Henoch-Schönlein Purpura Nephritis: Pathophysiology, Treatment, and Future Strategy

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Summary
Henoch-Schönlein purpura nephritis is a rare kidney disease leading to chronic kidney disease in a non-negligible percentage of patients. Although retrospective studies suggest beneficial effects of some therapies, prospective randomized clinical trials proving treatment efficacy are still lacking. The dilemma of spontaneous recovery even in patients with severe clinical and histologic presentation and of late evolution to chronic kidney disease in patients with mild initial symptoms renders it difficult for clinicians to expose patients to treatment protocols that are not evidence-based. A better understanding of the pathophysiology of progression to chronic kidney disease in Henoch-Schönlein purpura patients could be achieved by designing prospective international multicenter studies looking at determinants of clinical and histopathological evolution as well as possible circulating and urinary markers of progression. Such studies should be supported by a database available on the web and a new histlogic classification of kidney lesions. This paper reports clinical, pathologic, and experimental data to be used for this strategy and to assist clinicians and clinical trial designers to reach therapeutic decisions.

Introduction
Henoch-Schönlein purpura nephritis (HSPN) and IgA nephropathy (IgAN) are currently considered related diseases. Indeed, in a set of identical twins, one can present with IgAN and the other one with HSPN (1). Furthermore, both diseases display similar histologic features and IgA abnormalities (2). The common clinical pattern of IgAN is an indolent progressive disease with slowly increasing proteinuria and loss of renal function with flair-ups of macroscopic hematuria in half of the patients. HSPN, in contrast, presents most often with an initial acute episode followed by complete healing in the majority of patients. Persisting proteinuria and progressive chronic renal failure occur in a minority of patients (2). Nephritic and/or nephrotic syndromes are more often seen at presentation in HSPN (2). End-stage renal failure (ESRF) caused by HSPN is infrequent in adults (3), but it reached 5.1% in a large series of children from Necker-Enfants Malades Hospital (4). The prevalence of HSP is difficult to assess from the literature (5). Using the controversial American College of Rheumatology criteria for vasculitis classification (6,7), which may result in overdiagnosis, the yearly incidence varies between 6.1/100,000 children in The Netherlands to 20.4/100,000 children in UK (8–11). It is generally agreed that the incidence of HSP decreases with age (3). The proportion of children presenting with renal involvement reported in studies varies from 20 to 100% (for a review, see reference 12). In one study using a cohort of adult patients in whom the diagnosis was based on the findings of the characteristic leukocytoclastic skin vasculitis accompanied by IgA deposits (13), 49% of patients presented with abnormal urinary signs. In selected series, HSPN leads to chronic kidney disease (CKD) 20 years after the diagnosis in up to 20% of children (14), whereas this percentage falls to less than 5% in unselected series (15). The risk of CKD in adults is higher. It varies from 35 to 69% in 388 patients followed up at least 5 years in four published series (16–19). Furthermore, adults have more often joint symptoms at presentation (20).

Our knowledge on treatment of HSPN is quite limited. Randomized clinical trials (RCTs) are scarce and often inconclusive. Spontaneous complete recovery in patients with severe initial presentation and/or extended histologic lesions and the late evolution to CKD of patients with mild initial symptoms makes the interpretation of treatment efficacy difficult (12,14,21). The main goal of the present paper is to propose a strategy aimed to better define patients at risk, using renal symptoms, histologic lesions, and possible new markers of progression to assist clinicians and clinical-trial designers to reach therapeutic decisions.

