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HENOCH-SCHÖNLEIN PURPURA IN CHILDHOOD: TREATMENT OF RAPIDLY PROGRESSIVE GLOMERULONEPHRITIS WITH IMMUNOSUPPRESSIVE ANTICOAGULANT THERAPY*

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Henoch-Schönlein purpura (HSP) is a disease of unknown etiology manifested by a characteristic skin rash, abdominal pain and arthritis or arthralgia. Renal involvement occurs in 20-70 percent of cases and is variable in degree[1-3], usually occurring within the first four weeks of onset of the illness, but may appear as long as two years after the initial symptoms[3]. The clinical manifestation of renal involvement includes macroscopic hematuria, proteinuria, nephrotic syndrome, acute nephritic syndrome and rapidly progressing glomerulonephritis (RPGN). Patients over seven years of age with Henoch-Schönlein nephritis (HSN) who have had an onset of nephritis after four weeks of illness, or present clinically with nephrotic syndrome or acute nephritic syndrome tend to have a poor prognosis[4,5]; those patients with RPGN are known to have the poorest prognosis[6].

RPGN is characterized by a progressive loss of renal function within a period of a few weeks to several months and is associated with severe and diffuse glomerular lesions characterized by the presence of crescents filling Bowman's space[5,6]. In untreated patients RPGN is almost uniformly fatal[7,8]. Treatment with steroids or immunosuppressive drugs singly or in combination has not been particularly successful[7-10]. However, patients who received anticoagulants such as heparin and/or dipyridamole as well as steroid and immunosuppressive agents – the so-called "Quadruple Therapy" – seem to have had a better response to treatment[11-14]. In this paper, the response to quadruple therapy in ten patients with severe HSN is presented.

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Material and Methods

Ten patients with severe HSN showing one or more indicators suggesting RPGN were given quadruple therapy. The patients presented to the Renal Unit of the Royal Hospital for Sick Children, Glasgow, United Kingdom, between the years 1974 and 1984 with rapidly deteriorating renal function (at least 50 percent reduction of GFR) occurring over a period of four weeks in the presence of glomerular crescents affecting 50 percent or more of the glomeruli on renal biopsy material. The clinical data of the patients are shown in Table I. All had the characteristic rash of anaphylactoid purpura and nine out of ten had abdominal pain and arthritis.

The GFR was calculated using indices of serum creatinine and patients' height, the values being corrected for surface area[15].

Percutaneous renal biopsy was carried out at a time when the GFR showed progressive fall-off. Biopsy specimens showing at least ten glomeruli in any given section were accepted as adequate samples. Eleven biopsy specimens were available for examination by light microscopy before treatment, of these, two were inadequate. The second renal tissue examinations of six patients were available during or after treatment.

The tissue was fixed in neutral buffered formalin and processed in paraffin wax. Sections were examined by light microscopy using the standard hematoxylin and eosin (HE), periodic acid Schiff (PAS), silver methanamine (PASM) and Lendrum's Martius Scarlet Blue trichrome (MSB) stains. Fourteen biopsies from ten patients were examined by immunofluorescence and electron microscopy.

The quadruple therapy consisted of the following: prednisolone 2 mg/kg/day, decreasing to 0.25 mg/kg on alternate days over a period of 1-3 months; azathioprine 2 mg/kg/day, or cyclophosphamide 3 mg/kg/day; subcutaneous heparin was prescribed three to four times a day in a dose sufficient to double the prothrombin time; dipyridamole was prescribed in a dose of 10 mg/kg/day[12]. The general aim was to continue all four drugs for approximately one year. In one patient (No. 7) showing melena as part of his overall disease, anticoagulant was not used. Four patients (Nos. 5, 6, 8, and 10) received the therapy for less than six weeks. Of these, one patient (No. 10) died, one (No. 8) developed pseudomonas septicemia and in two patients (Nos. 5 and 6) treatment was discontinued because of lack of response. One patient (No. 1) had a grand mal convulsion after commencing therapy, and because of the risk of intracerebral hemorrhage anticoagulant drugs were discontinued after five days. Two patients (Nos. 4 and 6) developed nausea and vomiting with azathioprine and thereafter received cyclophosphamide for a period of 13 weeks and 4.7 weeks, respectively. In one patient (No. 9) azathioprine was substituted for cyclophosphamide after three days because of hemorrhagic cystitis.

