Characteristics and Management of IgA Vasculitis (Henoch-Schonlein) in Adults Data From 260 Patients Included in a French Multicenter Retrospective Survey

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Characteristics and management of IgA vasculitis (Henoch-Schönlein purpura) in adults: data from the 260 patients included in the IGAVAS survey

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Abstract (249 words)

Objectives: Data on adult IgA vasculitis (IgAV) are scarce. This survey was designed to better define clinical spectrum and efficacy of treatments in this population.

Methods: We analyzed data from 260 patients with IgAV included in a French multicenter retrospective survey.

Results: Mean age at diagnosis was 50.1±18 years, and 63% were male. Baseline manifestations included purpura (100%), arthralgia (62%), glomerulonephritis (70%) or gastro-intestinal involvement (53%). Thirty percent showed at baseline renal failure. In univariate analysis, response was 80% (n=64/80) in patients treated with corticosteroids (CS) alone compared to 77% (n=23/30) in patients treated with cyclophosphamide (CYC) and 10/17 (59%) treated with colchicine (P=0.17).

Multivariable analysis showed that patients treated with CS or CS plus CYC were more effective than colchicine in achieving response using different statistical analysis: logistic regression model [OR (95% CI) 3.68 (1.10-12.33), P=0.03], inverse probability weighting on Propensity Score (PS) [OR 3.75 (1.28-10.99), P=0.02]. Efficacy of CS plus CYC versus CS were discordant according to the method used. The use of multivariable logistic regression model [OR 0.88 (0.29-2.67), P=0.82] did not demonstrate difference, in contrast, inverse probability weighting on PS with [OR 1.79 (1.00-3.20), P=0.049] showed that CS plus CYC were more effective.

Conclusion: This series constitutes the largest series reported so far in the literature of adults IgAV. It provides data on clinical and histological presentation and therapeutic efficacy, suggesting that CS alone appears to be a reasonable first-line therapy in patients with IgAV, while the benefit of adding CYC to CS remains uncertain.

Introduction

Immunoglobulin A (IgA) vasculitis, formerly called Henoch–Schönlein purpura, is an immune complex small vessel vasculitis with IgA1-dominant immune deposits (1). IgA vasculitis (IgAV) is the most common systemic vasculitis in childhood with an annual incidence of 3 to 26 per 100 000 children (2). In adults, the disease is less common with an annual incidence of 0.1 to 1.8 per 100 000 individuals (3, 4),(5). IgAV frequently involves the skin, the gastrointestinal tract, the joints with arthralgias and/or arthritis, and the kidneys (6). Gastrointestinal tract and renal involvements represent the main causes of morbidity and mortality in adults. In a large study of 250 IgAV in adults, 11% of patients reached end-stage renal disease (ESRD), 13% had severe renal failure with an estimated glomerular filtration rate (eGFR) <30 mL/min/1.73m^2, and 14% had moderate renal failure with eGFR<50 mL/min/1.73m^2(7). Factors associated with evolution to ESRD included baseline renal function, baseline proteinuria >1 or 1.5 g/day, macroscopic hematuria, hypertension, and proteinuria ≥1 g/day during follow-up (7-9). In a study from Southern European population, hematuria at disease onset, renal involvement during the course of the disease, anemia at the time of diagnosis and onset of the disease in summer were more common in patients with renal sequelae (10). On renal biopsy, degree of interstitial fibrosis, sclerotic glomeruli and fibrinoid necrosis were also associated with a poor renal prognosis (7).

Treatment has been poorly investigated in adults. Management of IgAV is often symptomatic because of the frequent benign course of the disease with spontaneous remission. However, in case of severe involvement with organ and/or life-threatening complications, corticosteroids (CS) or/and immunosuppressive drugs are often initiated. Pillebout et al. conducted the only prospective, multicenter, open

label trial in adults, comparing CS alone versus CS plus cyclophosphamide (CYC) in patients with severe IgAV (11). Fifty-four patients with biopsy-proven IgAV and severe manifestations, including proliferative glomerulonephritis and/or severe gastrointestinal manifestations, were included. At 12 months, no difference was found between the 2 groups in terms of remission rate, renal outcomes and adverse events. However, overall survival at 12 months tended to be better in the CS plus CYC group compared to CS alone [96% (95% CI 89–100) vs. 79% (95% CI 64–93); P=0.08). Hence, the optimal therapeutic strategy has yet to be defined in adults.

