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The Therapy of Rapidly Progressive Glomerulonephritis

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Summary. Of 30 therapy studies which distinguish between improved and non-improved renal function, 350 patients with rapidly progressive glomerulonephritis (RPGN) were evaluated. Pure descriptions of cases were not included. The cases of RPGN were divided into autoantibody-induced and non-autoantibody-induced groups. This latter group was subdivided into idiopathic and symptomatic RPGN. A further distinction was drawn between the different forms of symptomatic RPGN, but no separate evaluations were made, on account of the small numbers of cases. Therapies were divided into immunosuppression, anticoagulant therapy, pulse therapy, and therapeutic plasmapheresis. In autoantibody-induced RPGN, improved renal function was evidenced in only five cases out of 27. In contrast to this, 66% of the non-oliguric patients with creatinine levels >6 mg/dl showed improved renal function after plasma separation. In non-autoantibody-induced RPGN, the least favourable results were shown by anticoagulant treatment, where improvement in renal function was produced in only 34% of the cases treated, and haemorrhagic complications occurred in 25%, about half of which had a fatal outcome. Under pulse therapy, 27 out of 38 patients (71%) showed improvement, as against 59 out of 93 (63%) under plasmapheresis. In contrast to the situation in autoantibody-induced RPGN, it is possible in non-autoantibody-induced RPGN to achieve therapy-induced improvement also in a high percentage of cases where terminal renal insufficiency is present, and even when dialysis treatment has just been commenced. The collected statistics for therapeutic results achieved in RPGN are compared and contrasted with two controlled studies which showed diverging findings.

Key words: Rapidly progressive glomerulonephritis (RPGN) – Goodpasture's syndrome – Immunosuppression – Anticoagulant therapy – Pulse therapy – Plasmapheresis

Introduction

The swift and usually dramatic course of rapidly progressive glomerulonephritis (RPGN), with, until recently, a lethality of 90% within 12 months, justifies the substantial cost of treatment.

Interest in the therapy of this disease seems much greater than would be expected from its comparatively rare occurrence. Our increasing knowledge of the disease-triggering immunological processes taking place at the commencement of a glomerulonephritis and of the inflammatory processes these induce is opening up a number of new avenues for therapy. Chronic glomerulonephritis (GN), which is much more common, has a slower course, and the reasons why it is chronic are less easily understood; it is certainly not so suitable for therapy studies.

It is therefore understandable that it is hoped to be able to use information gained in the treatment of RPGN, with its much faster course, for the benefit of therapies for chronic GN. The fact that RPGN is not a single disease entity is however a limitation here. It is also not clear whether the renal changes which occur in systemic immune diseases, which can run their course in both RPGN and other glomerulonephritides, may have a common cause. On present knowledge it is probable that several basic immunological principles play a role in the genesis of all glomerulonephritides. Whether any successes which may be achieved in the treatment of RPGN can be transferred to treating other forms of glomerulonephritis is a question which it is certainly very difficult, and at present probably still impossible to answer. Thus the utility of the present forms of therapy for RPGN will be discussed at first separately.

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Reasons for Presently Used Forms of Therapy

The therapy of RPGN rests in many cases on theoretical considerations, which themselves are based on pathogenetic knowledge. Some forms of therapy have been adopted from forms of treatment which seemed effective in other immunological diseases.

Immunosuppressive Drugs

Treatment with ACTH and glucocorticosteroids alone was first used over 30 years ago, initially in primary glomerulonephritis with nephrotic syndrome with the idea that this would succeed in suppressing a hyperimmune reaction. In RPGN this treatment remained unsuccessful. More favourable results were reported in various glomerulonephritides by supplementing this treatment with cytostatically effective substances. Cytostatically effective substances, alone or in combination with glucocorticosteroids, were initially also used with the same idea of being able to suppress a hyperimmune reaction. Nowadays, however, many authors assume that the precipitating cause of glomerulonephritis is an immune deficiency: it is supposed that immunosuppressive drugs have a stronger effect on the T-lymphocytes, which act as mediators, than on the B-lymphocytes, and that this can result in renormalisation of the pathologically disturbed immune system (Saxon et al. [28]). Particularly the sometimes highly favourable results reported from treatment with steroids and cytostatics for Wegener's granulomatosis and for SLE have been able to be attributed to a modulation of the immune system. However, the effects of applying this therapy to idiopathic RPGN have so far been disappointing.

