Steroid Resistant Nephrotic Syndrome

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INTRODUCTION

Minimal Change disease (MCD) is the most common cause of Nephrotic Syndrome (NS) in children accounting for 70 to 90% of cases under the age of 10 years and 50% in older children. In adults MCD is found in 10 to 15% of cases with primary nephrotic syndrome. Most patients with MCD remit with steroids. Remission is defined as absence of proteinuria (urine albumin nil or trace on 3 conservative days by dipstick). In children with steroid sensitive nephrotic syndrome, treatment with daily prednisolone results in remission by first 4 weeks in 95% of cases. Additional 3% of children may remit after another 4 weeks of therapy. Approximately 10-20% of children suffer from steroid resistant nephrotic syndrome. (SRNS)

Some authors define SRNS in adults as absence of proteinuria after 6 months of therapy. In a number of case series, roughly 20 to 25% of cases of MCD will manifest with steroid resistance. SRNS is quite often due to focal segmental glomerulosclerosis (FSGS) in adults, varying from 8 to 28%. It may be also due to membranous glomerulonephritis (MN-40%) or membranoproliferative glomerulonephritis (MPGN-7%). We will deal mainly with MCD(20%) and FSGS(15%) as it is a common cause of SRNS. FSGS is a heterogenous disorder and the most severe frequent form of all types of Glomerulopathy in children leading to End Stage Renal Disease (ESRD). The rate of complete remission of SRNS after induction therapy using different immunosuppressive agents ranges between 30 to 84% depending on the treatment schedule and underlying types of FSGS. Children or adults with genetic type of FSGS (podocin or nephrin mutation) barely respond to immunosuppressive therapy. An overtreatment leads to iatrogenic complications in these patients.

Management of SRNS

Role of renal biopsy:
Renal histology in SRNS helps in predicting response to steroid therapy. In children with SRNS 30-40% of patients have MCD and FSGS. A smaller group has mesangiproliferative GN. Presence of FSGS or chronic tubulointerstitial changes is associated with unsatisfactory outcome in children.

MINIMAL CHANGE DISEASE- SRNS

Cyclophosphomide given in the dose of 2mg/kg/body weight for 12 weeks only with prednisolone 1.5 mg /kg/ bodywt either daily or alternate days gives remission in only 25% of cases. If cyclophosphomide is given as a pulse dose 500 to750mg once every month for 6 months along with prednisolone in the dosage mentioned earlier s remission is observed 40 to 60% of cases in children.

Cyclophosphomide has been reputed to induce and maintain remission in 25 to 60% of patients for up to 5 years in adults with steroid dependent and relapsing MCD. But the drug seems to be less beneficial in SRNS. Cyclophosphomide combined with prednisolone has been reported to induce remission in 60% of patients but lower percentage is also
Cyclosporine (CsA) is observed to achieve a more rapid remission than cyclophosphamide. However, a large percentage of patients relapse after discontinuation of medications, making CsA dependency a major problem. Probably CsA given as mentioned under treatment for FSGS, for a prolonged period, may give better results in SRNS with MCD since there are not many controlled trials in MCD with SRNS in adults. We should probably follow the same treatment as outlined for FSGS to get better results.

Steroid response depends upon whether it is MCD or mesangiproliferative type of GN (MSGN). In one series there was complete remission in 46% of the cases. However, relapse was reported in 1/3rd of the children after achieving remission by the end of 12 months of treatment.

SRNS due to FSGS

FSGS is a heterogenous disorder and the most severe and frequent type of all GN in children leading to ESRD in 50% of the children requiring renal replacement therapy. The podocyte is at the centre of development of FSGS and plays a major role in integrity of glomerular structure and permeability and development and progress of FSGS. The rate of complete remission of SRNS after induction therapy and different immunosuppressive agents was reported to range between 30 to 84% depending upon the treatment schedule and underlying defects of FSGS in children. Corticosteroids - prednisone or methylprednisolone (MP) used for at least 3 months before tapering become the mainstay of treatment of FSGS in adults. In the recent review steroid treatment with complete remission in 30 to 40% of patients, the most obvious difference causing diverged response was duration of therapy. Poor response was in those treated for less than 2 months and better remission response was in those treated for 5 to 9 months.