Experimental Data and Pathophysiological Hypothesis
The pathophysiology of HSPN has been extensively described elsewhere (2,22). Endocapillary and extracapillary inflammation as well as glomerular fibrin deposits are more frequent in HSPN than in IgAN. No major biologic differences have been found between the two illnesses excepted for the IgG content and bigger size of the circulating IgA-containing complexes (IgA-CC) and the higher incidence of increased
IgE plasma levels in HSPN (23–25). Our own study on the possible role of immunological mechanism (25) was initiated on the basis of reports of HSP associated with allergy and high IgE plasma levels and on the observation of a 7-year-old boy with HSPN that started 1 day after he fell into stinging nettles (Jean-Claude Davin, personal communication). This information led us to postulate that stimulation of IgE-sensitized mast cells (present in skin, intestine, and lungs) by specific antigens in the presence of IgA-CC might lead to the release of vasoactive substances, increasing capillary permeability and perivascular deposition of IgA-CC. Although mast cells are not usually found in the mesangium, circulating vasoactive substances released by other organs might account for increasing the deposition of large IgA-CC in glomeruli.

**IgA Abnormalities**

HSPN and IgAN might result primarily from an abnormal IgA1 glycosylation. The lack of terminal β1-galactosyl residues in the hinge region of IgA1 observed in both diseases might be due to a reduced activity of the β1,3-galactosyltransferase in peripheral B cells (26–28). This abnormality is present only in HSP complicated by nephritis, which suggests a pathophysiological role (26). N-Acetylgalactosamine (GalNac) residues exposed on IgA1 because of the lack of terminal β1 galactosylation constitute a novel antigen inducing a humoral auto-immune response (29). The possible impaired resistance to antigen penetration at mucosal levels suggested in HSPN by an increased intestinal permeability (30) and in IgAN by a reduced mucosal immune reaction to novel antigen (31) might contribute to the production of large amounts of GalNac-IgA1 that cannot be cleared by the asialoglycoprotein receptor of hepatocytes binding specifically to β1,3-galactosyl-IgA1. Accumulating GalNac-IgA1 in polymeric forms (pIgA) in circulating blood favors the formation of large IgA-CC that deposit in different tissues and induce local inflammation. IgA1 binding to leukocyte FcαRI receptors is followed by cleavage of the FcαRI extracellular domain, resulting in a release of IgA1/FcαRI receptor complexes that amplifies the molecular size of IgA-CC (32). In glomeruli, IgA1 complexes localize in a mesangial or in a subendothelial pattern (33) according to their physicochemical properties. CD71 mRNA coding for the transferrin receptor, which preferentially binds GalNac-IgA1, is expressed on mesangial cells (32,34). In vitro studies have shown binding of pIgA to mesangial cells to enhance cell proliferation, cytokine release, and production of extracellular matrix (ECM) (35–37).

**Complement Activation**

Activation of the complement pathway is probably an important effector event in the pathophysiology of glomerular lesions. C3 deposits are seen in a vast majority of patients with HSPN (38). Alternative pathway components, such as FB in contrast to C1 and C4, and the membrane attack complex C5b9 are regularly present, accompanying predominant IgA deposits in a mixed mesangial and capillary pattern (33). The glomerular deposition of MBL, L-ficolin, MASP, C4d, but not C1q shown to be associated with a higher grade of proteinuria and hematuria and more severe histological lesions in HSPN (39) strongly suggests, as seen in IgAN (40), a predominant pathophysiological role of the activation of the complement system by the lectin pathway. This emphasizes the need of studies examining the value of blood and urinary complement splits product and of the membrane attack complex to evaluate the disease activity.

**Mesangial Cell Activation, Proliferation, and Glomerulosclerosis**

The deposition of IgA-CC in glomeruli is favored by their high plasma concentration and their biochemical features in HSPN (23,24). Once in the mesangium, different components of IgA-CC (for example, Fcγ and Fcy fragments, fibronectin, C3b, etc.) can bind to their specific receptors on the surface of mesangial cells (MCs) (2,41) and trigger cell proliferation, ECM production, and synthesis of chemokines monocyte chemoattractant protein-1 and IL-8 (34–37) that might account for the attraction of polymorphonuclear leukocytes and monocytes found in patient biopsies. MCs can also be stimulated by cytokines of the acute phase (IL-1, TNF-α, and IL-6) and of the chronic phase (PDGF and TGF-β) produced by themselves (for a review, see references 41–46) and/or by infiltrating cells.