Anticoagulants

Almost regularly, fibrin, fibrinogen and also fibrin-related antibodies can be detected in the glomerular capsule space by immunofluorescence microscopy in RPGN. Electron microscopy has shown fibrin in a portion of the cells which form the crescents, mainly in the phagocytes. Fibrin degradation products were found in the urine. These findings are used today to justify the use of anticoagulants, although their use was originally based on finding intracapillary fibrin clots. Treatment with heparin or coumarin derivatives is often used in conjunction with other forms of therapy, especially immunosuppression. Only a few case-histories of treatment with ancrod have been reported.

Pulse Therapy

Pulse therapy, that is the administration of 1–3 g prednisolone or methylprednisolone per day for 3–7 days, is a method taken from therapy for rejection after kidney transplantation. This therapy is mainly used in cases of cellular rejection: it is less successful in cases of vascular rejection. The lymphocyte infiltrates of the kidney rapidly recede under this treatment. The mechanism by which it acts in RPGN is still largely unexplained. In RPGN, pulse therapy is usually applied after low-dosage oral glucocorticosteroid treatment, or it may be given together with immunosuppressive therapy. If the treatment is successful, the diuresis and clearance usually rise within a few days (24–48 h).

Therapeutic Plasma Separation

Therapeutic plasma separation was initially used for treating the antibasal membrane antibodies in glomerulonephritis of Goodpasture type or in Goodpasture's syndrome. It succeeds in rapidly removing the antibodies which are attacking the glomerular basal membranes (anti-GBM antibodies) from the plasma. Repeated treatments are needed before complete removal is achieved. The re-forming of anti-GBM antibodies is prevented by administering immunosuppressants at the same time. This treatment has since been much used in glomerulonephritides not induced by autoantibodies. The original intention was to remove circulating immune complexes from the plasma. It has since been found that, under plasmapheresis, the previously suppressed activity of the reticulo-histocytary system increases. The possibility of immune modulation taking place by a feedback mechanism through withdrawal of immunoglobulins and the resultant stimulation of B-cells and T-cells, and of increased receptiveness of the immune system to concurrent or subsequent immunosuppressive therapy, are being discussed. Furthermore it is possible that this treatment becomes effective through the removal of fibrinogen, through the administration of heparin, or possibly by the contact with plastics. The fact that RPGN has been observed to improve also under dialysis treatment could support the last-named supposition.

Evaluation of the Literature

The object of this paper is to critically evaluate the existing therapeutic results available for RPGN and if possible to draw up therapeutic guidelines. The majority of the publications are anecdotal reports, which are not suitable for this particular

purpose. Only 30 of the reports quote both successful and unsuccessful cases of therapy. There have to date been no controlled studies providing substantiated information for RPGN (Table 1).

In evaluating the therapeutic results the following three main difficulties arise:

1. The majority of the studies do not distinguish between the various different forms of RPGN.
2. The schemes of treatment adopted are not easily comparable.
3. The selected treatment was frequently not consistently adhered to and carried through.

A further problem is that precise information about the spontaneous course of the various forms of RPGN, which would be necessary for comparison, is difficult to find.

The Spontaneous Course

Cameron [11] has summarised the information from several investigators regarding the spontaneous course of RPGN. They all agree in quoting a rapid decrease in survival time during the first few months. There were however differences in the percentage of patients in whom renal insufficiency first occurred after several years' course (maximum 5 years) of the disease. No cases of spontaneous remission were observed. Although, of all patients, more than 70% showed extracapillary crescent formations in the glomerula, it is not clear how many children or patients with intracapillary proliferations were contained in the groups. The number of glomerular biopsies taken, to which the figure "70%" relates, is also not clear.

An analysis of the spontaneous course separately for the various different forms of RPGN was needed, to correspond to the same subdivisions selected for the therapy groups.

