patients with 24 weeks hormone combined with FK506. 17 cases (68%) showed proteinuria deduction, 10 cases (40%) got complete remission, 2 cases (8%) got partial remission, 5 cases (20%) showed significant proteinuria reduction and 8 cases (32%) showed no response. All of them got remission within 112±24 days and 10 cases (40%) had irreversible renal damage due to tacrolimus dependence. In 2009, Li et al [57] treated 17 patients with nephritic syndrome who resist to hormone and cyclosporine, including 5 MCD, 7 FSGS and 5 MsPGN patients. After treated with tacrolimus for 24 weeks, 11 patients (64.70%) got complete remission, 3 patients (17.65%) got partial remission, 3 patients (17.65%) were ineffective and 9 FSGS patients got remission (57.14%).

Besides kidney toxicity and neurotoxicity, the adverse reaction of FK506 also includes increasing blood sugar. So far, a few clinical experiments showed that kidney toxicity led by FK506 was less than by cyclosporine.

4. Rituximab treatment options and efficacy

In 2008, Ahmed et al [64] reported that FSGS patients treated with rituximab showed few serious side effects. In the
same year, Guigonis et al. [65] reported the only III clinical trial in which patients were treated with rituximab. 22 FSGS patients with hormone-resistance or cyclosporine-sensitive were enrolled with ages between 6.3-22 years. After second to fourth treatments, three nephrotic syndrome patients (13.64%) out of 7 (31.82%) had the symptom eased. During the treatment, 19 cases (86.36%) can reduce one or more immunosuppressant without recurrence of proteinuria and 10 cases (45%) showed a mild transient side effect.

5. Plasma exchange treatment options and efficacy

Therapeutic plasma exchange (TPE) is an effective blood purification technology which can clear macromolecules in plasma. TPE includes both centrifugal and membrane plasma exchange.

In 1998, Mitwalli et al. [66] reported 11 FSGS patients who failed to respond to hormone or hormone combined cyclosporine. Among them, 5 were male and 6 were female with verage age at 32.10±6.60 years. After treated with prednisone combined with cyclosporine, 17 plasmapheresis during 15-25 weeks and 4 weeks after last replacement, 8 patients (72.7%) showed reduced proteinuria and stable renal function, 3 patients (27.3%) failed to respond and their renal function gradually deteriorated.

During the 27.45±6.31 month follow-up visit, symptom for six patients eased continuously and the renal function was stabilized. Plasma exchange presented no serious side effect and was well tolerated. Results: after therapeutic plasma exchange, 50% of the patients who failed to respond to hormone and hormone combined cyclosporine had their symptom eased and maintained stable renal function. In the same year, Feld et al. [67] reported 8 patients treated with 40mg/d prednisone for 8 weeks. 3 patients who failed to respond to 40mg/d prednisone combined 1g/d methylprednisolone pulse therapy took plasma exchange six times every two weeks. In 24 month follow-up visit, two of them had symptom eased and renal function recovered. In 2001, Passerini et al. [68] observed that for nephrotic syndrome, therapeutic plasma exchange can effectively reduce proteinuria and protect renal function.

Conclusion

Due to complex causes of disease and pathogenesis, various clinical symptoms and pathological types, a few treatments for FSGS have been developed. All FSGS patients should accept both non-immune therapy and immunotherapy treatments. The non-immune treatment includes controlling blood pressure, lipids and weight while the immunotherapy treatment includes hormone to treat patients with mild symptom. For patients who relapse repeatedly, resist to or depend on hormone, it is effective to use hormone combined with alkylating agent, Immunosuppressive agents (azathioprine and mycophenolate mofetil), calcineurin inhibitors (cyclosporine and FK506) or rituximab. Critically ill patients should further be treated with plasma exchange. Each treatment has its own advantages, disadvantages and focus. However, the remission rate is not satisfactory for neither of them. Physicians should analyze comprehensively and develop individualized treatment plan according to patients’ basic state, illness stage, hormone sensitive and complication to achieve ideal treatment. Currently, adult FSGS therapeutic approaches get certain effectiveness, but it’s necessary to do further research, optimizing and innovation. Our primary task is to combine multi-target treatments in the early period.

Acknowledgments

Foundation item: “Technological Border Support” program of MOST (Contract No. 200840102-38) and scientific and technological issues of Xinjiang Uygur autonomous region (Contract No. 200910015).

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Lu Chen et al. Therapy and prognosis of adult Focal Segmental Glomerulosclerosis


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