Chemokines generated by IgA1-stimulated MCs can interact with their receptors on podocytes and in this way may influence their metabolism, local migration, and adhesion to the basement membrane and control of proteinuria (47,48). The urinary excretion of podocytes (u-podo excretion) seems to be a good parameter for predicting glomerulosclerosis in HSPN and IgAN because chronic histology scores and glomerulosclerosis both correlate well with cumulative u-podo excretion (49). Patients with severe histologic progression of disease also had persistent u-podo excretion (49).

**Crescent Formation**

Because the presence of crescents is a prominent histologic feature of HSPN that represents an important prognostic factor and constitutes the basis for the International Study Group of Kidney Disease in Childhood (ISKDC) pathology classification (38), the study of crescent pathophysiology might provide useful information for therapeutic strategy (50–52). As already mentioned, crescents are much more often seen in HSPN than in IgAN, and their number is related to the severity of clinical signs and to the prognosis of HSPN in most series (16,17,53–60). They are frequently seen in association with capillary wall destruction and endocapillary cell proliferation (33). The presence and extension of crescents are related to the finding of subendothelial immune deposits of IgA and complement using immunofluorescence microscopy and with the presence of subendothelial electron dense deposits (33).

Histology of patient biopsies combined with studies on experimental crescentic glomerulonephritis (61–75) suggest that the following succession of events is involved in the crescent formation in HSPN (2): (1) subendothelial and mesangial deposition of IgA-CC; (2) local complement activation; (3) IL-8 production by mesangial and endothelial cells inducing neutrophil attraction; (4) stimulation of endothelial cells to express von Willebrand factor and tissue
factor that initiate the coagulation cascade, leading to glomerular-fibrin deposition; (5) destruction of the basement membrane; (6) macrophages attraction and cytokine-induced epithelial cells proliferation in the Bowman’s space; and (7) disruption of the capsular integrity and infiltration of the Bowman’s space by interstitial fibroblasts resulting in fibrosis formation. Importantly, genetically-determined differences in both glomerular and bone-marrow-derived cells influence individual susceptibility to crescent formation (76).

**Prognostic Value of Renal Symptoms**

The use of the severity of initial renal symptoms to adapt the treatment should be justified by the correlation between the latter and the prognosis at long term. The interpretation of data from reported series is complicated by the possible influence of treatment, which is most often heterogeneous and not precisely reported (dosage, duration of administration). Moreover, the latter has varied through the years. Until the 1980s, HSPN was considered to be mostly an illness with spontaneous recovery (77). This concept began to change after the publication of long-term follow-up studies (53–55). Parallel to this change and despite the lack of evidence-based data, recommended treatments in text books changed from supportive measures (77–79) to the use of steroids and immunosuppressive drugs (80,81) even in the absence of a picture of rapidly progressive glomerulonephritis (80). Another difficulty resides in the development of CKD up to 20 years after disease initiation, especially during pregnancy, even after complete apparent resolution (14,21). This implies that only series with sufficient follow-up might be informative. Finally, most series of long-term follow-up relate outcome to initial symptoms and biopsy without intermediate observational moments, discarding the potential role of relapses and of a progressive active process. This lack of information does not allow for the differentiation of different patterns of pathologic events leading to CKD: (1) one unique episode with apparent complete recovery but leading to an important nephronic reduction and CKD at long term by hyperfiltration; (2) recurrence of acute episodes; c/progressive indolent process as in IgAN. The latter is suggested by several reports of HSPN observed in patients known to have had IgAN for many years (82–85). In general, there is a good relationship between the severity of initial clinical presentation and the risk of CKD at long term (14,21) (Table 1), but it is far from being a constant rule.