TABLE I: Clinical Data

Patient No.	Sex	Age at onset (Yr)	Age at onset (Mo.)	Duration of preceding illness until treatment (Wk)	Nephrotic syndrome	Macroscopic hematuria	Oliguria	Blood Pressure (mm Hg)	GFR at start of treatment (ml/min/1.73 m^2)
1	F	4	5	8	+	+	–	125/85	20
2	M	10	6	6	+	+	–	125/95	34
3	F	5	1	21	+	+	–	140/95	41
4	M	14	–	28	+	+	–	140/100	41
5	M	10	3	63	+	+	+	185/135	14
6	M	10	8	40	+	+	+	180/100	11
7	F	8	1	36	+	+	–	140/90	34
8	M	5	1	6	+	+	+	130/90	15
9	M	9	4	14	+	+	–	150/90	15
10	M	6	10	6	+	+	+	140/90	14

Results

Renal histology: Details of the findings on histological examination of the renal biopsies or postmortem material and the electromicroscopic deposits are shown in Table II. Immunofluorescent studies were carried out on all patients before treatment and in three patients (Nos. 1, 3, and 4) after treatment. All patients showed C_3 deposition and apart from two patients (Nos. 6 and 10) all showed IgA and fibrinogen deposition. After treatment all three patients demonstrated a decrease in fibrinogen deposition.

Complement studies were carried out on all patients. C_3 levels were normal in all patients. Elevated C_4 levels were noted in five patients (Nos. 1, 4, 6, 7 and 9) as well as the high level of C_1 inhibitor in two patients (Nos. 1 and 8) at the start of treatment, presumably indicating acute phase response in these children.

Response to therapy: The response to therapy was assessed in each patient by alteration in renal function, and in six of the ten patients by histological examination, also. The results were graded as good, partial or poor on the basis of a permanent, transient or negligible improvement in GFR, respectively. There were three out of ten patients with a good response, three with a partial response and four with a poor response. Figures 1, 2 and 3 demonstrate the renal function

