What is new in therapy of glomerulonephritis in the 2003/2004

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Abstract

The article reviews reports and opinions dealing with management of human glomerulonephritis that have appeared in the years 2003/2004. The following glomerulopathies have been covered: primary focal and segmental glomerulosclerosis, IgA nephropathy, membranous nephropathy, lupus nephritis, ANCA positive vasculitis and HCV-positive membranoproliferative cryoglobulinemic glomerulopathy. Aside from original studies, expert opinions and recommendations have been cited.

Key words: glomerulonephritis therapy, primary and secondary glomerulopathies.

The problems of pathogenesis and treatment of human glomerular diseases are particularly complex and multifactorial, as much as clinical management of glomerulonephritis. Despite a notable improvement made in the past decade in this field, in particularly regarding secondary glomerular disease, satisfactory results have not been reached in majority of glomerulonephritides. Therefore, this presentation aimed at underlining novel approaches to management of these diseases, is based upon my personal, based selection of, in my opinion, interesting and representative reports, that have been published in the years 2003/2004. Thus it doesn't mean that the reports and opinions cited herein reflect a complete upate of this complicated and multifaceted subject.

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Received 5.05.2004 Accepted 3.06.2004

Primary focal and segmental glomerulosclerosis (FSGS)

A prolonged treatment with corticosteroids is a first therapeutic option. In resistant cases cytotoxic agents, cyclosporine, mycophenolate mofetil (MMF), plasmapheresis or LDL-apheresis have been tried with variable results. In adults resistant to corticosteroids several months' course of cytotoxic therapy is warranted. Some benefit has been reported of treatment with MMF, although in uncontrolled studies. Nonetheless, as for now, a 6 months trial of cytotoxic drugs or MMF may be recommended in steroid-resistant FSGS to identify few responsive cases. Plasma- or lipopheresis is also promising but awaits confirmation of effectivity in future trials [1]. Some 50-70% of steroid-resistant FSGS cases will have a marked reduction of proteinuria as result of treatment with cyclosporine A (CsA). Apropriate titration of dosage to avoid nephrotoxicity is necessary and a course of up to 12 months is advisable without a substantial risk of cyclosporine-dependence. Given the above, CsA therapy could be regarded as primary treatment in patients with FSGS at high risk of steroid toxicity [2]. The rationale of employing corticosteroids in therapy of FSGS has been questioned by the group of Ron Falk (Glomerular Disease Collaborative Network; [3]). An aggressive and multifactorial therapy of collapsing glomerulopathy, a variant of FSGS, has been proposed by Gerald Appel and his coworkers [4]. It includes steroids or CsA, ACE-inhibitors, AII receptor blockers and statins. Moreover, 6-12 months' course of AII receptor antagonist losartan (50 mg/day) was effective in ameliorating nephrotic syndrome in normotensive patients with FSGS resistant to immunosuppressive treatment [5]. Contrary to the above cited opinion of R. Falk and coworkers, Indian authors demonstrated

in a controlled trial that patients with FSGS should be given steroids for at least 4 months before they could be regarded non-responsive to these drugs [6]. In a study assessing long-term effects of CsA or chlorambucil treatment (6 months trial) of patients with nephrotic syndrome due to FSGS, investigators of the German Collaborative Glomerulonephritis Study Group [7] revealed that at 4 years after the trial mean serum creatinine in group receiving CsA was appx. 1.7 mg/dl, while in that treated with chlorambucil was 1.9 mg/dl (difference not statistically significant). Total remission of nephrosis was seen in 28% of patients taking CsA. Thus this form of therapy appears to be relatively safe and effective in the FSGS, also in the long run, however the results were not significantly better than those of chlorambucil treatment. Stewart Cameron has also contributed to the above cited discussion on usefulness of corticosteroids in FSGS by stating that nowadays, contrary to the past, a 4-6 months course of steroids is warranted in all adult nephrotic patients with FSGS to establish if they fall into the 20-30% who will thus achieve a remission of proteinuria [8]. These steroid-sensitive patients have a benign prognosis as to progression of renal disease and their management could rely on long-term (24 months) low dose steroids and/or CsA (up to 12 months). A study reported in children, but equally applicable to young adults with steroid-resistant FSGS, proposed combined use of MMF and ACE-inhibitors or AII receptor blockers if all other measures failed [9]. After 6 months of such medication proteinuria was reduced by 72% and this level maintained for at least 24 months. Nonetheless this study, as many other similar reports, has suffered from a low number of cases.