To better define the clinical spectrum and the efficacy of treatments in IgAV in adults, a nationwide survey was initiated in France in 2013. Data from the 260 cases of IgAV in adults included in the IGAVAS survey are reported here.

Patients and methods

Patients

This multicentric retrospective survey was conducted in French university and general hospitals in departments of Internal Medicine, Nephrology, Dermatology and Rheumatology. The study was performed in accordance with ethical standards of the Helsinki Declaration, and was approved by Institutional Review Board. The inclusion criteria for the study were (1) age >18 years old, (2) IgA vasculitis, and (3) diagnosis of IgAV between January 1990 and January 2015. Patients were considered to have IgAV if they presented (1) purpura, (2) histologically proven small vessels vasculitis, (3) IgA histologically proven deposits and (4) involvement of at least one organ among kidney, joint, or intestinal tract. Exclusion criteria were IgAV associated with a diagnosis of cancer in the 5 previous years before vasculitis onset.

Clinical and biologic data

Clinical and biologic data were recorded for each patient at the time of the initial evaluation, during follow-up (6 and 12 months after initial evaluation), and at the end of follow-up, by the practitioners in charge of the patients with the use of a standardized form. Laboratory assessment included in particular the determination of serum creatinine level and a urinalysis to screen for hematuria and a 24-hour urine protein examination. Renal failure was defined as an eGFR<60 mL/min/1.73m^2, assessed with the Modified Diet in Renal Disease equation (12). Proteinuria was defined as 24-hour urine protein excretion >0.5 g/day, and hematuria was defined as >10 red cells/mm^3 in the urine considered as macroscopic if >1500 red cells/mm^3. Elevated IgA levels was defined as IgA >3.5 g/L.

Histological data

Histological data (skin and renal biopsies) were recorded at the time of diagnosis. Pathology reports for renal biopsies were examined by two independent nephrologists (ET and EP) blinded to the clinical features. According to the presence of focal or diffuse distribution, extracapillary proliferation, number of glomeruli involved, interstitial fibrosis, proportions of glomeruli involved by crescents, fibrinoid necrosis and global sclerosis, all biopsies were classified according to the classification previously described by Pillebout et al. (7).

Response to therapy

The response to therapy of IgAV was defined by analysing the course of the following main clinical signs: skin involvement (purpura), articular manifestations (arthralgia and/or arthritis), gastrointestinal symptoms and renal involvement (normalization or improvement of eGFR, proteinuria and hematuria). Response were evaluated by 2 independent physicians (AAV and BT) blinded to the treatment received. A complete response was defined as an improvement in all baseline clinical manifestations and

in case of renal involvement by a proteinuria <0.5 g/d, the disappearance of hematuriaand no decrease of the glomerular filtration rate (GFR) greater than 20% from baseline. A partial response was defined as an improvement in at least one-half of the baseline clinical manifestations, and in case of renal involvement as an improvement of proteinuria > 50% of the baseline value, disappearance or not of hematuria, and no decrease of the GFR greater than 20% from baseline. All others patients were classified as non-responder. Relapse was defined as the reappearance of clinical signs of vasculitis, occurring after a period free of symptoms of at least a one month. Minor relapse was defined by increase of prednisone no greater than 20 mg/day and major relapse by addition of immunosuppressive drug or increase of prednisone greater than 20 mg/day. Others patients were considered as having no relapse.