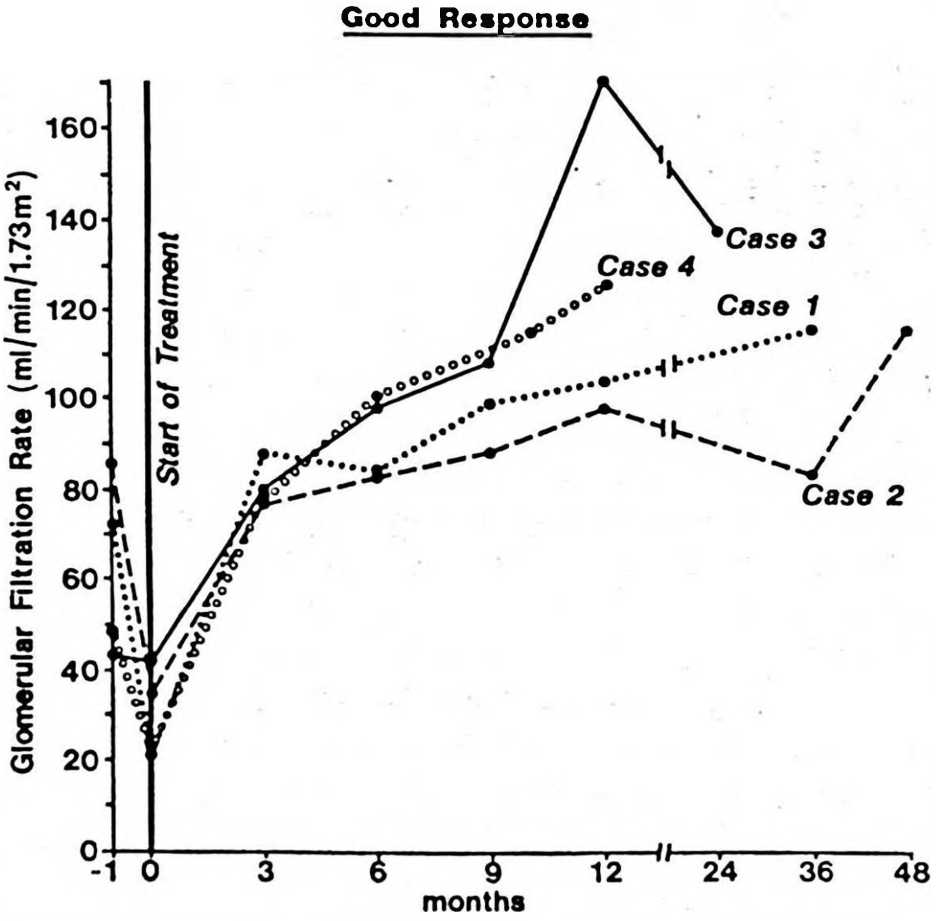

Fig. 1. Serial measurements of GFR in the good response group.