The discussion is mainly decided to primary FSGS. Secondary FSGS may be due to Hypertension, DM, HIV, parvo virus, morbid obesity, sickle cell disease, reflux nephropathy, IgA nephropathy, Henoch schonlein syndrome or due to drugs-pamidronate.

Idiopathic FSGS is not a disease but lesion with no definite prognostic value. A recent working group has classified FSGS into 5 variants - classic Perihilar variant, cellular variant, tip variant and collapsing variant FSGS. It is not very easy to achieve this classification because the disease is focal or zonal. The number of available glomeruli is too small for classifying the glomerulopathy with certainty. Tubulo interstitial lesions are more indicative of impending threat to renal function than the glomerular appearance. Classifying the lesions of lupus nephritis has been extremely rewarding. This is not the case in nephrotic FSGS - a condition in which the only predictive element of progress is the response of proteinuria to treatment irrespective of histology.

The common denominator of all FSGS variants is a podocyte disease. The most interesting breakthrough was bought by the identification of nephrin, podocin, CD2AP and alpha actinin4. - to site few molecules whose mutations are responsible for FSGS amongst the array of those that have been identified in the podocyte cell body and foot processes. The mean age at presentation in multigeneration forms was 32.5 +/- 4.6 years and in single generation forms 20.1 +/- 12.1 years. This indicates that FSGS due to germ like mutations may become apparent late in life. This sheds a new and somewhat ironic light on new treatment strategies based on ‘Shelhoub’s hypothesis’ Raf et al presented data on 29 steroid resistant patients with podocin mutation. None responded satisfactorily to Cyclophosphamide or CsA. It is now various mutations of podocins eg; NFNPHS2 mutation 229q heterogenous variant, ACTN4 encoding alphaactin4 are all shown to be causes of familial FSGS. The implication of this disclosure led to some pediatric units systematically seeking podocin mutations in children with idiopathic NS in order to avoid useless course of steroids and other immunosuppressive drugs. A test is available in the US to predict steroid resistance. (Athena Diagnostics Worcester MA) It is clear that in near future molecular genetic profiling will more precisely define the incidence of podocyte mutation in larger series of patients with FSGS.

Table I. Aims of treatment for SRNS and FSGS

<table>
<thead>
<tr>
<th>Aims of treatment for SRNS and FSGS</th>
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<tbody>
<tr>
<td>Normalisation of proteinuria</td>
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<tr>
<td>Reduction of fluid overload</td>
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<tr>
<td>Normalisation of arterial hypertension with ACEI, ARB or both as primary antihypertensives</td>
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<tr>
<td>Prevention of complications of nephrotic syndrome</td>
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<td>Restoration of normal glomerular filtration rate or prevention of progression of chronic kidney disease</td>
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<tr>
<td>Prevention of side effects of therapy</td>
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<td>Prevention of relapse of Nephrotic syndrome or proteinuria</td>
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Aim of treatment: (Table I)

**Corticosteroids in FSGS**

**Prevention:**
Though the definition of steroid resistance is absence of remission after 4 weeks of prednisone and a last attempt using 3 pulses of MP, it has been repeatedly shown that adults need a dose of prednisolone ranging from 0.5 mg to 2 mg/kgwt/day. The highest complete remission rates of > 30% were observed in cases treated for > 5 months. A lower remission of < 20% was observed in patients treated for < 2 months. It is now established that corticosteroids must be sufficiently given for longer duration - full dose of 1 mg/kgwt/day prednisolone for 8 to 12 weeks followed, even in partial remission cases, by a slow tapering dose over 6 months to avoid rebound effect. Some adult nephrologists label SRNS only after giving full dose of steroids for 6 months 1mg/kgwt/day of prednisolone daily or alternate days and tapering the dose for another 4 months. It is a fact that reducing proteinuria excretion at least partially is the only means of slowing or arresting the progress to CKD and there no doubt that prolonged treatment improves the prognosis of FSGS.11

Mendoza and Tune have a protocol for FSGS using pulse dose of MP. Vide - Table II. Remission in 66% and partial remission in 9% was achieved.