Statistical analysis

Descriptive statistics included the mean (SD) or median [Q1; Q3] when appropriate for continuous variables, and frequency (percentage) for categorical variables. Univariate analysis included the Chi2 or Fisher exact test as appropriate to compare categorical variables and the nonparametric Mann-Whitney test to compare continuous variables. To evaluate efficacy of therapeutic regimens, we performed a multivariable logistic regression model to assess factors independently associated with response to therapy. All important factors in the literature as well as those associated with being treated or with response to therapy in univariate analysis were included in the final model. Correlated variables were not all entered in the model to avoid the risk of collinearity. To account for a potential indication bias (ie, patients treated with corticoids or CYC may be more severe than those treated with colchicine only), we also estimated a propensity score corresponding to the probability of being

treated with corticosteroids or CYC rather than Colchicine according to patients' characteristics (age, gender, gastro-intestinal bleeding, creatininemia, proteinuria, necrotic purpura) using a logistic regression model (13, 14). We performed an evaluation of the distributions of propensity scores by treatment groups checking for sizeable overlap among the treatment groups (ie, it is not possible to use a propensity score when the two groups are too different, this is why, it is important to check whether the two groups overlap). There are several ways to use the propensity score in analysis including adjustment on propensity score as a covariate in the model, matching of individuals treated and not treated on their propensity score and inverse probability weighting by propensity score. The 2 preferred methods are matching and weighting (15). However, it is not always possible to use matching as participants not matched (ie, patients treated and not treated for which the propensity score is not the same) do not participate in analysis. In this study, we used both adjustment on propensity score and inverse probability weighting on propensity score in logistic regression models to assess whether a treatment by corticosteroids or CYC was associated with a better response compared to colchicine and to assess whether a treatment by CYC was associated with a better response compared to corticosteroid alone. Because inverse probability weighting analysis may be sensitive to extreme propensity scores (13, 14), we did a sensitivity analysis excluding the 5% of patients with the lowest propensity scores.

Adjusted Odds ratios for all covariates in the model without propensity score are showed in the **Supplemental Material Table 1**.

Results

Of the 304 patients assessed for eligibility in the IGAVAS survey, 260 patients were included. Forty-four patients were excluded because of absence of proven IgA deposits (n=27), absence of proven vasculitis (n=4), concomitant cancer (n=6) or missing data (n=7).

Clinical and biological patient characteristics

The characteristics of the 260 patients with IgAV are shown in **Table 1**. The mean age at diagnosis was 50.1±18 years and 164 patients (63%) were male. Clinical manifestations included constitutional symptoms in 87 patients (33%), cutaneous involvement with purpura in all patients (100%), arthralgia/arthritis in 159 patients (61%), renal involvement in 182 patients (70%) and gastrointestinal involvement in 137 patients (53%). Thirty percent of the patients showed renal failure (eGFR<60 ml/min/1.73m^2) at baseline. Patients with renal involvement displayed a 90 mL/min/1.73m^2 [66; 110] median eGFR, a 1.5 g/day median proteinuria level [0.6; 3], and 88% presented hematuria. The median serum IgA level was 3.6 g/L [2.7; 4.8] and 85/159 patients (53%) presented elevated IgA levels.

Anti-neutrophil cytoplasmic antibodies (ANCA) were detected in 9/225 patients (4%) and antinuclear antibodies (ANA) in 33/231 patients (14%), both without any specificity (data not shown).

Histological features

The characteristics of skin and renal biopsies performed in the patients are summarized in **Table 2**. Skin biopsy was performed in 222 patients (85%), and renal biopsy in 144 of the 182 patients with kidney involvement (79%). The skin biopsy demonstrated leukocytoclastic vasculitis in 205 patients (92%). Direct immuno-fluorescence revealed IgA and complement deposition in blood vessels of the upper

dermis in 174/216 (81%) and 47/222 (21%) patients. In 6 skin biopsies, direct immuno-fluorescence was not performed. The renal biopsy demonstrated IgA mesangial deposits in 142/144 patients (99%) and extracapillary proliferation in 59/143 patients (41%). Of the pathology reports that were independently reviewed (n=67), majority of patients were classified as class 2 in 33/67 (49%), i.e. a focal and segmental glomerulonephritis with segmental endo- and extracapillary proliferation involving less than 50% of the glomeruli, and class 3a in 18/67 (27%), i.e. an endocapillary proliferative glomerulonephritis with moderate endocapillary proliferative lesions.