According to the study of Goldstein et al. (14), CKD is encountered at long term in less than 5% of patients when clinical signs at presentation are hematuria and/or minimal proteinuria, 15% when proteinuria is heavy but not nephrotic or in the case of nephritic syndrome, 40% with nephrotic syndrome, and in more than 50% when nephritic and nephrotic syndromes are associated. It is remarkable that some (rare) patients presenting with mild initial symptoms are seen with CKD at long term (14,86). A particular example is CKD observed after repeated episodes of isolated macroscopic hematuria (87,88). Even patients with no urinary abnormalities at all have been reported to present with hypertension later on (89).

Bias in the interpretation of initial symptoms for prognostic purposes has resulted in the consideration of other clinical parameters. Failure to reach a creatinine clearance of >70 ml/min per 1.73 m² at 3 years and increasing proteinuria levels during follow-up correlate better with the risk of progression to CKD than decreased renal function, severe proteinuria, hypertension, or crescents present at onset of disease (88,90) (Table 1). On the other hand, although there is no specific report of late follow-up of patients with untreated initial severe renal symptoms at presentation (nephrotic proteinuria, nephrotic syndrome combined or not with nephritic syndrome), it is commonly accepted that HSPN might heal completely when presenting with severe renal symptoms even when no treatment has been used (77,86,90,91).

**Prognostic Value of Histologic Lesions**

Histologic lesions have been classified by the ISKDC in five categories (I, II, III, IV, and V) according to the presence and number of crescents. Grade VI is used for a membranoproliferative aspect (38). A rough appreciation

| Table 1. Clinical prognostic factors for chronic kidney disease at long term in Henoch-Schönlein purpura |
|-------------------------------------------------|-----------------|
| Symptoms                                         | Patients (%)    |
| Initial renal symptoms¹                           | CKD             |
| nephrotic-nephritic syndrome                      | >50             |
| nephrotic syndrome                               | 40              |
| nephritic syndrome                               | 15              |
| heavy non-nephrotic proteinuria                   | 15              |
| hema/turia and/or minimal proteinuria             | <5              |
| Renal symptoms during follow-up¹                 | ESRD            |
| GFR < 70 ml/1.73 m² per min at 3 years           | 100             |
| Initial symptoms vs. increasing proteinuria during follow-up² | Progression (significance) |
| Mean follow-up proteinuria (g/d)                  | RR = 3.83 (P = 0.20) |
| Severely impaired vs. normal GFR (onset)         | RR = 4.74 (P = 0.17) |
| Nephrotic vs. minimal proteinuria (onset)         |                 |

¹From reference 14.
²From reference 88.
³From reference 91. Univariate analysis of predictors related to renal survival by using dialysis therapy as end point.
⁴Relative risk 1.77 for each 1-g/d increase for doubling of creatinine level. GFR has been calculated using the Schwartz formula.
of mesangial hypercellularity is also considered in this classification.

