Long-Term Prognosis of Membranoproliferative Glomerulonephritis Type I

Significance of Clinical and Morphological Parameters: An Investigation of 220 Cases

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Key Words

Membranoproliferative glomerulonephritis

Long-term prognosis

Survival rate

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Hypertension

Abstract

We carried out a retrospective investigation in 220 patients to assess the influence of various parameters on the long-term course of membranoproliferative glomerulonephritis (MPGN) type I. 50 patients (23%) died during the follow-up period of 59 months on average, in another 57 (26%) end-stage renal failure developed. 54 patients (24%) suffered from chronic renal failure, stable renal function (creatinine below 1.3 mg/dl) was preserved in 59 patients (27%). 5 years after biopsy 49% of the patients had already died or needed regular dialysis treatment; after 10 years this proportion increased to 64%. Morphological findings: The outcome was – with the exception of focal crescent formations – not determined by the severity of glomerular changes; the survival rate, however, decreased significantly, if tubulointerstitial lesions were present as defined by acute renal failure, interstitial fibrosis or a combination of both. Clinical parameters: A progressive deterioration of renal function and an increasing number of renal deaths was noticed, when elevated serum creatinine levels at the time of biopsy and high blood pressure values during the follow-up period were observed. 26 patients died from hypertension, 18 of whom before reaching end-stage renal failure. Nephrotic syndrome and the degree of proteinuria as well as antiphlogistic and immunosuppressive treatment did not influence the prognosis of MPGN type I.

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Studies on the long-term course of membranoproliferative glomerulonephritis (MPGN) have previously been carried out only on small numbers of cases, due to the rarity of the disease [1–13]. The prognosis is generally considered unfavorable [1–16], but there is still uncertainty about the factors causing the progression to end-stage renal failure or even death of the patient. In earlier investigations [14, 17–19] we noticed certain correlations between the severity of tubulointerstitial changes at the time of biopsy and renal function in MPGN. Therefore we were interested in determining whether, and to what extent, these changes as well as the clinical parameters blood pressure (BP), creatinine, proteinuria and hematuria are of prognostic significance.

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Material and Methods

Among 36000 patients in our renal biopsy registry we found 346 in whom idiopathic MPGN was diagnosed between 1965 and 1984. By further investigations (immunohistology, electron microscopy) 108 patients had to be excluded from our study because primary diagnosis was not correct. They either suffered from other renal disorders (endocapillary/mesangioproliferative/membranous glomerulonephritis) or renal involvement due to underlying diseases such as lupus erythematoses, cryoglobulinemia and monoclonal gammopathy/multiple myeloma; 18 patients with MPGN type II (dense deposits) were also excluded. In the remaining 220 cases (male:female ratio = 1.75:1; mean age 36.4 ± 15.5 years) the light-microscopic diagnosis of MPGN was confirmed and type I (subendothelial deposits) could be revealed by electron microscopy and/ or immunohistology; all these cases were reviewed by our senior author A.B. who is a referee pathologist in renal pathology. The biopsies were then classified according to the severity of histological lesions; we first distinguished between five grades of glomerular changes (fig. 1) as defined previously [19]: grade I – segmental form

Membranoproliferative Glomerulonephritis: Long-Term Prognosis

243

Fig. 1. Severity of glomerular changes in patients with MPGN type I. a Grade I. b Grade II. c Grade III. d Grade IV. e Grade V (for explanation see text), a-e PAS reaction, a-d Magnification 128:1. e 250:1.

-b

Fig. 2. Categories of tubulointerstitial findings in patients with MPGN type I. a Normal findings, b IF. c ARF. d ARF in combination with IF (for details see text), a, b, d PAS reaction, c Giemsa stain. Creatinine: 0.8 mg/dl (a), 2.8 mg/dl (b), 3.35 mg/dl (c) and 3.41 mg/dl (d).

of MPGN, grade II – MPGN with diffuse attachment of the glomerular capillary loops, grade III – MPGN with slight accentuation of the lobular glomerular structure in addition to the aforementioned changes of grade II, grade IV – lobular glomerulonephritis, and Grade V – MPGN with focal crescent formations, regardless of the other glomerular lesions. Furthermore, four categories of tubulointerstitial findings were differentiated (fig. 2) as described previously [19]: (1) normal findings, (2) interstitial fibrosis (IF) with tubular atrophy, (3) acute renal failure (ARF), (4) acute renal failure in combination with interstitial fibrosis (ARF + IF). ARF was defined

as rapidly developing impairment of renal function (serum creatinine above 1.5 mg%) with loss of concentrating ability and in part with oliguria or anuria. As early histological change we found a massive swelling of tubular epithelial cells. If renal biopsy was taken several days after the onset of the disease morphological examination showed dilated tubules with flattened epithelium and signs of cellular regeneration. The validity of our histological classification for tubulointerstitial findings was confirmed by morphometric investigations in IgA nephritis. The method has been reported in detail [20].