Autoantibody Induced RPGN. The demonstration by Lerner et al. [18] of anti-GBM antibodies in Goodpasture's syndrome made it possible to separate this syndrome from other rapidly progressive glomerulonephritides with pulmonary haemorrhages, which are found not infrequently in SLE and Wegener's granulomatosis, and which have also been found in other forms of RPGN.

The prognosis for anti-GBM antibody mediated RPGN with definite evidence of linear deposits of IgG on the basal membrane and raised anti-GBM antibody titre in the plasma is extremely unfavourable. The patients usually die within a few weeks or months after diagnosis, from pulmonary haemorrhage (present in about 70% of the cases) or from renal insufficiency. Of 32 patients, 26 reached end-stage renal failure within 12 months (mean course 2.5 months) [35]. Spontaneous recovery was only observed in a few patients with primarily milder and clinically nonprogressive glomerulonephritis (Table 2).

Idiopathic RPGN (Non-autoantibody-Induced). The spontaneous course of idiopathic RPGN appears less favourable in adults than in children. The prognosis shows a very close correlation with the percentage of glomerula affected and with the extent of the extracapillary crescent formations. If more than 70% of the glomerula show extracapillary crescent formations and if these crescent formations include more than 50% of the glomerular circumference, then the spontaneous remission rate is less than 10% [11]. Usually there is no, or very little, intracapillary proliferation. Patients with pronounced intracapillary proliferation are though to have a better prognosis, according to the study by Morrin et al. [22]. The objection must however here be raised that the RPGN in these patients could have been of post-streptococcal type, even though no streptococcal infection and no elevated antistreptolysis titre were found.

Symptomatic RPGN (Non-autoantibody-Induced). This group includes a variety of diseases: (1) Post-Streptococcal RPGN, (2) Systemic lupus erythematosis, (3) Panarteritis nodosa, (4) Wegener's granulomatosis, (5) Schönlein-Henoch purpura, (6) Infectious endocarditis, (7) Polyclonal cryoglobulinaemia.

It is understandable that in the relatively rare diseases, which nowadays are also all given therapy, there are no longer any large numbers of cases showing the spontaneous course of the individual subgroups. It has been assumed that, for histological changes in the glomerula of equal extent, the prognosis for the various symptomatic RPGN would be the same as for idiopathic RPGN [11]. A more favourable spontaneous prognosis has been assumed for post-streptococcal RPGN with extensive intracapillary proliferations. Schreiner et al. [31] quote 66% spontaneous remissions of the cases they observed. The extent of the extracapillary crescent formations was however small in their collective of patients.

Even though there is no uniform data available on the spontaneous course of extracapillary glomerulonephritis, it can be assumed in this study that, after 1 year, certainly less than 30% of the patients and probably only around 10% will still have adequate renal function, and that spontaneous remission is not statistically important.

Table 1. Summary of the therapeutic results taken from the literature

a) Autoantibody-induced RPGN

n	Therapy[a]								Duration of therapy	Improved	Max. length of observation	Age <15 y.	<50% crescents	Raised AST	Creatinine-cl.		Side effects 1) haematol. 2) haemostas. 3) infection 4) gastro-intest. 5) hepatic	Literature
	C	A	G	H	W	D	P	Pl							<5 ml/min	improv.		
3		×	×						−22 mo.	−	−22 mo.	−	−	−	−		−	[32] 1977
24		×	×	×		×			−14 d.	5	− 5 y.	1	9	−	−			[3] 1977
7	×	×	×					×	2 mo.	3	−16 mo.	−	−	−	−			[19] 1976
4	×		×				×	×	−13 mo.	2	−13 mo.	−	1	−	−		(3)=1	[16] 1978
4	×		×		×	×		×	−221 d.	3	−15 mo.	−	2	−	−			[21] 1979
1	×	×	×	×	×			×	40 d.	1	9 mo.	−	−	−	−			[2] 1980
2	×	×	×					×	?	1	?	−	−	−	1	−	(3)=1 fatal=1	[13] 1981
2		×	×					×	?	−	?	−	−	−	−		−	[34] 1982
5		×	×					×	?	2	?	−	−	−	−			[5] 1982
44	×	×	×					×	2 mo.	16	− 6 y.	+	−	−	27	1	(3)=3 fatal=3	[26] 1982