As for clinical symptoms, it is generally accepted that the risk for the development of CKD increases with the severity of the histologic lesions at presentation. Combining three studies (55,57,86) with a follow-up of about 6 years (38), all ISKDC grades combined result in 25% of severe complications (active renal disease and/or CKD and/or ESRF): 15, 15, 35, 70, and 66% for classes II, III, IV, V, and VI, respectively. Class I, which includes minimal glomerular abnormalities, is the only class without long term complications. Only four (18,19,21,92) from 15 series (eight in children and seven in adults) (14,16–19,21,53–60,92) reporting on the relation between outcome and the histology of the first renal biopsy do not mention a predictive value of crescents for CKD and ESRF. In contrast, the latter studies also show that low grade histologic lesions can also lead to CKD and that high grade lesions can heal definitively. The reasons for those discrepancies can be multiple: (1) A renal biopsy is only a small fragment of renal tissue; it is therefore possible that lesions observed are either over-represented or on the contrary under-represented, giving a biased image of the reality in its totality. (2) Reversibility with minimal or no scarring can be expected when crescents are not yet fibrotic and still remain predominantly cellular without a significant fibroblast or collagen component; this spontaneous resolution can be expected with a triggering event of short duration such as episodes of macroscopic hematuria accompanying respiratory infections in HSPN (53). (3) The ISKDC classification does not consider some other important well-accepted prognostic factors such as tubular lesions, interstitial fibrosis, interstitial and glomerular inflammation, crescent features (localized or completely surrounding the glomerulus, fibrotic or not), segmental sclerosis, and arteriosclerosis; this classification neither takes electron microscopy nor immunofluorescence features into consideration; and the importance of this issue is illustrated in a recently reported large series of French patients (93) in whom interstitial fibrosis and the percentage of sclerotic glomeruli, but not crescents, were associated with a poor renal prognosis. (4) Another possible explanation for this discrepancy is the prompt use of aggressive immunosuppressive treatments suggested by Ronkainen et al. (21) to explain the worse outcome of ISKDC grades II–III than grades IV–V in their series. This has led the latter authors to advise repeated kidney biopsies when severe symptoms do not improve and to rely more on symptoms than on histology for therapeutic decisions. It is remarkable that the four studies that did not show a relationship between crescents at first biopsy and outcome report data from the last 15 years, when the use of prednisone and immunosuppressive drugs had become the rule. This suggests indirectly that treatment might prevent cellular crescents to progress to fibrosis and to contribute to CKD. (5) Finally, delaying the kidney biopsy could play a role because crescentic glomeruli can rapidly lead to complete glomerulosclerosis if not treated (53,94).

In conclusion, those observations suggest that histologic documentation should consider all factors that may provide prognostic information using a new detailed histologic classification similar to that recently published for IgAN (95). The latter should take into account the mesangial cellular score, the presence and extension of glomerulosclerosis, endocapillary hypercellularity, inflammatory cells infiltration, the integrity of the Bowman’s capsules, cellular versus fibrotic crescents, and interstitial fibrosis/tubular atrophy. The difficulty in predicting outcome underlines the necessity to develop markers of activity that can be repeated easily with blood or urine samples (for example circulating GalNac-IgA1 and anti-GalNac-IgA1 antibodies, various cytokines and products of the activation of the complement system, and urinary podocyte excretion) to avoid unnecessary renal biopsies.

Treatment Strategies According to Pathophysiology

The strategy to treat HSPN should take into account the different steps of the pathophysiological process leading to HSPN.

Antigen Penetration at a Mucosal Level

Because acute HSPN episodes are often triggered by an upper respiratory tract infection (11), the removal of any source of chronic bacterial infection should be theoretically beneficial. That is the reason why some authors have performed tonsillectomy in patients with IgAN and HSPN. Unfortunately, not a single report mentioned in recent reviews on that topic (96–98) gives a level of evidence sufficient to recommend this treatment, because it is often associated with other therapies.

Reduction of IgA1 Production

All types of immunosuppressive drugs (steroids, cyclophosphamide, azathioprin, and calcineurin inhibitors) have been used to prevent CKD in HSPN. No study has been designed up to now to show drug efficacy on the production of IgA1, pIgA1, or GalNac-IgA1. Interestingly, efficacy of rituximab (RTX) therapy in chronic HSP has been suggested in three pediatric patients treated with RTX for severe refractory chronic HSP characterized mainly by neurologic and gastroenterological symptoms resistant to steroids and cyclophosphamide (CPH). All three patients responded to one or two courses of RTX without serious adverse events. The response was related to the suppression of the CD19 expression on mononuclear cells (99).

Removal of IgA1 and IgA1 Complexes

Several case reports relate the dramatic improvement of extra renal symptoms (gastrointestinal, pulmonary, or cerebral) after plasma exchange (PE) (100–110). Interestingly, Hattori et al. (109) and later on Shenoy et al. (110) reported encouraging results on the use of PE as the only treatment in patients with severe initial acute HSPN. In both series, patients presented with acute renal impairment, heavy proteinuria, or nephrotic syndrome and a histologic class equal to or higher than III (110) or equal to V (109). At last review after 4 (110) and 10 years (109), 13 of 14 and 6 of 9 patients, respectively, had a normal GFR and complete or almost complete resolution of renal symptoms. The three patients having reached ESRF were treated at least 1 month after the start of symptoms. Apart from removing circulating complexes, the favorable role of PE might also be due
to the removal of inflammatory and procoagulatory substances.