Treatments used

Treatments used were colchicine only in 27 patients, corticosteroids alone in 122 patients, and corticosteroids in combination with cyclophosphamide in 35 patients. Ten patients received various therapies, including dapsone in 4 cases, rituximab in 2 cases, mycophenolate mofetil in 2 cases and hydroxychloroquine in 2 cases. Sixty-six patients did not receive a specific treatment.

Baseline characteristics of the 250 patients according to the treatment used (except the 10 patients with various treatments) are shown in **Table 3**. Compared to patients who received no treatment or who received only colchicine, patients treated with CS or CS plus CYC were more frequently male (P=0.004), presented at baseline more frequently with necrotic purpura (P=0.006), renal involvement (P=0.0001), higher levels of proteinuria (P<0.0001) and hematuria (P=0.0005), more frequent endo- and extracapillary proliferation (P<0.0001), and more frequent and severe gastrointestinal tract involvement (P<0.0001). These factors, as well as significant factors previously described in the literature were included in the multivariable logistic regression model and the estimation of the propensity score.

Effect of therapeutic regimen on response to treatment and outcome

Of the 260 patients, 132 patients received either colchicine, CS or CS plus CYC, and had a follow-up >6 months. Follow-up data were missing for 5 patients, who did not differ from the remaining patients (data not shown). Finally, 127 patients were analyzed. Patients characteristics according to the achievement of partial or complete response in comparison with those with no response within the first 12 months of follow-up are summarized in **Table 4**.

In univariate analysis, no characteristic or treatment was significantly associated with the achievement of partial or complete response. Partial or complete response was obtained in 64/80 patients (80%) treated with CS, 23/30 patients (77%) treated with CS plus CYC, and 10/17 (59%) treated with colchicine (P=0.17).

Among the 66 patients who did not receive any treatment, 34 could be analysed because they were followed-up for at least 6 months. In univariate analysis 85% (n=29/34) presented spontaneous remission at month 6 and/or 12.

Although patients were not comparable in each treatment group, **Supplemental Material Table 2** shows that cutaneous and renal manifestations persisted between month 6 to 12 in 7 to 41% and 10 to 40% according to treatments used, respectively.

We then evaluated the efficacy of treatments after adjusting for confounding factors. The results of the multivariable logistic regression model, adjusted for gender, creatinine, proteinuria, digestive bleeding and necrotic purpura. The multivariable propensity score adjusted logistic regression model, and the inverse probability weighting on propensity score, with or without sensitivity analysis excluding outliers are indicated in **Figures 1** and **2**.

Treatment with CS or CS plus CYC were more effective than colchicine in achieving a partial or complete response using multivariable logistic regression model [OR (95% CI) 3.68 (1.10-12.33), P=0.03], the multivariable propensity score adjusted logistic regression model [OR (95% CI) 3.58 (1.07-11.94), P=0.04] and inverse probability weighting on propensity score [OR (95% CI) 3.75 (1.28-10.99), P=0.02] (**Figure 1**).

We also compared the efficacy of CS plus CYC versus CS (**Figure 2**) and found discordant results according to the method used. The use of multivariable logistic regression model [OR (95% CI) 0.88 (0.29-2.67), P=0.82] and the multivariable propensity score adjusted logistic regression model [OR (95% CI) 0.90 (0.29-2.78), P=0.86] did not demonstrate any difference between the 2 therapeutic strategies in achieving a partial or complete response. In contrast, the use of inverse probability weighting on propensity score with [OR (95% CI) 1.79 (1.00-3.20), P=0.049] or without sensitivity analysis excluding outliers [OR (95% CI) 2.33 (1.29-4.18), P=0.005] showed that treatment with CS plus CYC were more effective than CS in achieving a partial of complete response.