**Table II. Treatment Protocol for SRNS FSGS**

<table>
<thead>
<tr>
<th>Weeks 1-2</th>
<th>MP</th>
<th>30 mg/kg once daily</th>
<th>Prednisolone: none</th>
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</thead>
<tbody>
<tr>
<td>Weeks 3-10</td>
<td>MP:</td>
<td>30 mg/kg weekly</td>
<td>Prednisolone: 2 mg/kg once daily</td>
</tr>
<tr>
<td>Weeks 11-18</td>
<td>MP:</td>
<td>30 mg/kg once a week</td>
<td>Prednisolone: +/- taper</td>
</tr>
<tr>
<td>Weeks 19-52</td>
<td>MP:</td>
<td>30 mg/kg monthly</td>
<td>Prednisolone: slow taper</td>
</tr>
<tr>
<td>Weeks 53-78</td>
<td>MP:</td>
<td>30 mg/kg monthly</td>
<td>Prednisolone: slow taper</td>
</tr>
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**Alkylating Agents:**
The rationale of treating FSGS with cytotoxic drugs is based on the postulate that the proteinuria is due to immunological background - ie- secretion of lymphokine by a clone of T-lymphocytes. These drugs target cells of immune response including those that have nothing to do with the disease. Cyclophosphamide or chlorambucil have been used since 1950’s in the treatment of nephrotic FSGS. It has been established in children that 12 week course is more effective than a shorter course. It is common practice to add a maintenance dose of steroids in the hope of increasing efficiency. In steroid resistant cases, alkylating agents are a failure in 69% of the cases. Therefore alkylating agents do not benefit SRNS FSGS as emphasized by a control study from International study of Kidney diseases (ISKD).12

**Immunophilin Modulators**

**Cyclosporine A (CsA):**
CsA is now considered as one of the most useful agents in treatment of idiopathic NS including FSGS. The rationale for trying the molecule is based on the hope that it might inhibit the production of the cytokine responsible as it does for IL2 and gamma interferon. It is clear that complete remission obtained within weeks in MCD is keeping with the therapy. CsA in steroid resistant cases produces complete remission, partial remission and failure in 29%, 22% and 49% respectively, whereas in steroid responsive cases the percentage is 73%, 07% and 22% respectively. In the pediatric group, combination of CsA and steroids has induced additional remission in a significant subset of patients. Steroids enhance the efficacy of CsA and CsA has the major advantage of being a steroid sparing agent. However it has been found by Frische et al, Ponticelli et al and by Catran et al that longterm CsA treatment improved renal function in SRNS-FSGS. The finding reflects its capacity, having a favourable effect on the tubules reducing proteinuria more than reflecting an improvement of the glomerular lesions of FSGS. The better bioavailability of Neoral leads to recommending a dosage distinctly lower than 5mg/kg. Serum cholesterol levels should be taken into consideration for the dosage of CsA. Hypercholesterolemic nephrotic SRNS-FSGS may require higher dose of CsA. CsA dependency was observed from the very first trials of treatment. However the notion of CsA dependency was partly reconsidered when they analysed the prolonged treatment with CsA for 1 to 5 years. These patients had undergone repeat renal biopsy. None of them showed evidence of CsA toxicity. 20% of these cases tapered CsA slowly after 1 year and these patients remained in remission in extremely low doses - < 3mg/kg/day and in one case 1 mg/kg/day. The longest follow up was for 12 years. The trough levels should be maintained between 80 to 120 ng/ml.

There are good reasons to believe that besides its immunological action, CsA interferes with glomerular permeability to albumin, It increases charge selectivity in MCD and pore selectivity in Idiopathic GN.13 CsA interfered with glomerular permeability to albumin independently from
a mere hemodynamic effect of glomerular vasoconstriction. Cattran et al showed that long term CsA treatment improved renal function in FSGS.\textsuperscript{14}

**FK506 (Tacrolimus):**
Trials of treatment of FSGS with tacrolimus are anecdotal. However Segarra et al found combined therapy of tacrolimus and steroids in SRFSGS, when CsA had not obtained remission had better results if given for more than 6 months.\textsuperscript{15} Time to remission was long (112 +/-25 days). Reversible nephrotoxicity was observed to be 60%. Majority of them was found to be tacrolimus dependent. Loeffler et al used tacrolimus (0.1mg/kg/day) and follow up period ranged from 0.5 to 18 months. Complete remission was 18% and partial remission was 13%. Despite side effects, tacrolimus is effective, well tolerated medication for treatment of SRNS. The trough level should be kept at 5-8 ng/ml.