Complement Activation

As stated above, activation of the lectin pathway of complement in HSPN is associated with more severe renal damage (39). It can be hypothesized that the latter might be prevented by impeding the formation of some end products of the complement activation playing a role in the inflammatory response such as C5a and the membrane attack complex C5b9. Eculizumab is a high affinity humanized monoclonal antibody that binds to and blocks the cleavage of C5, leaving the upstream components of complement, most notably C3b, intact. Eculizumab has been shown to be very efficacious in preventing acute episodes of paroxysmal nocturnal hemoglobinuria and atypical hemolytic uremic syndrome, two diseases resulting from defective inhibition of the complement system at different levels (111–115). This suggests that eculizumab might also be of value in other kidney illnesses in which complement activation plays a role.

Fibrin Formation

The possible role of fibrin in the pathogenesis of crescents has been strongly suggested by clinical and experimental observation. That is the reason why warfarin, dipyridamol, and acetylsalicilic acid have been used along with immunosuppressive agents by several authors (for a review, see references 96–98). Difficulty of interpretation results from the following cause of bias: retrospective studies, no controls, and heterogeneity of histology and clinical symptoms as well as of heterogeneity of treatment. Aside from the lack of reliable data, the possible bleeding complications in the case of gastroenterological complications often seen in those patients might discourage clinicians from using anti-coagulation.

Mesangial Proliferation, Glomerulosclerosis, and Proteinuria

HSPN might possibly progress by continuous depo-

sition of IgA-CC inducing mesangial proliferation, ECM accumulation, and glomerulosclerosis such as IgAN (82–85). Proteinuria persisting after the acute phase might be due to two different mechanisms: either hyperfiltration due to nephronic mass reduction during the acute phase or the effect of chemokines produced by persistently stimulated MCs on podocytes (47,48,116,117). Theoretically, both mechanisms could be counteracted by ACE inhibitors, whereas corticosteroids might prevent MC proliferation and metabolic stimulation. Although prolonged administration of both classes of drugs has been shown to be valuable in reducing proteinuria and preventing progression in IgAN (118–120), no similar studies have been done in HSP. Despite the report of proteinuria reduction by cyclosporine in some patients with HSPN not having responded to steroids and immunosuppressive drugs (121), this treatment should not be recommended before the publication of the results of a RCT comparing cyclosporine to high dosage methylprednisolone (MPNS) followed by predni-

sone (122), because of the potential nephrotoxicity of cyclosporine.

Crescent Formation

Because renal prognosis is related to crescent progression to sclerosis, it is important to detect histologic signs predicting such an evolution (e.g. disruption of the Bowman capsule and presence of fibroblasts in the Bowman’s space) to initiate anti-sclerosis strategies. Because genetically-determined differences in both glomerular and bone marrow-derived cells influence individual susceptibility to crescent formation in rats (76), studies directed to the latter will be initiated in humans. Known susceptibilities should indicate more aggressive treatments.

Treatment has to be initiated early to prevent fibrotic transformation (53). As mentioned above, prevention of the development and resolution of crescents might be obtained by the removal of IgA-CC by plasmapheresis (109,110). The use of pulses of high doses of MPNS instead of the usual oral dosage of prednisone is sustained by experimental results. In a rat model of crescentic glomerulonephritis, the maximal therapeutic effect is obtained with 30 mg/kg IV MPNS (123). In a prospective noncontrolled study, Niaudet and Habib (124) suggested improved outcome of severe HSPN (nephrotic syndrome or association of nephrotic and nephritic syndrome) when MPNS pulses were used initially. In the latter series, only 11% progressed to end-stage renal failure in comparison with 38 and 27% of patients in two historical series of the same center receiving, respectively, a supportive treatment or various immunosuppressive drugs but not MPNS. Overall, these observations suggest that MPNS pulses should be used preferentially at the initiation of the steroid treatment. A favorable role of initial high dosage of steroids is suggested by other noncontrolled studies (125–128).