b) Non-autoantibody-induced RPGN. Idiopathic RPGN

8	×	×	×						?	5	−43 mo.	−	−	3	3	2		[15] 1974
15	×	×	×						−56 mo.	7	−56 mo.	−	−	−	−		(2)=1 fatal=1	[32] 1977
3		×	×	×	x	×			−45 d.	2	− 6 mo.	−	−	−	1	1	(2)=3	[1] 1972
3		×	×	×		×			− 5 w.	3	− 5 w.	−	−	−	−		(2)=3	[25] 1973
2	×	×	×	×	×	×			−33 mo.	2	−33 mo.	−	−	−	1	1	−	[8] 1974
14		×	×	×		×			−17 w.	1	−17 w.	−	−	−	−		(2)=5	[30] 1976
1		×	×	×		×			21 mo.	−	21 mo.	−	−	−	−		(4)=1	[4] 1981
29	×	×	×	×					−21 mo.	10	− 8 y.	−	−	4	−		(3)=4, (4)=1 (5)=1, fatal=6	[22] 1978
8	×		×	×					2 mo.	1	22 mo.	−	−	−	−			[27] 1980
87			×				×		16 w.	4	−24 mo.	−	−	−	−		(2)=1 fatal=1	[6] 1979
10			×				×		−21 mo.	4	−21 mo.	−	−	−	−		−	[23] 1979
5			×				×		4 w.	5	−36 mo.	−	−	−	−		(3)=1 fatal=1	[24] 1980
9	×		×				×		−7 mo.	7	12 mo.	−	−	−	−		(3)=1	[9] 1981
2		×	×	×		×		×	−100 d.	−	−100 d.	−	−	−	−			[2] 1980
4	×	×	×					×	?	3	?	−	−	−	2	1	(3)=1 fatal=1	[13] 1981
6		×	×					×	?	4	?	−	−	1	−		(1)=2 (3)=2	[34] 1982
2		×	×					×	?	2	?	−	−	−	−		−	[34] b
3		×	×					×	?	2	?	−	−	−	−			[5] 1982
3	×	×	×					×	−12 mo.	2	?	(+)	−	−	−			[14] 1983
6	×		×	×			×	×	2 mo.	4	22 mo.	1	−	−	−			[27] 1980
8	×		×					×	− 7 mo.	4	12 mo.	−	−	−	−		(3)=5	[9] 1981
9	×		×					×	?	4	−40 w.	−	−	−	5	1	(1)=1, (3)=1 fatal=2	[20] 1977

Table 1 (continued)

