

Steroid Resistant Nephrotic Syndrome: Recent Developments

Nephrotic syndrome, characterized by altered permselectivity of the glomerular filter, is a common chronic renal disorder in children. Most patients with nephrotic syndrome show minimal change disease (MCD) on renal histology; the remaining is contributed by focal segmental glomerulosclerosis (FSGS), mesangioproliferative (MesPGN) and membranoproliferative glomerulonephritis (MPGN). While most respond to corticosteroid therapy with remission of proteinuria (steroid sensitive), approximately 20% patients are steroid resistant (SRNS)(1). The frequency of histological types and pattern of steroid response is relatively uniform across the world, though an increase in the incidence of FSGS(2) and SRNS(3) has been reported recently.

Pathogenesis

The precise pathogenesis of MCD is unclear, but there is sufficient evidence of dysregulation involving cell mediated immunity (4). The tendency of nephrotic syndrome to relapse after viral infections, therapeutic response to steroids and cyclosporine (CsA), and occurrence of remissions following measles support this view. Knowledge on functional divisions of cell mediated immunity has been applied to understand the pathogenesis. Broadly, antigen presentation to T lymphocytes results in a polarized immune response, which is type 1 [dominated by γ -interferon, interleukin (IL) 2] or type 2 (IL4,

IL10, IL13). The association of nephrotic syndrome with atopy, increased plasma levels of IgE, and upregulated gene expression for type 2 cytokines in peripheral blood and renal tissue suggest type 2 cytokine bias(4,5). The response to treatment with prednisolone and levamisole, which augment type 1 and downregulate type 2 cytokines also support this hypothesis(6).

Although nephrotic range proteinuria has traditionally been considered a consequence of an aberration of the glomerular basement membrane, there is increasing evidence of a primary defect in the visceral epithelial cell (podocyte)(1). Viruses like HIV, parvovirus B19 and simian SV40 are known to directly injure podocytes(7). Mutations in genes encoding key podocytes proteins (nephrin, podocin, CD2 activated protein, α -actinin) have been identified in children with familial and sporadic SRNS(8). It is proposed that structurally defective podocytes or deficient basement membrane protein/s lack permselectivity, resulting in proteinuria. Such patients do not respond to steroid treatment (initial resistance) and show progressive renal failure(9).

A hypothesis unifying immune abnormalities, increased glomerular permeability and podocyte defects is yet to be proposed. The speculation that podocyte proteins might be potential targets for cytokines or permeability factors is attractive, but not confirmed.

Therapy

The treatment of SRNS is challenging. On one hand, patients are at risk for complications of unremitting nephrotic syndrome and progressive renal disease, and on the other

show side effects of treatment with steroids and immunosuppressive drugs(10). Issues in long-term management include prevention and treatment of infections, anasarca, hypovolemia, thrombosis, hypertension, hyperlipidemia, growth retardation and bone disease(1). The aim of therapy is induction of remission, while avoiding medication related toxicity. The number of medications that have been used is ample testimony to the lack of satisfactory treatment for these patients.

Tune and Mendoza first showed satisfactory results following treatment with pulse intravenous (IV) methylprednisolone, given in a tapering schedule over 30 months, combined with oral alkylating agents (cyclophosphamide or chlorambucil for 12 weeks) and alternate day steroids(11). In view of steroid toxicity and need for multiple admissions, others have used shorter protocols with benefit ranging between 10-70%(1, 12). Substitution of methylprednisolone by, the less costly, dexamethasone showed similar effectiveness(13).

Review of uncontrolled studies show a limited role for oral cyclophosphamide and prednisolone in inducing remission in patients with SRNS(1). In a randomized trial, remission rates were similar (25%) in the steroid-only versus steroid plus oral cyclophosphamide group(14). Pulse IV cyclophosphamide given once monthly is also effective, though remission rates vary from 25-60%(1,15,16). A recent randomized trial compared treatment with IV dexamethasone and oral cyclophosphamide, versus IV cyclophosphamide and oral prednisolone in patients with SRNS. Both regimes showed similar rates of remission (47.8 versus 53.8%) and comparable frequency of infections at 12 months(17). Repeated courses of pulse corticosteroids or cyclophosphamide are associated with multiple complications

including serious infections, dyselectrolytemia, decreased bone density, induction of diabetes mellitus and gonadal dysfunction, and poor statural growth, besides the cost and inconvenience of hospitalization.

Benefits following treatment with CsA are better defined. Randomized controlled trials, in patients with SRNS, show remission of proteinuria in 45-60% patients with MCD compared to 30-45% with FSGS(1,18,19). The response rates to CsA alone are 30%, but increase to 40-50% when co-administered with steroids(19). Side effects of treatment include hypertrichosis (50%), gum hyperplasia (40%), hypertension and chronic nephrotoxicity (30%)(1). The risk of CsA nephrotoxicity is higher in subjects who continue to show nephrotic range proteinuria despite therapy, and with prolonged use beyond 24-36 months(20).

Patients who respond to CsA might relapse on its discontinuation. Reintroduction of treatment might be necessary, and an occasional patient may show late CsA resistance. Another approach involves replacement of CsA with mycophenolate mofetil (MMF), a selective inhibitor of de novo purine synthesis(10, 21). MMF has been used in patients with SRNS(10,22) with variable results; its advantage lies in a better side effect profile compared to prednisolone and CsA. Other modes of recent treatment include intensive plasmapheresis and immunoadsorption, and administration of vincristine, tacrolimus and mizoribine(1).