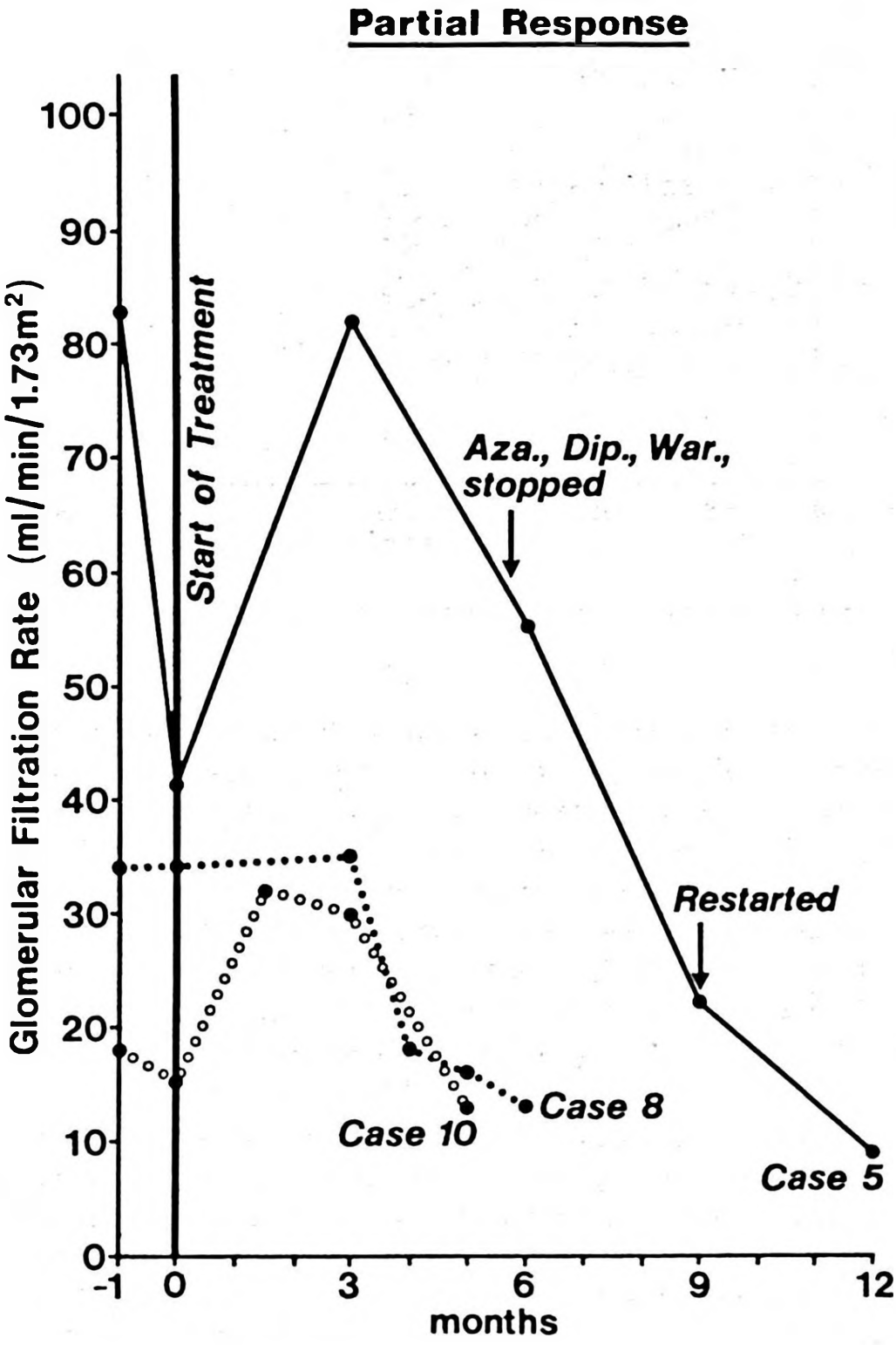

Fig. 2: Serial measurements of GFR in the partial response group.
Aza: Azathioprine,
Dip: Dipyridamole,
War: Warfarin.

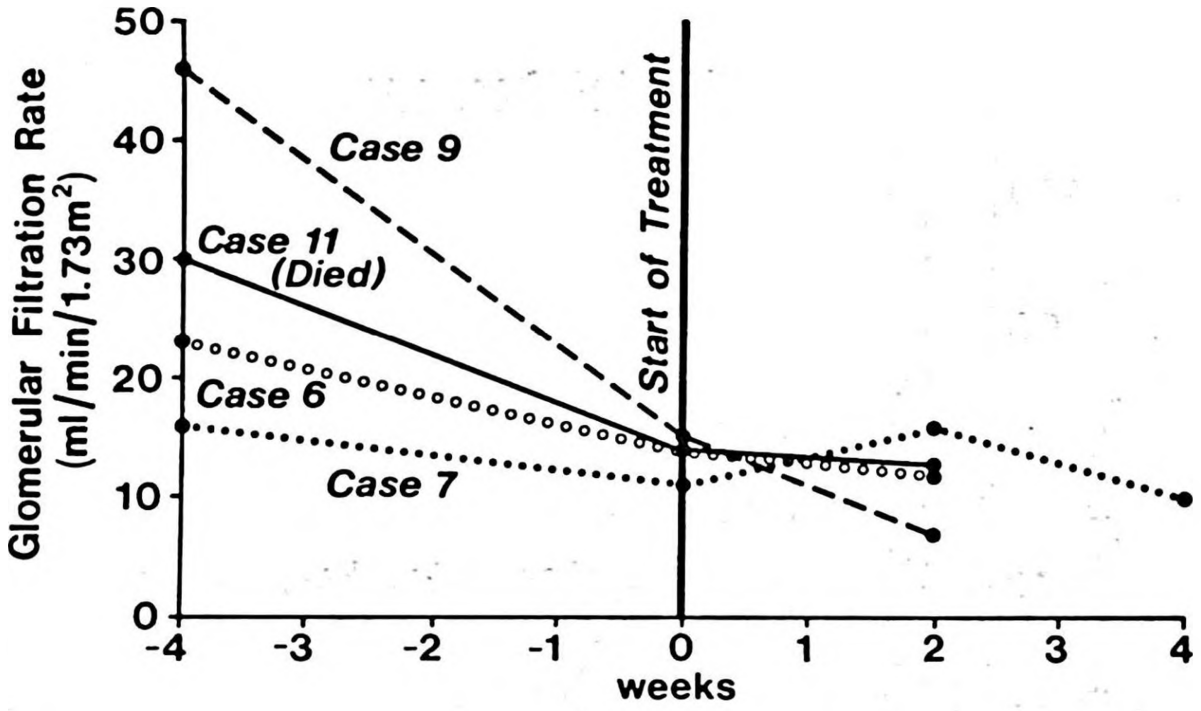

Fig. 3: Serial measurements of GFR in the poor response group.

before and after treatment in these three groups. In Group 1 following treatment the GFR increased to more than twice the starting value within one to three months and this level was maintained more than nine months later. In Group 2 there was a partial response, the patients showing either a stable GFR or at least a twofold increase in GFR within the first three months of therapy, but this was not maintained. In Group 3 the patients showed a poor response with an increase in GFR of less than 10 ml/min/1.73 m^2 or a decrease in GFR during the first month of therapy and no subsequent recovery in function was documented. Table III outlines the nature and criteria of the response according to the categories defined above and the present status of the children.