c) Non-autoantibody-induced RPGN. Symptomatic RPGN

n	Therapy								Duration of therapy	Improved	Max. length of observation	Age <15 y.	<50% crescents	Raised AST	Creatinine-cl.		Side effects 1) haematol. 2) haemostas. 3) infection 4) gastro-intest. 5) hepatic	Literature
	C	A	G	H	W	D	P	Pl							<5 ml/min	improv.		
S.L.E.																		
7		×	×						−68 mo.	2	−68 mo.	−	−	−	−		(3)=2 fatal=2	[32] 1977
4	×	×	×	×	×	×			−33 mo.	2	−33 mo.	−	−	−	2		−	[8] 1974
4	×	×	×				×		−19 w.	4	− 3 y.	−	−	−				[12] 1978
3	×	×	×					×	?	2	?	−	−	−	2	1	−	[13] 1981
1		×	×					×	?	1	?	−	−	−	−		−	[34] 1982
5		×	×					×	?	2	?	−	−	−	−			[5] 1982
Panarteritis nodosa																		
4	×		×						−20 mo.	2	−20 mo.	−	−	−	−		(3)=1 fatal=1	[32] 1977
3			×						?	−	?	−	−	−	−			[7] 1982
1		×	×	×					5 d.	−	5 d.	−	−	1	−		(2)=1 fatal=1	[1] 1972
1		×	×	×		×			− 5 w.	−	− 5 w.	−	−	−	1	−	(2)=1 fatal=1	[25] 1973
2	×	×	×	×	×	×			−33 mo.	−	−33 mo.	−	−	−	2	−	(2)=1	[8] 1974
3							×		?	3	?	−	−	−	−			[7] 1982
5		×	×					×	?	5	?	−	−	1	−		(3)=1	[34] 1982
7	×	×	×					×	−12 mo.	3	?	(+)	−	−	7	3		[14] 1983
Wegener's granulomatosis																		
3		×	×						− 6 mo.	2	− 9 y.	−	−	−	−			[36] 1982
4	×	×	×					×	?	3	?	−	−	−	3	2		[13] 1981
1		×	×					×	?	1	?	−	−	−	−			[5] 1982
17	×	×	×					×	−12 mo.	12	?	(+)	−	−	17	12		[14] 1983
Schoenlein-Henoch																		
2			×						−44 mo.	1	−44 mo.	−	−	−	−		−	[32] 1977
1		×	×	×	×				126 d.	1	10 mo.	−	−	−	1	1	(2)=1	[1] 1972
1		×	×	×		×			− 5 w.	1	− 5 w.	−	−	−	1	1	(2)=1	[25] 1973
2		×	×	×	×	×			−33 mo.	1	−33 mo.	2	−	−	1		(2)=1	[8] 1974
1		×	×	×	×	×			18 mo.	?	18 mo.	1	−	−	−			[10] 1975
2	×							×	68 d.	2	68 d.	−	−	−	−			[17] 1981
1		×	×					×	?	−	?	−	−	−	−			[5] 1982
GN with cryoglobulinaemia																		
1			×	×					11 d.	−	11 d.	−	−	−	1		(2)=1	[1] 1972
1		×	×	×		×			− 5 w.	1	− 5 w.	−	−	−	1	1	(2)=1 fatal=1	[25] 1973

[a] C=cyclophosphamide, A=azathioprine, G=glucocorticosteroids, H=heparin, W=warfarin, D=Dipyridamole, P=pulse prednisolone, Pl=plasmapheresis

Table 2. Evaluation of the therapeutic results in autoantibody-induced RPGN

	Patients treated	Improved n	%	Confidence limit %	Fatal compl.
Without therapeutic plasmapheresis	27	5	18	6–38	
With therapeutic plasmapheresis	69	28	41	29–53	4
Non-oliguric patients >6 mg/dl creatinine	41	27	66	49–80	

Therapy Studies

Since in most of the 30 therapy studies since 1972 no distinctions were drawn between the various different forms of RPGN, the cases have been divided into the categories "autoantibody-induced RPGN", "idiopathic RPGN" and "symptomatic RPGN". The category "symptomatic RPGN" was then subdivided into the individual forms of disease.

The reports were only included in the evaluation when the following conditions were fulfilled:
1. The clinical course must correspond to the clinical picture of a rapidly progressive glomerulonephritis.
2. Histologically at least 50% of all glomerula must show crescent formations. Post-streptococcal glomerulonephritides and cases with pronounced intracapillary proliferation were excluded so far as they could be recognised. Papers with already selected patients were not included [33].

The following factors were included in the evaluation: duration of therapy, number of cases treated, number of responders, and maximum duration of observation.

As far as the data permitted, patients with a glomerulum filtrate of less than 5 ml (if not stated, serum creatinine <6 mg/dl) were additionally evaluated as a separate group.

Autoantibody-induced RPGN (of Goodpasture Type, or Goodpasture's Syndrome). In the literature evaluated here, there were few cases which were *not* treated by therapeutic plasmapheresis. These cases were collected into a single group of 27 patients, of whom the therapy applied only produced improvement in five cases. In nine of the 27 patients, less than 50% of the glomerula were attacked by extracapillary crescent formations. Taking the statistical confidence limits into account, the prognosis under treatment would be no better than the spontaneous course, if a spontaneous remission rate of around 10% were to be postulated. In the light of these unfavourable results, it is understandable that before the advent of plasma separation, Goodpasture's syndrome was treated by bilateral nephrectomy, almost in despair, to control the pulmonary haemorrhages.