**Mycofenolate Mofetil (MMF):**
Due to its successful performance as an immunosuppressive in transplant, MMF has been tried in SRNS. Uncontrolled trials have demonstrated remission in some cases and reduction of proteinuria in others. However more data from controlled studies are required to consider it as an alternative therapy in SRNS. The fact that it does not prevent recurrence of the original disease (FSGS) in the transplant kidney does not support MMF.

**Rituximab- A New therapeutic Hope? \textsuperscript{16}**
Rituximab (RIT) is a chimeric monoclonal antibody that acts by inhibiting CD\textsubscript{20} mediated B cell proliferation and differentiation. The CD20 antigen is a membranous protein found on B cells as well as on malignant cells as in non-Hodgkins’s lymphoma (NHL). It was first introduced in late 1990 for the treatment of B cell NHL. Since then it has been used over half a million patients with hematological malignancies as first line and maintenance treatment. Review of literature shows 13 case reports, 4 case series and one prospective study. RIT was used in various GN including idiopathic MN, MCD and FSGS.

In SRMCD, there are 4 case reports wherein RIT was given 375mg/M\textsuperscript{2} at weekly intervals for 2 weeks. One large series by Annet Bruckfeld et al (report of 9 cases) have used 375/m\textsuperscript{2} at weekly intervals for 4 weeks. The degree of \(\beta\) cell depletion was assessed. Whenever the CD\textsuperscript{19} lymphocytes were detectable at 1% or above either 500mg or 1000mg IV was used at weekly intervals for 2 doses. Complete remission was maintained in follow up upto 18 months, in different case reports. RIT probably acts by inhibiting \(\beta\) cells that have regulating function over T cells as MCD is related to T cell immunity. Thus the increased production of IL\textsubscript{13} and elevated expression of IL\textsubscript{13} was blocked. It is also believed that there is evidence of \(\beta\) cell activation in Idiopathic MN.

**RIT in FSGS:**
RIT can be used in the same dosage as described in MCD in SRNS. There are several reports of RIT usage in pediatric group. Usually after 2 infusions of RIT, there is complete remission. In some cases relapses have occurred after 40 days. This is also successfully treated by one or 2 additional infusions. Interestingly RIT is the valuable drug of choice in FSGS, which recurs after kidney transplant in 20 to 30% of cases. Homer et al believe RIT should be given early in FSGS post transplant. This is because there are 2 case reports of post transplant NS with FSGS with the onset of diffuse large \(\beta\) cell lymphoma and Ebstein-Barr virus driven diffuse large cell lymphoma. The proteinuria disappeared immediately after disappearance of \(\beta\) cell suggesting an important role of \(\beta\) cells in the pathogenesis of NS-FSGS. No serious adverse effects have been observed till present. However prospective randomized controlled trials and long term follow up are required before recommending RIT in SRNS due to FSGS.

**Non specific therapy for SRNS**
This includes
- control of blood pressure should be with ACEI and ARB which reduce proteinuria besides reducing BP. They are also anti-inflammatory, anticytokine and play a pivotal role in preventing progression of the renal disease
- Reduction of fluid intake according to urine output
- Optimum protein Intake - 1 to 2 gm /kg.wt; higher in children or according to GFR
- Correction of dyslipidemia- with statins and fenofibrate Statins are pleotropic and have additional benefits with their anti- inflammatory, anticytokine, antiproliferative and antiplatelet adhesive effects. The PPARgamma agonist effect of fenofibrate assists vasodilatation and reduction of hyperinsulinemia
- SRNS is associated with increased RAAS activity and aldosterone antagonists- aldactone or eplerenone are useful adjuncts to reduce proteinuria, cell apoptosis tubulointerstitial fibrosis and glomerulosclerosis.

**CONCLUSION**
Corticosteroids combined with CsA remain the main stay of
therapy for SRNS. Alkylating agents have limited indications and disappointing success rates. Tacrolimus with steroids seem to remit patients who had not responded to CsA. MMF might be of value but large scale studies are lacking. A spectacular advance has been made by identifying cases due to genetic defect. In the next few years, research in identifying the elusive substance(s) that induce podocyte foot process flattening, proteinuria and podocyte cell cycle dysregulation will without doubt revolutionise the treatment approach to FSGS.

REFERENCES