244

Schmitt/Bohle/Reineke/Mayer-Eichenberger/Vogl

25.9

19.1

6.8
22.7

54 19
28 7
24.6
8.7
12.7
3.2

Chronic renal failure

Creatinine 1.4–2.0 mg% Creatinine 2.1–5.0 mg% Creatinine > 5.0 mg%

57 42 15

End-stage renal disease Hemodialysis Kidney transplantation

50

Deaths

The duration of follow-up was 59 months on average.

%

35

52 28 14

Table 2. Causes of death and renal function at time of death in 50 patients with MPGN type I

19

Uremia

26 14

7 4 1

Hypertension Stroke

Myocardial infarction Congestive heart failure Aortic dissection

Sepsis

2

0

48

52

Pulmonary embolism

0

24 26

Renal function at time of death Normal renal function Chronic renal failure End-stage renal disease

Apart from this we registered the clinical parameters BP, creatinine, proteinuria, nephrotic syndrome and hematuria, both at the time of biopsy and at various intervals until the last follow-up.

Altogether the 220 patients, of whom only 5.5% were younger than 15 years at the time of biopsy, could be followed up for an average of 59 months (median value: 50 months). The time when the diagnosis was established did, however, not correspond with the onset of the illness. Thus the objective duration of the disease prior to biopsy – determined by anamnestic data – was on average 24.2 months (median value: 10 months).

Statistical analysis was carried out with the evaluation system SAS. The survival curves were calculated following the method of Kaplan and Meier [21]. This is a so-called ‘nonparametric’ procedure; the estimation of survival probabilities is not based on any assumption about the distribution of survival time. Also ‘right censored values’ are taken into analysis, i.e. data concerning patients who are still alive at the time of evaluation. In the survival curves the functional value $s(t)$ indicates the probability of surviving the point t in time. In order to assess the differences among curves the likelihood-ratio test was used which, in contrast to the χ^2 test, also provides reliable p values with small numbers of cases. Statistical significance was reached with a p value < 0.05 .

1 There were 8 with cerebral hemorrhage and 6 with cerebral thrombosis.

100-90-

70-

5 60

20

10-

0 12 3 4

Follow-up, years

9 10 11 12 13 14 15 16 17

Results

Fig. 3. Probability of maintaining renal function (survival curve) in 220 patients with MPGN type I; ‘dead’ means death plus end-stage renal failure.

Of the 220 patients, 50 (= 22.7%) died during the observation period; in another 57 patients (= 25.9%) end-stage renal failure developed, they either needed regular dialysis treatment ($n = 42$) or received a kidney transplant ($n = 15$) (table 1). The survival curves were calculated according to the duration of follow-up (fig. 3).

Patients who suffered from end-stage renal failure were treated as ‘dead’ like those who died from renal causes or complications. ‘Survivors’ were patients with normal renal function or chronic renal failure not requiring dialysis treatment.

The average survival time after biopsy was 85.0 ± 5.7 months (mean $\pm$ SD). The probability of maintaining a

residual renal function for at least 3 years after establishing the diagnosis was only 68%; it decreased to 51% after 5 years and 36% after 10 years (fig. 3). Only 52% of those who died suffered from end-stage renal failure. In 38% complications of uremia were the cause of death, most of the remaining patients (53%) died of hypertension, still having a sufficient residual renal function (for details see table 2). Complete remissions of the disease with normal urinary findings could be observed in 11 cases (5%); partial remission with normal renal function but persisting proteinuria and/or microscopic hematuria was found in 19 patients (8.6%) at least 5 years after biopsy.