More specific treatment might be considered for clinical trials to prevent the influx of monocytes in the Bowman’s space. Indeed selective blockade of IL-1 with IL-1 receptor antagonists and of TNF with soluble TNF receptors markedly reduces crescent formation (68,70) by reducing the expression of adhesion molecules and the recruitment of macrophages in experimental models of glomerulonephritis.

Actual Choice for the Clinician

As usual, the clinician has to balance the risk of CKD versus the risk and the cost of the proposed treatment. The effect of treatment is particularly difficult to evaluate considering possible spontaneous complete recovery or apparent restoration of renal function masking a nephronic mass reduction that could be sufficient to lead to CKD after prolonged hyperfiltration. The lack of benefit of steroids and immunosuppressive treatment reported in old series (14,54) and the lack of data allowing a high level of evidence-based recommendations make the choice of therapy more difficult, and one may wonder if treatment is really useful. However, pediatric nephrologists with expertise in this field (21,80,81,98,124) are actually convinced of this necessity. This opinion is based on the impression of a reduction of CKD caused by HSPN parallel to treatment intensifica-

tion and on several reports mentioning a worse evolution when treatment is delayed (21,109,110,124,126). Re-
Table 2. Proposed strategy to improve Henoch-Schönlein purpura nephritis prognosis

| Determination of risk factors | Commercialization of kits for detecting specific markers of the disease as GalNac IgA1 and anti-GalNac IgG setting up a new histological classification taking into account all suspected risk factors for developing CKD blood and/or urinary measurements of markers possibly involved at different stages of the pathophysiological process (i.e. II-1, II-6, II-8, TNF-α, TGF-β, C5b-9, etc.) development of a registry available on the web multicenter studies recording prospectively and parallel clinical symptoms, biological markers values, histological data, and treatment features determining from registry data different grades of risk. | Clinical trials features | no placebo-controlled RCT allowed except for low grade risk treatment started as soon as possible after disease initiation tonsillectomy tested adequately study treatment adapted according to risk grade and treatment toxicity for highest risk, steroid treatment preferably with initial methylprednisolone bolus for highest risk, plasma exchanges alone compared with other treatments biological treatments considered (rituximab, antibodies anti-cytokines involved in inflammation and fibrosis processes, etc.). |

In the case of nephritic syndrome or nephrotic proteinuria, even without clinical nephrotic syndrome, treatment might be recommended (80) considering a risk of 15% to develop CKD at long term (14). A course of steroids initiated as intravenous high dosage MPNS given without delay might be proposed because oral prednisone alone has been claimed to be of no benefit (14,54,81,124–128). The addition of immunosuppressive drugs might be considered when improvement is delayed or in situations of higher risks. However, considering negative RCTs and side effects, CPH should probably not be recommended anymore. Although PE might be seen as an aggressive treatment, the risk of complications with modern devices is minimal in expert hands in comparison with the risk of CKD in patients with a severe clinical presentation especially in association with ISKDC pathology classification class IV or V. The encouraging results cited above suggest that PE should be considered promptly in patients where steroids and immunosuppressive drugs are not effective or even initially when nephritic and nephrotic syndromes are associated with a high percentage of crescents. Reports of long term follow-up of previous studies on the use of PE as sole treatment will help to further determine the latter indication (109,110). ACE inhibitors may be added at any level of proteinuria and may be used alone in the case of persistent proteinuria with a high chronicity index at biopsy. As mentioned above, early treatment initiation might be a major factor for preventing the progression to CKD (21,109,110,124,126).