Follow-up of patients

After a median follow-up of 17.2 months [9.1-38.3] corresponding to 593 patient-years, 8 patients died, including 3 deaths directly related to IgAV (2 mesenteric ischemia and 1 multivisceral failure). Eight patients experienced end stage renal failure treated by renal transplantation (n=2) or dialysis (n=6). Among patients who received a treatment, data concerning relapse during the first 12 months after treatment were available in 107 patients and showed 15 minor relapse (14%) and 9 (8%) a major relapse. Among untreated patients, data concerning relapse during the

first 12 months of follow-up were available in 10 patients and showed one minor relapse (10%).

Discussion

It has been clearly reported that the clinical presentation and prognosis of adults IgAV differs from that of children. Because randomized controlled trials are lacking in the literature, evaluation of efficacy of the different therapeutic regimens, which is mandatory to improve the management of IgAV patients, was a main goal of the IGAVAS survey. To better define the clinical spectrum and the therapeutic management of IgAV, we analyzed the data from 260 patients included in the French multicenter and transdisciplinary IGAVAS survey, which constitutes the largest series of adults reported so far in the literature.

Patients in our study were comparable to those previously described by others (16-20). They were predominantly male, while mean age was 50 years compared to 32 to 44 years in previous series (16-20) and 48 years in a northwestern Spanish epidemiologic study (5). The incidence of cutaneous, articular and gastrointestinal tract involvement were also comparable with those described in others series, except for the renal involvement which was more prevalent in our series (70% versus 30 to 60% in others series) (16-20). This finding is probably related to the high rate of patients that were included by nephrologists in our survey. Considering laboratory findings, the prevalence of increased serum IgA levels (53%) was slightly more important than in other series (31 to 52%) (16-20).

Treatment of IgAV is often symptomatic because the disease course is usually benign. In more severe forms, some reports dealt with the use of CS and immunosuppressive agents (21), but randomized controlled trials are lacking in adult

IgAV. Corticosteroids are effective on arthralgia and abdominal pain and there is a considerable controversy on the benefit of corticosteroids to treat renal involvement and prevent evolution to end-stage renal disease especially in both pediatric and adult population (22-25). In adult IgAV with severe nephritis, Ren et al. suggested that mycophenolate mofetil could be useful for inducing remission and as steroid-sparing agent, but long-term effect on renal function is not known (26). By analogy with severe autoimmune diseases, CYC has been used in patients with organ- or life-threatening IgAV manifestations. Pillebout et al. compared CS with or without CYC in severe adults IgAV, in a prospective open-label trial (11). Fifty-four patients with biopsy proven IgAV and severe manifestations were included and randomized to receive CS alone or CS plus CYC. At 6 months, no difference was found between the 2 groups for the primary endpoint, i.e. the achievement of complete disease remission defined as zero on the Birmingham Vasculitis Activity Score (BVAS) (27), with no persistent or new clinical and/or biological vasculitis manifestation. The secondary endpoints, i.e. renal outcome, deaths, and adverse events, also did not differ at 12 months. However, only 54 patients of the 200 initially planned were included, explaining why data should be interpreted with caution. In addition, overall survival at 12 months tended to be better using CYC, with an overall survival of 96% in the CS plus CYC arm compared to 79% with CS alone (P=0.08), explaining why the interest of CYC remains controversial. Recommendations from the Kidney Disease Improving Global Outcomes (KDIGO) suggest that IgAV-related nephritis in adults should be treated similary as children and should not be used except for CYC in crescentic glomerulonephritis (crescents in >50 % of the glomeruli) with nephrotic syndrome or rapid degradation of eGFR (28).

The descriptive analysis of real-life patients may also provide interesting findings on the efficacy of the different therapeutic regimen. In this study, we used several complementary approaches to compare treatment efficacy. First, we did a multivariable analysis taking into account potential confounding factors which was not frequently done in previous studies because of their limited sample size. We also used a propensity score to take into account a potential indication bias as patients treated with CS plus CYC may be more severe at baseline than those treated with CS alone or colchicine (15). We took the propensity score into account in analysis with both adjustment and ponderation by inverse variance. All approaches showed concordant results for the comparison between CS or CS plus CYC versus colchicine. Futhermore, our cohort may have a cohort biased toward more severe disease and the prevalence and course of less serious disease cannot be interpreted to the same extent as more serious disease.