Membranoproliferative Glomerulonephritis: Long-Term Prognosis

245

9 10 11 12 13 14 15 16 17

Follow-up, years

Fig. 4. Probability of maintaining renal function (survival curves) in MPGN type I according to the severity of glomerular lesions (1 = grade I, $n = 55$; 2 = grade II, $n = 68$; 3 = grade III, $n = 54$;

4 = grade IV, n = 25; 5 = grade V, n = 18). Significant difference with a more unfavorable prognosis only for grade V, MPGN with focal crescent formation ($p < 0.01$).

Follow-up, years

Fig. 5. Probability of maintaining renal function (survival curves) in MPGN type I according to the tubulointerstitial findings (1 = normal findings, n = 92; 2 = IF, n = 77; 3 = ARF, n = 32; 4 = ARF in combination with IF, n = 19). Significantly more unfavorable prognosis if tubulointerstitial alterations can be found ($p < 0.0002$); no difference in outcome between ARF and IF.

0 12 3 4 Follow-up, years

10 11 12 13 14 15 16 17

Fig. 6. Probability of maintaining renal function (survival curves) in MPGN type I according to the BP values during the follow-up period (1 = normal BP, n = 67; 2 = moderate hypertension, n = 95; 3 = severe hypertension, n = 34). Significant differences in prognosis corresponding to the BP level (p value = 0.0002; p 1–2 = 0.0001; p 1–3 = 0.0001; p 2–3 = 0.0045).

the difference is statistically significant (fig. 4). Ten years after biopsy the probability of maintaining renal function varies from 30 to 47% for grades I–IV, whereas 87% of the patients with grade V either died or needed dialysis treatment/kidney transplantation within the same period.

Tubulointerstitial Findings

The tubulointerstitial changes are of decisive significance for the outcome of the renal disease. In detail we found that patients with a normal cortical interstitium and normal tubules – 10 years after biopsy – still had sufficient or even normal renal function in 63% of cases, while this proportion decreased to 13 or 25%, respectively, in the presence of IF or ARF (fig. 5). The prognosis is particularly poor if there is ARF in addition to IF. In these cases all patients died within the first 5 years after biopsy or reached end-stage renal failure. The differences in survival probabilities between normal tubulointerstitial findings on one hand and IF and ARF on the other are highly significant in each case (fig. 5).

Glomerular Changes

The five different grades of glomerular changes were observed at varying frequency (fig. 4). Mean survival time does not depend on the severity of glomerular lesions, with the exception of grade V. The survival curves are close together for grades I–IV. Only for grade V the curve shows a much more unfavorable course of the disease;

Hypertension

MPGN is in a high percentage accompanied by severe arterial hypertension which proved difficult to control with drug treatment, thus probably explaining the high number of deaths related to elevated BP (table 2). At 1- to 2-month intervals BP was measured – usually in a sitting position – either by the family doctors or during ambula-

246

Schmitt/Bohle/Reineke/Mayer-Eichenberger/Vogl

90 80 70 60–50 40 30 20 10 0

10 11 12 13 14 15 16 17

0 1 2 3 4 5 6 7 Follow-up, years

Fig. 7. Probability of maintaining renal function (survival curves) in MPGN type I according to the serum creatinine concentration at the time of biopsy (1 = creatinine < 1.3 mg/dl, n = 96; 2 = creatinine 1.4–2.0 mg/dl, n = 60; 3 = creatinine 2.1–5.0 mg/dl, n = 44; 4 = creatinine > 5.0 mg/dl, n = 13; 5 = renal failure requiring dialysis treatment, n = 7). With increasing creatinine concentration the prognosis becomes more unfavorable ($p < 0.0002$); no significant difference between groups 3 and 4.

tory visits to the hospital. The patients were divided up into three groups according to the BP level: group 1 -normal BP values during the complete observation period (diastolic BP < 90 mm Hg, systolic BP $\leq$ 140 mm Hg); group 2 – long-term mild to moderate hypertension (diastolic BP 91–110 mm Hg, systolic BP 141–180 mm Hg). Group 3 – long-term severe hypertension (diastolic BP $\geq$ 110 mm Hg, systolic BP $\geq$ 180 mm Hg). ‘Long-term’ means that the above-mentioned values could be found in the same patient for more than half of the follow-up period. Renal functional outcomes and survival rates were examined using this classification. The long-term prognosis of MPGN becomes considerably worse, if elevated BP values are measured; highly significant differences are found among the survival curves of the various groups (fig. 6). Twenty-six percent of the patients with mild to moderate hypertension (group 2) and 59% of those with severe hypertension (group 3) died within 10 years after biopsy. This proportion merely amounts to 15% for patients with normal BP (group 1). Furthermore, a progressive deterioration in renal function is observed parallel to the degree of BP elevation. Renal outcome, however, is rather favorable in MPGN without hypertension: after 10 years only 14% of the patients with normal BP suffer from end-stage renal failure, on the other hand almost two thirds (64%) still have a creatinine below 1.3 mg/dl.