This issue of the Journal features three articles on the profile and management of SRNS. Gulati, *et al.*(23) review the outcome of 136 consecutive subjects with SRNS followed for over 12 years; the commonest renal histology was FSGS (59%). Following different treatment protocols, most patients

with MCD were in remission, but the majority of FSGS and MesPGN showed persistent proteinuria. The authors emphasize the importance of renal histology in prognosticating long-term outcome in these subjects. While they dismiss the relative importance of initial versus late steroid resistance on outcome, it is important to note that 54% of their patients with MCD had initial resistance compared to 72% others. A better long-term outcome in patients with late resistance and normal renal histology has been reported previously by the same(15) and other workers(1,16).

Nammalwar, *et al.* report results of a prospective protocol, comprising IV pulse methylprednisolone, IV cyclophosphamide and oral prednisolone in patients with SRNS (MCD, MesPGN and FSGS in one-third each)(24). Angiotensin converting enzyme inhibitors (ACEI) were not used during the first year of therapy; neither were other medications (including CsA) in those resistant to this protocol. On follow up at 3 yr, remission was seen in 82% patients with MCD, 67% with MesPGN and 17% with FSGS. These findings reemphasize the utility of kidney biopsies in SRNS, for assessing prognosis. While the outcome in patients with MCD following 12 months' therapy is exciting, there are some concerns. Of 42 patients enrolled, effectiveness of treatment was calculated after excluding 16 subjects from the analysis either because they did not complete the first yr of therapy (n = 8), died (n = 3) or were lost to follow up (n = 5). A drop out rate of 31% (excluding deaths) is high for a prospective study, despite the authors' belief that lack of follow up probably indicates satisfactory outcome! An increased risk of infections is also of concern and reflects the intensity of treatment.

There is strong evidence based data on the

efficacy of ACEI in subjects with SRNS. Reviews from multiple studies in children show that their administration results in reduction of proteinuria by 40-50%, without significant adverse effects(1,19). Despite the benefits of the protocol proposed above(24), it is recommended that all patients with SRNS receive an ACEI, the dose of which may be modified depending on severity of proteinuria.

The third study(25) pertains to the efficacy of CsA monotherapy in inducing remission in 41 patients with steroid dependent (n = 30) and SRNS (n = 11). CsA was initially given at a dose of 6-7 mg/kg per day, and adjusted to maintain trough levels between 100-200 ng/mL. In consonance with published experience, the authors show a favorable response in 86% subjects with steroid dependent and 42% with SRNS. An important observation was the high risk of CsA dependence in children with onset of disease below 18 months' of age. Patients who did not respond to CsA were at risk for infections and chronic renal failure. An interesting finding was a high degree of steroid responsiveness in MPGN, with 70% subjects showing steroid dependence. Most patients did well following treatment with CsA. Since both these observations are at significant variance from established literature(26), they require confirmation before recommending the use of CsA in children with MPGN.

Conclusions

Although specific mutations in genes encoding key podocyte proteins are identified in a subgroup of patients with SRNS, the pathogenesis of nephrotic syndrome remains elusive. Screening tests, for genetic mutations, shall become available for clinical use in the future. Consensus is likely to emerge that patients with these mutations should not receive intensive immunosuppressive therapy, but be managed conservatively. Novel

therapies with agents that inhibit or reverse fibrogenesis, or affect vascular remodeling (*e.g.*, ACEI, monoclonal antibodies, aldosterone antagonists) might be applied.

Currently, the optimal treatment of patients with SRNS is unclear. Therapy with IV corticosteroids, IV cyclophosphamide or CsA (along with alternate day prednisolone and ACEI) have each been shown to induce remission of proteinuria in 30-70% patients, in anecdotal reports and few controlled trials (1, 19). Adequately powered and well-designed studies are needed to assess the benefits and adverse effects of CsA, and of IV steroids with oral or IV alkylating agents in children with SRNS. These trials must have ethically acceptable study and control arms, and be of sufficient duration to assess remission and relapse rates, renal function and adverse effects. Until then, the choice of treatment for these patients shall largely depend on their physician's preference and experience.

Two such trials are in progress. Tacrolimus, a calcineurin inhibitor similar to CsA, has comparable toxicity but less cosmetic side effects and decreased incidence of nephrotoxicity, hypertension and dyslipidemia. Since anecdotal reports show that tacrolimus is effective in inducing remission in patients with steroid resistant FSGS (27), a randomized trial comparing the efficacy and safety of the two agents has been initiated. Results from this trial, expected in the next 3 yr, shall provide information on the preferred calcineurin inhibitor. The second study is based on preliminary data that high dose oral dexamethasone reduces proteinuria in patients with FSGS. The National Institutes of Health (USA), in 2003, initiated a prospective, randomized, multicentric trial to compare the effectiveness of CsA to a combination of pulse oral dexamethasone and MMF in 500 subjects with steroid resistant FSGS. Both groups shall

receive low dose alternate day prednisolone and an ACEI. Results from these and other studies are expected to enable formulation of standards of care for children with SRNS in future.

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