IgA nephropathy

Among many reports on beneficial effect of anti-angiotensin treatment in this nephropathy, a group from Korea [10] has documented an additive antiproteinuric influence of combined ACE-inhibitor and AII receptor blocker. Interestingly, in a group of type 2 diabetic nephropathy patients treated in parallel, such synergism against proteinuria could not be observed. A controlled trial assessing effect of steroid therapy in patients with moderate proteinuria (0.5 - 2.0 g/d) was performed in Japan [11]. The result revealed not only significant reduction in proteinuria in steroid-treated patients, but also remarkable improvement of renal histology assessed on repeated biopsy at 3 years' follow-up. Another controlled trial in Japan featured over 5 years' observation of patients treated with low dose steroids (20 mg tapered to 5 mg/day) for histologically moderate IgA nephropathy. As result, this dosage, while reducing proteinuria, was ineffective in arresting deterioration of glomerular filtration. Authors concluded that higher doses of corticosteroids are mandatory in management of this entity [12]. On the other hand, histopathologically severe crescentic IgA nephropathy was successfully managed with pulse methylprednisolone and intravenous cyclophosphamide repeated monthly for 6 months. Marked histopathologic improvement was noted on repeat biopsy along with significant reduction in proteinuria. At 36 months' follow-up end-stage renal disease was observed in 1/12 patients of treated group versus 5/12 historical controls [13]. A 10 years' follow-up study was performed in Greece on patients with IgA nephropathy and heavy proteinuria (>3 g/d). Results revealed beneficial effect of treatment with corticosteroids and azathioprine (24 months) on progression of glomerular disease to end-stage renal insufficiency [14]. In advanced cases of nephropathy presenting with reduction in glomerular filtration (creatinine > 1.5 mg/dl) it may be advisable to combine pulse methylprednisolone treatment with tonsillectomy. This approach significantly decreases rate of progression to ESRD in over 5 years' follow-up [15]. Similarly advanced (creatinine >2 mg/dl) and progressing (25% increase of serum creatinine in the past 3 months) noncrescentic IgA nephropathy was evaluated for response to cyclophosphamide pulse therapy (750 mg/m^2 monthly for 6 months) and low dose prednisolone by Rasche FM et al. [16]. This treatment reduced the rate of renal function loss from 16% to 4% along with significant decrease of proteinuria and was therefore regarded effective in this subgroup of patients. A group of children or young adults with moderate proteinuria (normocholesterolaemia) and mild histopathological changes responded favourably to combined treatment with fluvastatin and dipyridamole (12 months) in terms of diminution in proteinuria, hematuria and serum creatinine concentration [17]. Finally, a group of 110 patients with mesangial proliferative nephropathy and IgM deposits (IgM nephropathy) was observed for 15 years by Finish investigators: 29% were resistant to corticosteroids and 80% of steroid-sensitive were steroid-dependent [18].

Membranous nephropathy

Despite extensive clinical investigations in the past 2 decades, the jury is still out on optimal scheme of management of this type of glomerulonephritis. In particular, the efficacy and safety of majority of protocols employing corticosteroids and alkylating agents must be regarded at least controversial. In a recent review, a group of Chapel Hill, USA, suggests more selective, innovative strategies aimed at modulating immune response to pathogenic antigen, inhibition of B and T cell activation, blockade of complement cascade, interference with peroxidation of GBM components and others [19]. With regard to steroid and cytotoxic drugs, the authors of original scheme of treating membranous nephropathy with alternating monthly schedule admit that although significant antiproteinuric effect was noted, long-term nephroprotective influence was uncertain and severe side effects were observed in patients with impaired renal function [20]. CsA has been shown in a number of controlled trials to markedly diminish proteinuria and arrest progression of renal failure in at least 2/3 of patients characterised as being at high risk of progression (reviewed in [21]). The evidence in favour of MMF efficacy in these patients is much weaker and derived from pilot studies: half of the patients will have a 50% reduction in proteinuria and no effect on renal function. Down the line suggested by the above cited selective approach to treatment, the group of G. Remuzzi reported on a successful use of anti-B cell (CD20) monoclonal antibody, rituximab in patients with membranous nephropathy at high risk of progression to ESRD [22]. Specifically after 12 monthly infusions renal function sta-

bilized and proteinuria decreased to <0.5 g/d. Finally, a report from Hong Kong described effective treatment with tacrolimus of 3 patients with membranous nephropathy nonresponsive to steroids and cytostatics: there was complete remission in 1 and partial in 2 patients [23].