Table 3. Correlation between tubulointerstitial findings and creatinine/BP level at the time of biopsy

ARF+IF

ARF

Normal IF

Creatinine, mg% 1.0 ± 0.2 $2.7 \pm 2.1^{**}$ $3.1 \pm 2.8^{**}$ $4.3 \pm 2.6^{**}$

BP, mm Hg

Systolic 147 ± 24 $170 \pm 28^{**}$ $172 \pm 28^{**}$ $178 \pm 26^{**}$

Diastolic 92 ± 15 $103 \pm 16^{**}$ $99 \pm 15^*$ $101 \pm 22^*$

With IF and/or ARF the creatinine and BP values are significantly elevated (t test). * $p < 0.01$;

** $p < 0.001$, versus normal.

Creatinine

At the time of biopsy patients with MPGN relatively often (in 44% of cases) have normal serum creatinine concentrations, even when glomerular changes are severe. The proportion with normal creatinine, however, decreases to 23% after a 5 year course, and then remains almost constant at 17% up to the 10th year. These 17% represent the few patients with complete remission of the disease and those patients with still pathological urinary findings (proteinuria/hematuria) but without remarkable impairment of renal function (creatinine < 1.3 mg/dl). If the serum creatinine was above 1.3 mg/dl at the time of biopsy, there was a marked tendency toward a further increase during the course of the disease, clearly shown by significant differences among the survival curves in figure 7. There is a close relationship between the level of serum creatinine or hypertension on one hand and the tubulointerstitial findings on the other. If cortical interstitium and tubules revealed no pathological findings, then BP and creatinine values lay

within the normal range, whereas they were significantly elevated in the presence of IF and/or ARF (table 3) [19].

Proteinuria

High proteinuria leading to nephrotic syndrome is often found in MPGN already in the early stages. In 36% of the patients it amounted 3–6 g/day, and in 40% more than 6 g/day at the time of biopsy. In the later course of the disease proteinuria generally decreased significantly. At the same time, the number of patients who had to be treated with dialysis, and therefore were oliguric or anuric, increased considerably. As a result of low diuresis protein loss via urine is low too in these patients. The degree of proteinuria has no prognostic significance; even patients with a nephrotic syndrome (n = 161) did not have a poorer prognosis compared to those without ne-

Membranoproliferative Glomerulonephritis: Long-Term Prognosis

247

phrotic syndrome (n = 51) (fig. 8), nor was there any difference between the two groups in duration of the disease before biopsy (25.4 and 20.4 months, respectively; median value 10 months in both groups).

Hematuria

Urine erythrocyte count was performed in a semi-quantitative manner according to the following classification: 1 = negative: 5.6%, 2 = less than 20 erythrocytes/ μ l: 27.9%, 3 = 20–50 erythrocytes/ μ l: 34.0%, 4 = more than 50 erythrocytes/ μ l: 28.8%, and 5 = gross hematuria: 3.7%. Gross hematuria is only seldom found at clinical manifestation of MPGN. Almost as rare are patients in whom no erythrocytes can be observed in the urinary sediment (5%). Microscopic hematuria of varying degrees makes up the overwhelming majority of pathological findings (91%). This was still demonstrable even 10 years after biopsy in more than half of the patients. The course of MPGN was influenced neither by microscopic nor by gross hematuria (p value among the survival curves = 0.70).

Complement

We got sufficient data concerning the complement components C3 and C4 only in a small number of cases. Thus an assessment of the prognostic significance of these parameters was not possible in the material available.