Repeat renal biopsy was carried out in three patients (Nos. 1, 2 and 3) in the good response group. The percentage of crescents had decreased markedly and the crescents present tended to be fibrous or fibrocellular. Only one patient (No. 4) in the partial response group had a repeat biopsy. The crescents present were cellular and fibrocellular. Postmortem specimens available from two patients (Nos. 9 and 10) in the poor response group showed 100 percent and 70 percent crescents, respectively, and they were predominantly fibrous. The mean pre-treatment urinary protein excretion in good responders was 103 mg/hr/m^2, in partial responders it was 75 mg/hr/m^2 while in poor responders, 116 mg/hr/m^2. Table III shows the actual values. All patients but two (Nos. 4 and 9) showed a decrease in urinary protein excretion with treatment.

TABLE II: Summary of Initial and Repeat Biopsy Findings

Patient No.		Total No. of glomeruli	No. of glomeruli with crescents	Crescents (%)	Type of crescents	TUFTS: No. of glomeruli with total sclerosis	TUFTS: Mesengial proliferation	Tubular atrophy	Interstitial changes	EM deposits
1	Before	35	33	94	C, Fc	–	+	++	++	None
	After	28	4	14	F	8	–	+	+ fibrosis	None
2	Before	26	25	96	C	–	+	+	+	Mes/cap
	After	20	3	15	F	5	–	+	+ fibrosis	None
3	Before	16	9	56	C, F	3	++	+	++	Mes
	After	15	1	6	Fc	5	+	+	+	Mes
4	Before	Insufficient								Mes/cap
	After	29	15	51	C, Fc	3	+	+++	++ fibrosis	Mes
5	Before	17	5	29	F, C	9	+	+	+ fibrosis	Not available
	Before	10	10	100	F, C	9	–	+++	+++ fibrosis	None
6	Before	30	17	56	F, Fc, C	4	+	–	–	Mes/cap
7	Before	21	18	85	F, Fc, C	2	–	+	+	None
8	Before	25	23	92	Fc	25	–	+	++	None
9	Before	24	22	92	F	19	+	+++	+++	Subepith
	PM			100	F	100%	–	+++	+ fibrosis	Not available
10	Before	Insufficient								
	PM			70	F, C	60%	+	+	+	Not available

C = cellular, Fc = fibrocellular, F = fibrous, N = normal, Mes = mesangial, Cap = capillary, Subepith = subepithelial.

TABLE III: Criteria of Response to Quadruple Therapy

Patient No.	GFR ml/min/1.73 m^2	Urinary protein mg/hr/m^2	Oliguria	Crescents (%)	Type of crescents	Duration of treatment response (mo.)	GFR at present ml/min/1.73 m^2
Good response							
1	20	128	–	94	C, Fc	45	116
2	34	57	–	96	C	56	116
3	41	124	–	56	C, F	35	101
Partial response							
4	41	61	–	Insufficient	Insufficient	6	Dialysis
7	34	112	–	85	F, Fc, C	3	Renal transplant
9	15	54	–	92	F	3	Died
Poor response							
5	14	185	+	100	F, C	–	Dialysis
6	11	89	+	56	F, Fc, C	1/4	Renal transplant
8	15	111	+	92	Fc	–	Died
10	14	81	+	Insufficient	Insufficient	1/4	Died