Lupus nephritis

It is now recognized that this disease represents rather a clinical syndrome, than the unique pathogenic and clinical entity, therefore there cannot be a uniform therapeutic approach to all the types and patient subgroups. Each treatment strategy includes induction and maintenance phase and recommendations for both phases are still controversial. Whereas induction therapies outlined by the NIH (intravenous cyclophosphamide pulse therapy for diffuse proliferative lupus nephritis) and the Mayo Clinic trials are more or less widely accepted, the maintenance therapy abounds controversies as to whether cyclophosphamide or azathioprine are effective and safe in this regard [24]. Recently, Contreras G et al. [25] published results of their prospective controlled trial comparing efficacy and safety of 3 regimens aimed at maintaining results of remission induction: quarterly pulse cyclophosphamide, oral azathioprine and oral MMF. Following the pulse-cyclophosphamide induction phase that caused remission in 83% patients, they obtained much better results in maintenance phase (72 months event-free survival and relapse-free survival, as well as incidence of hospitalization and side-effects) in the azathioprine and MMF groups than in the cyclophosphamide group. New drugs currently employed in other autoimmune diseases haven't been extensively used in treatment of lupus nephritis: methotrexate, CsA, high dose intravenous immunoglobulins [26]. The same applies to immunosuppressive drugs used in transplantation (MMF, tacrolimus). There are interesting attempts with monoclonal antibodies against immune cells, cytokines and components of the complement system, as well as with autologous bone marrow transplantation in treatment of severe lupus nephritis. Recently, a group from the Heidelberg University compared outcomes of lupus nephritis in patients treated at this institution in the years 1980-1989 and 1990 through 2000. In the later decade there were lower rates of renal failure and fewer histological signs of chronicity at diagnosis. Thus, although the treatment schedules were not significantly different, the outcome of disease was clearly better in the recent decade (40% of ESRD in the years 1980-89; no ESRD in the 1990-2000, [27]). A new immunosuppressive drug developped in Japan, mizoribine has been used to relieve flare of lupus nephritis in a pilot prospective study of 6 patients [28]. Oral pulse therapy resulted in reduction of proteinuria, serum anti-dsDNA antibody titers as well as significant histological improvement in 1 patient who has been rebiopsied after treatment. Yet another novel drug, rituximab (anti-CD20 monoclonal antibody) has been successfully employed (complete remission achieved) by a group from Navarra (Italy) in management of lupus nephritis refractory to cytostatics and steroids [29]. Evaluation of safety and efficacy of another monoclonal antibody, anti-CD 40L was performed by investigators from NIH, Bethesda, in 28 persons with proliferative lupus nephritis. The study was terminated prematurely because of thromboembolic phenomena occurring in some patients, however reduction in proteinuria and anti-dsDNA titers was observed in few persons available for assessment of efficacy [30]. Also from the NIH originated a review article summarizing current approach to treat lupus membranous nephropathy [31]. It was concluded that the patients with this entity should be treated from the earliest stages of the disease with angiotensin antagonists to minimize proteinuria, whereas after development of nephrotic syndrome active immunosuppression should be employed including corticosteroids, cyclosporine, MMF and cyclophosphamide.

ANCA positive renal vasculitis

The second wave clinical trials launched by the European Vasculitis Study Group (EUVAS) was aimed at testing new therapeutic approaches. Results of the part of the CYCLOPS (pulsed vs. oral continuous cyclophosphamide in generalized vasculitis) trial from the First Medical Department, Charles University (Prague) were recently published [32]. It appears from the outcome that mortality was higher in the oral cyclophosphamide arm, so was the cumulative dose of the drug and infection rate, although while remission rate was lower, the relapses were less frequent in the oral cyclophosphamide group. New trials by EUVAS include comparison of MMF and azathioprine in maintenance of remission (IMPROVE). The efficacy of both anti-TNF antibody and soluble TNF receptor in management of ANCA (+) vasculitis have been probed recently. A study from Bologna revealed that plasma exchange treatment (PE) improves prognosis in acute phase of ANCA (+) crescentic glomerulonephritis: in patients receiving both PE and steroids plus oral cyclophosphamide there was less mortality and lower rate of transfer to end-stage renal disease than in those given immunosuppressive drugs alone [33]. Tetracycline derivatives inhibit production and activity of matrix metalloproteinases; a single case report demonstrated remarkable subsidance of proteinuria in crescentic glomerulonephritis with tetracycline [34].

Miscelanous

Rather futuristic approach of treating glomerular diseases has been reviewed by Schena FP and Abbattista MR [35]: infusion of bone marrow-derived stem cells could repair injured glomeruli. Data from experimental animal studies indicate that this strategy may be employed in treatment of human glomerulopathies in the near future. The issue of combined ACE and AII receptor blockade in reducing proteinuria in glomerulonephritis has been tackled by few studies. The G. Remuzzi's group achieved a synergistic antiproteinuric effect when both drugs were used in concert [36], while investigators from Bern (Switzerland) observed reduction in serum matrix metalloproteinase activity with ACE inhibitor, but not with AII receptor blockers, or combined use of both anti-angiotensin drugs [37]. The major advantage of LDL-apheresis and

immunoadsorption as selective procedures over nonselective plasmapheresis in management of certain glomerulopathies has been underlined by Sułowicz W and Stompór T [38].

In patients with HCV infection and cryoglobulinemic glomerulonephritis (membranoproliferative, MPGN), a 12 months course of interferon alpha (IFNα) and ribavirin results in sustained virologic response, along with improvement of clinical and histologic features of glomerulopathy [39]. The treatment with IFNα alone may be complicated by relapses of HCV viremia and renal disease after discontinuation of therapy. In cases of rapidly progressive MPGN the treatment is initiated by pulses of methylprednisolone plus oral prednisolne with cytostatic, followed by the above antiviral therapy. In patients with genotype Ib HCV cryofiltation (double filtration plasmapheresis with a cooling unit) combined with IFNα and ribavirin is recommended [40].

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