Drug Therapy

In the numerous centers participating in our study the treatment regimens (antiphlogistics, immunosuppressive agents, corticosteroids, etc.) were quite different and were also frequently modified depending on relapses and remissions. From this heterogeneous material it was difficult to derive statistically utilizable data on the efficacy of drug treatment: 42.6% of the patients did not receive any immunosuppressive and/or antiphlogistic treatment; the remaining 57.4% either got prednisone, indomethacin, azathioprine or cyclophosphamide or a combination of two/three of these drugs. The duration of the therapy was on average 28.3 months (range 2–204 months). Improving or at least stable renal function was observed in 41.3% in the therapy group compared to 39.5% in the group without treatment; in 58.7 and 60.5%, respectively, renal function gradually deteriorated during the observation period. No difference could be found between the survival rates in both groups (p = 0.547; fig. 9). We, furthermore, analyzed the data of two subgroups: (1) nonaggressive treatment with corticosteroids and/or indomethacin

Fig. 8. Probability of maintaining renal function (survival curves) according to the presence or absence of a nephrotic syndrome in MPGN type I (1 = nephrotic syndrome, n = 161; 2 = no nephrotic syndrome, n = 51). No significant difference between the two groups.

Fig. 9. Drug therapy: Probability of maintaining renal function (survival curves) for treated and untreated patients in MPGN type I (1 = immunosuppressive and/or antiphlogistic therapy, n = 109; 2 = no therapy, n = 81). No significant difference between the two groups.

(53% of the patients) and (2) aggressive treatment including azathioprine or cyclophosphamide in addition to corticosteroids and/or indomethacin (47% of the patients). Statistical evaluation shows a slight tendency -however not reaching significance – towards a better outcome for patients with nonaggressive treatment ($p = 0.091$). One patient died due to a therapy-induced complication (septicemia following bone marrow toxicity of azathioprine).

248

Schmitt/Bohle/Reineke/Mayer-Eichenberger/Vogl

Discussion

The results of our investigation on 220 patients (95% adults, 5% children) with MPGN type I confirm that the long-term prognosis of this disease is generally unfavorable, though in a given case it may be variable. Within 5 years after biopsy 49% of the patients had died or needed regular dialysis treatment/had received a kidney transplant; this proportion increased to 64% after 10 years (fig. 3). Our results are in agreement with those of other authors who have reported similar survival rates with smaller numbers of cases [1–3, 5–10, 12, 13, 16], mostly including many children as well as cases with MPGN type II [1–3, 5–9, 12]. Only Barbiano di Belgiojoso et al. [4] got more favorable results with a 70% probability of maintaining renal function after 10 years. In contrast, in the studies published by Kincaid-Smith [10] and Mandel-anakis et al. [11] 50% of patients had already died or reached end-stage renal failure after 3 years. Our data suggest that the prognosis of MPGN is essentially determined by tubulointerstitial findings in the renal cortex (fig. 5). The outcome is comparably favorable, if the tubules and the cortical interstitium appear normal in histology. Ten years after biopsy 63% of these patients still have a nearly normal renal function or have chronic renal failure not requiring dialysis treatment (fig. 5). If, however, the tubulointerstitial system is altered at the time of biopsy, either by IF or ARF, then the probability of maintaining renal function decreases from 40% after 5 years to about 20% after 10 years. With ARF in addition to IF all patients either die or reach end-stage renal failure within 5 years from biopsy. This relationship between tubulointerstitial changes and prognosis has not been noted previously for MPGN. Merely in an abstract [22] a strong correlation has been described between an interstitial chronicity index (a measure for IF and tubular atrophy) and the progression of renal damage; 7 patients could be followed up for 40 months. There is, on the other hand, from our results no evidence that the long-term prognosis of MPGN type I is affected by the severity of glomerular changes – with the exception of grade V (fig. 4). The fact that glomerular lesions are not significant for the course of the disease is also shown by earlier studies [1, 7, 8]; only Barbiano di Belgiojoso et al. [4] found a poorer prognosis for lobular glomerulonephritis which corresponds to our grade IV. Even though we observed an unfavorable influence of focal crescent formation (grade V) on the course of MPGN – as other authors before us [1, 2, 4, 7, 8, 10], we still do not believe that the crescents cause the progression of the disease; rather we