C = Cellular
Fc = Fibrocellular
F = Fibrous

Discussion

Quadruple therapy was first used in six adult patients with oliguric renal failure by Kincaid-Smith et al[11]. The underlying renal histology was either severe diffuse proliferative glomerulonephritis with epithelial crescents or occlusive lesions of small arteries or arterioles such as microscopical polyarteritis nodosa or thrombotic thrombocytopenic purpura. Their prompt improvement in renal function suggested that these drugs may have had a direct effect on the underlying lesions. Brown et al[12] used quadruple therapy in a series of 16 patients with RPGN, two of whom were children with HSP. The diagnosis of RPGN was based on rapidly deteriorating renal function in the presence of the histological picture of severe glomerular pathology including extra-capillary crescents in more than 60 percent of the glomeruli. The authors emphasize that quadruple therapy is capable of stopping and reversing the rapid renal failure associated with crescentic glomerulonephritis, but only in those patients who still have some renal function. Patients who were oligoanuric did not respond to treatment. It is known, however, that quadruple therapy can be associated with serious complications[16,17]. Arief and Pingerra[16] highlighted the incidence of hemorrhagic complications but postulated that these occurred because their patients received heparin by the intravenous route. Our criteria for including anticoagulant in the therapy regime has become stringent following the death of one patient of a cerebral hemorrhage. Gastrointestinal intolerance with azathioprine was severe in two patients and in one resulted in the receipt of an inadequate course of therapy. Seven patients developed complications of steroid therapy, all showing cushingoid appearance. Quadruple therapy had to be discontinued abruptly in one patient after the onset of life threatening pseudomonas septicemia and one child was taken off cyclophosphamide and put on azathioprine because of hemorrhagic cystitis.

From our data, the criteria of patient response to quadruple therapy is clear. All of the good responders showed a GFR greater than 20 ml/min/1.73 m^2 at the start of treatment and none showed oliguria. The histological finding was of crescents which were predominantly cellular.

In the poor responders the GFR was less than 20 ml/min/1.73 m^2 in all patients. All showed oliguria and three out of the four patients showed crescents which were predominatly fibrous or fibrocellular. The pretreatment urinary protein excretion of the patients in this group was higher than the patients of the other two groups. Patient 4 was a potentially good responder in that he showed an initial response, his initial GFR was 41 ml/min/1.73 m^2 and he was not oliguric. He had developed a drug intolerance early in his illness and received an inadequate course of therapy. Patients 7 and 9, despite the absence of oliguria showed mainly fibrous and fibrocellular crescents and their response was minimal or absent. The duration of

the illness, the age of the patients, the presence of nephrotic syndrome, hypertension or macroscopic hematuria, blood complement levels, the immunofluorescent and EM findings on renal biopsy tissue as well as the number of crescents were not found to be helpful prognostic indicators of response. Although our conclusions are drawn from a small number of patients and the study was uncontrolled, a review of the literature shows it to be the largest number of child patients with Henoch-Schönlein RPGN to be treated with quadruple therapy. In predicting the response of patients with RPGN to quadruple therapy we would say that four combined criteria are important (Table III): the absence of oliguria, confirming the previous findings of Brown et al[12], a GFR of more than 20 ml/min/1.73 m^2, the level of protein excretion at the start of treatment, and the presence of crescents which are predominantly cellular. Of these four criteria, the predominantly cellular nature of the crescents may be the most important determinant of response.

The high incidence of significant and serious complications combined with the satisfactory response of some patients who received modified regimes leads us to question the need for all four drugs in every patient; we are also concerned about the duration of the therapy. Our experience would suggest that a biopsy during the course of the treatment may be helpful in clarifying the second of these two points. A second biopsy allowed us to discontinue therapy in two patients and in two other patients the biopsy findings suggested persistent activity of the disease and their therapy was continued. In recent reports[18] very large doses of "pulsed" intravenous methylprednisolone or combined pulse and plasma exchange therapy in patients with RPGN has been successful and heparin therapy is now outmoded as a modality. We would advise that anticoagulants, especially heparin, be excluded from the therapy and that the patients have regular checks for steroid toxicity.

Summary

Ten patients with rapidly progressive glomerulonephritis (RPGN) were treated with prednisolone, azathioprine or cyclophosphamide, dipyridamole, heparin and/or warfarin for periods of 1.7 weeks to 144 weeks with a mean period of 44 weeks. Three patients responded well, their mean glomerular filtration rate before treatment being 31.7 ml/min/1.73 m^2 to a mean of 111 ml/min/1.73 m^2 after treatment, the follow-up period being 45.3 months. Three patients had a partial response, showing a temporary rise in GFR and four patients had no response.

Our observations suggested that this combined therapy has a place in patients with RPGN, especially in those patients where at the start of the treatment GFR is more than 20 ml/min/1.73 m^2, oliguria is absent and where crescents on renal

biopsy are predominantly cellular. The incidence of side effects was high and it is necessary that the therapy be used with caution.

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