Future Strategy
The future strategy will consist of better definition of patients at risk of CKD to adapting treatment and clinical trials to groups of patients according to their risk profiles (Table 2). The poor documentation of patient history constitutes a major pitfall in the interpretation of the prognostic role of the initial clinical signs and histologic data. The relationship of the latter to outcome has been shown to be variable, and parameters of variability can be multiple. Adequate assessment must consider all features of the therapy (moment of administration re-
lated to illness initiation, type of drugs used, dosage, and duration of drug administration). Instead of relating initial clinical and histologic data only to outcome, multiple intermediate moments should also be reported considering renal function, proteinuria, and relapses of purpura and of macroscopic hematuria. The report of the delay between initial symptoms and biopsy is of major importance because crescents can lead rapidly to glomerulosclerosis and tubular atrophy (53,94). It is now obvious that the ISKDC classification that grades the severity according to the amount of crescents only has become obsolete and should be replaced by a new detailed histologic classification similar to that recently published for IgAN (95), taking into account some or all of the following parameters that are shown to be independent predictors of renal functional decline and/or response to therapy: mesangial hypercellularity, endocapillary hypercellularity, crescents, segmental and global glomerulosclerosis, arterio- and arteriolosclerosis, interstitial inflammation, and tubular atrophy/intestinal fibrosis.

The high diversity of pathophysiological steps possibly involved between the hypothesized initial event (GalNac-IgA1 formation) and the final glomerular lesions enables different types of evolution according to the specificity of the markers participating in each step (i.e. size and composition of IgA1-CC, ability of the latter to localize in the mesangium or under endothelial cells and to induce inflammation, capacity of glomerular cells to produce cytokines and matrix after stimulation, fibroblast ability to invade the Bowman’s space and to generate fibrosis, etc.).

A better understanding of HSPN pathophysiology, defining the pattern of progression to CKD (scars from acute limited episodes or a slowly progressive active process as in IgAN) and the detection of patients at risk are sine qua non conditions to improving treatment strategies. This could be reached by prospective multicenter international studies initiated from disease presentation and pursued at long term in large cohorts of patients including also those presenting with minimal symptoms and resulting in apparent complete healing. The latter studies should be designed to look at regular intervals for correlations between clinical signs, histologic findings, treatments, and modifications of circulating and/or urinary markers (circulating GalNac-IgA1 and anti-GalNac-IgA1 antibodies, various cytokines, products of the complement system activation, and urinary excretion of podocytes) (26–29,34–37,43–47,131–132). This process should be supported by an electronic database available on the web.

Clinical trials might be coupled to this electronic registry. They should be designed by experts in the field who will decide on treatments according to risk profiles and on puzzling issues such as primary end points and follow-up duration. The results of studies looking for early clinical prognostic indications for long term outcome should help with the design (88,90). If placebo-controlled studies could be considered to study the value of treatments preventing the development of severe renal symptoms in patients with no or only minimal initial urinary abnormalities, as has been previously done (for a review, see references 96–98), it does not seem ethical to do this for all of the other presentations because of their association with a significant CKD risk.

Trials should be designed to determine the efficacy of immunosuppressive drugs, anticoagulation agents, and PE. The dramatic improvement after RTX therapy in three severe extrarenal cases of HSP resistant to steroids and immunosuppressive treatment supports this drug as a candidate for RCTs (99). However, its potential severe and sometimes fatal side effects (133) might limit its indication to a RCT devoted to cases resistant to PEs. Other biologic treatments such as eculizumab, for example, might also be considered. Finally, the efficacy of tonsillectomy should be tested adequately.

Acknowledgments

Jean-Claude Davin would like to thank Prof. Jan Weening for his useful comments and Dr. Sally-Ann Clur for the revision of the text.

Disclosures

None.

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688 Clinical Journal of the American Society of Nephrology


Published online ahead of print. Publication date available at www.cjasn.org.