The decisive turning point in the prognosis for this disease only occurred when therapeutic plasmapheresis was introduced [19]. Of 69 patients receiving this treatment, renal function was improved in 28 cases, sometimes with full normalisation of the clearance. At serum creatinine levels <6 mg/dl, particularly in oligo-anuric patients, improvement of renal function can no longer be expected [14]. When renal function has deteriorated to this extent, then in autoantibody-induced RPGN the proportion of glomerula affected by extracapillary crescents is 98%, that is, substantially higher than the proportion of around 70% found in non-autoantibody-induced RPGN. In Goodpasture's syndrome at this stage, only 0.5% of the glomerula show no changes at all [14]. If, from the total number of cases, those cases are subtracted in which, on present-day knowledge, plasmapheresis could not be expected to have produced any improvement, then improvement was produced in 27 of the remaining 41 cases. Rapid improvement of the pulmonary haemorrhages can be expected even in cases where the renal function can no longer be improved.

The long-term prognosis cannot yet be finally estimated at the present time. Even where renal function has not been fully restored, periods of up to 5 years with creatinine levels at a raised but constant level [14] have been observed. There are scarcely any reports of changes in the morphological findings after the treatment. Despite improvement of the renal function, we have found evidence of linear IgG deposits many months later in one case. Therapeutic plasmapheresis should if possible be performed once a day until the anti-GBM antibodies have disappeared from the plasma. Initial unsuccessful cases are probably attributable to the treatment not having been sufficiently fully applied.

The concurrent immunosuppressive treatment should preferably be started with cyclophosphamide, because of its immediate effect, and then changed over to azathioprine. The high glucocorticosteroid dosage given right from the start should be successively reduced.

Table 3. Evaluation of the therapeutic results in non-autoantibody-induced RPGN

Therapy	Idiopathic RPGN					Symptomatic RPGN					Idiopathic + symptomatic RPGN				
	Cases	Improved	%	Confidence limit 95%	Fatal comp.	Cases	Improved	%	Confidence limit 95%	Fatal compl.	Cases	Improved	%	Confidence limit 95%	Fatal compl.
Immunosuppression	23	12	52	31–73	1	18	7	39	17–64	3	41	19	46	36–62	4
Anticoagulants	60	19	32	20–45	6	15	7	46	21–73	3	75	26	34	24–46	9
Pulse-therapy	31	20	64	45–80	2	7	7	100	56–100	2	38	27	71	54–84	4
Plasmapheresis	47	28	60	44–74	3	46	31	67	52–80	0	93	59	63	53–73	3

Non-autoantibody-Induced RPGN (Idiopathic and Symptomatic RPGN). Since there is to date no difference in the therapeutic principles applied for idiopathic and for symptomatic RPGN, both these forms will be discussed and compared with one another under a single heading. The results were evaluated, even when used in combination with other therapies, according to the four most important forms of treatment:

1. Immunosuppression alone (cytostatically acting substances and glucocorticosteroids);
2. Therapy with anticoagulants (heparin, coumarin derivatives, and platelet aggregation inhibitors);
3. Pulse therapy;
4. Plasmapheresis.

These categories were not further subdivided, because the resultant subgroups would have been too small and no longer comparable. Table 3 shows the results of treatment for idiopathic and symptomatic RPGN, separately and combined together. Even if the comparison is made with the most favourable spontaneous remission rates, the figures show clearly that all the forms of treatment improve the prognosis. Grouping the figures for idiopathic and for symptomatic RPGN together, the proportion of cases showing improvement is lowest for the anticoagulant treatments, while in this group the proportion of fatal complications due to haemorrhage is highest. Treatment results for the pulse therapy and for therapeutic plasmapheresis are substantially better than for all the other groups. In all seven patients with symptomatic RPGN who were treated with pulse therapy, renal function improved. However, these figures, particularly after taking the statistical confidence limits into account, still do not allow any superiority of these methods of treatment over plasmapheresis to be inferred.