suspect that in these cases the almost obligatorily present tubulointerstitial lesions determine the outcome [19]. Among clinical parameters hypertension and an elevated serum creatinine concentration at the time of biopsy are of prognostic significance. Both show a statistically significant correlation to the tubulointerstitial damage, thereby explaining the influence on the course of MPGN (fig. 6, 7; table 5). More than half of the deaths resulted from hypertension (table 2); this appears to be remarkable since hypertension can usually be controlled by therapy. The variable control of BP seems to be caused by a more or less severe course of the underlying renal disease. Despite clear results provided for the patients studied here the significance of hypertension is a matter of controversy in the literature and has until now been underestimated. Some authors mention this important point [1, 3, 5, 10], others leave it out of consideration [2, 7, 8, 13]. With regard to essential hypertension the benefit of a systematic lowering of the BP has been shown in controlled trials [23–26]. Data on the effect of systematic antihypertensive treatment on renal function, hypertensive cardiovascular complications, and mortality in renoparenchymatous hypertension, however, are not available. The negative influence of an elevated serum creatinine concentration at the time of biopsy on the further course of the disease is beyond dispute [1–5, 7, 8, 10]. However, our results contradict the published data for the nephrotic syndrome. In the first few years the outcome seems to be poorer for patients with nephrotic syndrome; subsequently this difference completely disappears, so that the prognosis after 12 years is almost identical for patients with and without nephrotic syndrome. We are not able to provide an explanation for this discrepancy with the studies of other authors who have found the nephrotic syndrome to be associated with a less favorable prognosis. In previous investigations no correlation could be seen between the frequency and the severity of hypocomplementemia on one hand and the progression/remission of MPGN on the other [1, 4–6, 10, 12, 13, 16]. In a study of 40 patients Swainson et al. [2], however, found a lower survival rate in hypocomplementemic as opposed to normocomplementemic MPGN. We cannot contribute any results of our own on this subject. It is still uncertain whether, and to what extent, a therapy of MPGN type I, i.e. influencing the immunological process, alters the outcome of this disorder. Many authors believe that treatment with corticosteroids, azathioprine or cyclophosphamide does not result in an improvement of the prognosis. On the contrary, they are afraid of severe therapy-induced complications and con-

Membranoproliferative Glomerulonephritis: Long-Term Prognosis
249

sider the possible benefits to be less significant than the dangers [1, 2, 5–9, 12]. This attitude caused Cameron et al. [1] to neglect the influence of treatment completely in their study (104 cases, 69 of which type I). Interpretation of our own data is difficult as this study is retrospective and therapy regimens were therefore not standardized in the participating centers. Generally antiphlogistic and/or immunosuppressive treatment does not seem to improve the prognosis of MPGN type I; there was no difference in the survival rates between treated and untreated patients. On the contrary, we observed a tendency (not significant) towards a better outcome for moderate drug therapy with prednisone and/or indomethacin only; worse results were found for aggressive therapy including azathioprine or cyclophosphamide. A possible explanation might be that patients with a rapid progression of the underlying disease were treated more intensively compared to those with a benign spontaneous course who did not receive immunosuppressive agents at all.

Nevertheless, it should be mentioned that there have also been many reports about successful treatment of MPGN. Particularly impressive are the results of Kincaid-Smith [10], who achieved a significant improvement in survival rate within 30 months: she treated 16 patients with impaired renal function, with nephrotic syndrome and in part also with hypertension, and compared them to a control group of 13 patients with on average equally severe illness. The treatment consisted of a combination of cyclophosphamide, dipyridamole and warfarin. Not only the clinical parameters improved thereby, but even the histological changes were regressive in control biopsies. The favorable effect of this therapy has, however, not been confirmed by others [1, 5, 27]. Thus Cattran et al. [27] were not able to find any influence on the natural course of the disease in a recently published controlled study exactly using the treatment regimen recommended by Kincaid-Smith [10]. On the other hand, Zimmerman et al. [28] and Donadio et al. [29] observed an improvement of the prognosis merely by simultaneous administration of warfarin/dipyridamole or dipyridamole/acetylsalicylic acid, without cyclophosphamide. Good results were also achieved with indomethacin [30, 31] or an alternate-day steroid treatment [32]. Finally McGinley et al. [33] reported a favorable influence of plasma exchange in the treatment of MPGN.

None of these measures, however, have been generally accepted. If treatment is not considered as in the study by Cameron et al. [1], then the histological criteria of IF and ARF – either alone or in combination – proved to be

highly significant for the prognosis. They determine an unfavorable course of the disease. The clinical correlates to these tubulointerstitial changes are represented by an elevation in serum creatinine and hypertension, whereas the primarily glomerular parameters of proteinuria, nephrotic syndrome, and hematuria – according to our results – do not have a significant prognostic value. Thus, in MPGN type I a relevant prediction of the expected outcome can already be made on the basis of renal biopsy.

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250

Schmitt/Bohle/Reineke/Mayer-Eichenberger/Vogl

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