Rifle et al. [27] compared pulse therapy and plasmapheresis in a controlled study for two groups of seven patients each. Both groups were given pulse therapy at 15 mg/kg/day for two periods each of 3 days. The patients also received glucocorticosteroids, cyclophosphamide and heparin. Of the group who also received plasmapheresis treatment, a significantly higher number of patients was able to be released from dialysis treatment. In the plasmapheresis group, the mean clearance rose from 5.9 to 48 ml/min, whereas in the control group it rose from 2.5 to 9 ml/min. As the authors themselves point out, these numbers of patients are still too small for certainty.

The improvement in renal function produced by the various therapeutic methods was often maintained for a number of years. It was not possible to evaluate the duration of the improved condition as a function of the different forms of therapy, because pulse therapy and plasmapheresis only started to be used at a much later date than the other methods.

It was also not possible to answer the question of how long immunosuppressive treatment should be continued once it has commenced producing successful results. Cases of a maintained improvement despite discontinuation of the therapy have been observed, as have other cases of rapid deterioration on discontinuation. The medication should therefore only be reduced slowly and under sensitive and comprehensive monitoring.

Originally, therapy of non-autoantibody-induced RPGN was likewise thought to have little or no prospects of success where the clearance was

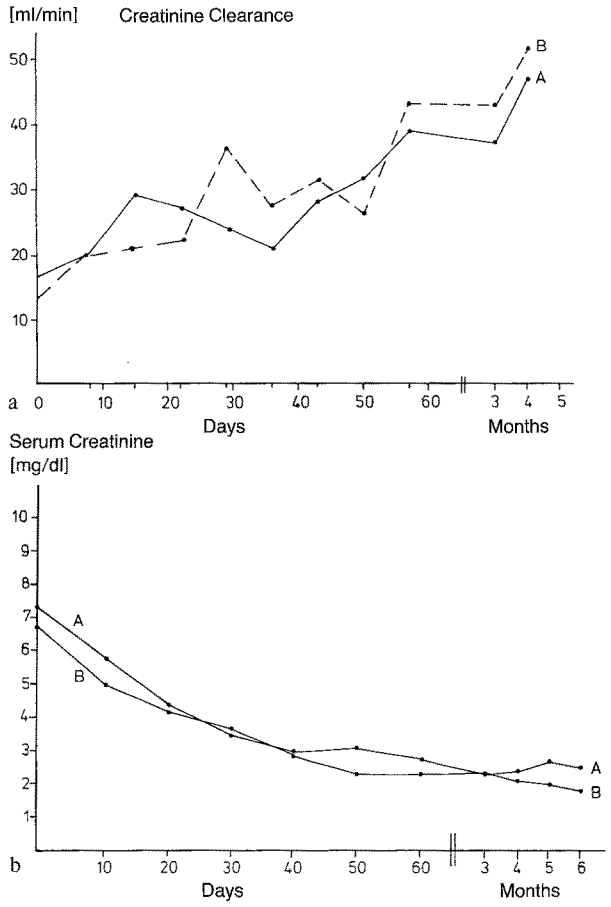

Fig. 1. a Variation of creatinine clearance during a randomised controlled therapy study. Immunosuppressive therapy was given under the same protocol to 24 patients. The patients of Group A (n = 11) served as controls. Patients of Group B were additionally treated by plasma separation three times per week for 4 weeks. **b** Variation of serum creatinine levels in the same patients as in **a**

< 5 ml/min. Hind et al. [14] have treated 27 patients having non-autoantibody-induced RPGN, who already required dialysis, with plasmapheresis and immunosuppression. In 17 of these cases, sufficient improvement in renal function was achieved that dialysis was no longer necessary. In contrast to dialysis patients with autoantibody-induced RPGN, in whom the identical treatment produced no improvement (98% of the glomerula showed crescents; only 0.5% of the glomerula were normal), the glomerula of the non-autoantibody patients only showed extracapillary crescent formations to the extent of about 70%. In those patients whose renal function improved under plasmapheresis, a mean of 18% of still-normal glomerula was found.

In a randomised, multicentre study[1] by ourselves, not yet published, 24 patients with non-autoantibody-induced RPGN were treated. All patients were given the same immunosuppressive therapy (immunosuppressants, cyclophosphamide, azathioprine and 6-methylprednisolone), while 13 of them were additionally treated by plasmaseparation at least three times per week for a period of four weeks. Both groups contained patients who already required dialysis. Before starting the study, the statistical criterion for success was selected as being the 30th day. Although on this day there was a statistically significant difference in the clearance rates in favour of the plasmapheresis group, 5 months later no difference between the two groups could be found (Fig. 1).

The number of cases of complications resulting from the therapy itself is certainly difficult to estimate, since it will not always be possible to distinguish with certainty between symptoms of the disease and therapy-induced complications. High lethality rates when plasmapheresis was first introduced also cannot be attributed just to insufficient experience with this therapy. In the early stages of plasmapheresis therapy, it was in particular those cases previously considered hopeless who were given the treatment and who were referred to those centres then active in this field.

1 Participants of the study see page 1009

Table 4. Cumulatative table of complications occurring under the various forms of therapy

	Patients treated	Complications					
		fatal	haematol.	haemo-stasiol.	infections	gastro-intest.	hepat.
Immunosuppression	50	4 (6%)	1	1	3		
Anticoagulants	75	9 (12%)		18 (24%)	4	2	1
Pulse-therapy	38	2 (5%)	2		2 (5%)		
Plasmapheresis	183	7 (4%)	2	1	14 (8%)		

Table 4 shows the ratio of the numbers of cases treated within each individual group to the numbers of complications reported for each. The rate of fatal complications was 5% in three of the groups, and a higher lethality of 12% was only shown under anticoagulant therapy. In about 25% of the patients treated with anticoagulants, haemorrhagic complications were observed, and half of these ended fatally. No statistically significant difference was found in the incidence of infections between pulse therapy and plasmapheresis.

Discussion

Within the space of about twenty years, the prognosis for RPGN has very substantially improved under the treatment regimens quoted here. If detected at an early stage, autoantibody-induced RPGN can be treated to give a long-lasting improvement in renal function and in many cases, after the formation of autoantibodies has ceased, also a complete cure.

In RPGN which is not autoantibody induced, treatment with immunosuppression alone and anticoagulant treatment each showed much lower success rates than those for pulse therapy or for plasmapheresis. For anticoagulant therapy, the 95% confidence limit was even below the corresponding limit for pulse therapy and plasmapheresis, for which improvement of renal function was reported in more than 60% of cases. The figures do not show any superiority of the pulse therapy, particularly when the confidence limits are taken into account.

Under pulse therapy or therapeutic plasmapheresis, improvement in renal function was produced in more than 60% of cases in both idiopathic and symptomatic RPGN.

The improvements resulting from therapy were maintained for a number of years, sometimes with restricted renal function. Even when renal function was already severely restricted and dialysis treatment had already been commenced, it was often possible to achieve a substantial improvement of renal function. None of the authors discussed the possibility that the need for dialysis could also have been due to acute renal failure superimposed on the basic disease, and that the improvement in renal function could have occurred after the acute renal failure had been completely cured.

Although these therapeutic results are extremely encouraging, they need to be confirmed by controlled studies. This present controlled study also permits us to at least suspect that the prognosis for patients who are the subject of a controlled study could be better than for those who are treated without any fixed treatment protocol. The results to date do not enable any final therapeutic protocol to be established. Since on the investigations performed to date, pulse therapy and therapeutic plasmapheresis show roughly equally good results, one could at least recommend that pulse therapy (whose effectiveness or otherwise is apparent within 48 h) be tried first, and that the patient only be treated with plasma separation if the pulse therapy remains ineffective [29]. This strategy is also advisable not least for cost reasons.

The evaluation results which we present here are also valuable in showing that without a fixed therapeutic protocol and controlled studies, information regarding the optimisation of therapy will remain of only limited validity. Since the disease is relatively rare, even controlled studies will usually only cover a small number of cases and will thus be vulnerable to the criticism of the Type II error by too small sample size. A rapid increase in our knowledge, particularly as regards therapy, could only be expected if patients with glomerulonephritis were to be registered in a system similar to the EDTA Registry. It would also be conceivable to extend the scope of the EDTA Registry to include those patients with chronic renal insufficiency not yet requiring dialysis.

Addendum (see Footnote 1)

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