However, this was not the case for the comparison between CS alone and CS plus CYC showing contradictory results according to the statistical methods used. Indeed, multivariable logistic regression model and multivariable propensity score adjusted logistic regression model did not demonstrate any difference between the 2 therapeutic strategies. In contrast, the use of inverse probability weighting on propensity score with or without sensitivity analysis showed that CS plus CYC were more effective than CS alone in achieving a partial of complete response. Propensity score weighting is frequently recommended but could be sensitive to outliers, so no definitive conclusion can be taken for this comparison (13, 14). In addition, we cannot exclude bias related to unknown confounders not taken into account in the propensity score.

These conflicting results reflect that, besides limitations related to the retrospective design and possibly to insufficient power to detect any difference, no firm conclusion can be drawn regarding the comparison between CS alone and CS plus CYC. In addition, the low number of patients receiving colchicine alone or CS plus CYC, as well as the number of non-responder patients, may have limited the power of the study. However, given potential adverse events related to the adjunction of CYC in this condition, CS alone seems appears to be reasonable in first-line in patients with systemic IgAV, except in very severe presentations in which decisions should be made individually.

In conclusion, this series constitutes the largest series reported so far in the literature of adults IgAV. It provides interesting data on clinical and histological presentation and therapeutic efficacy, showing that CS alone appears to be a reasonable first-line therapy in patients with systemic IgAV, while the use of CYC remains controversial.

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Figure legends :

Figure 1: Efficacy of Corticosteroids or Cyclophosphamide versus Colchicine

Figure 2: Efficacy of Corticosteroids plus Cyclophosphamide versus Corticosteroids alone

Tables

Table 1. Main characteristics at baseline of the 260 patients with IgAV included in the IGAVAS survey.

Baseline characteristics	
Epidemiologicalfeatures	
Age at diagnosis, y, mean ±SD	50.1 ± 18.6
Male, n (%)	164 (63)
Clinical manifestations	
Constitutionalsymptoms, n (%)	87/260 (33)
Fever	39/260 (15)
Asthenia	54/260 (21)
Weightloss	22/260 (8)
Skin, n (%)	260/260 (100)
Purpura	260/260 (100)
Lowerlimb	260/260 (100)
Upperlimb	93/260 (36)
Abdomen	63/260 (24)
Face	8/260 (3)
Necrosis	67/260 (25)
Hemorrhagic blisters	22/260 (8)
Joints, n (%)	159/260 (61)
Arthralgia	159/160 (100)
Arthritis	26/160 (16)
Myalgia	10/160 (6)
Gastrointestinal tract, n (%)	137/260 (53)
Abdominal pain	135/137 (99)
Bleeding	43/137 (31)
Diarrhea	36/137 (26)
Nausea	26/137 (19)
Ileus	13/137 (9)
Kidney, n (%)	182/260 (70)
Oedema	49/182 (27)
High blood pressure	40/182 (22)
Macroscopic hematuria	18/182 (10)
Others, n (%)	13/260 (5)
Peripheralneuropathy	4/260 (2)

Orchiepidymitis	4/260 (2)
Cardiopathy	2/260 (1)
Intraalveolarhemorrhage	1/260 (0.5)
Biologicfeatures	
Serum IgA level, g/L, median, [Q1; Q3]	3.6[2,7; 4,8]
Elevated serumIgA, n (%)	85/159 (53)
Serum creatinine level, μmol/L, median, [Q1; Q3]	77 [65; 99]
eGFR, mL/min/1.73m^2, median, [Q1; Q3]	90 [66; 110]
eGFR<60 mL/min/1.73m^2, n (%)	55/181 (30)
Albumin, g/L median, [Q1; Q3]	33[27; 38]
Haematuria, n (%)	153/174 (88)
Proteinuria, g/day, median, [Q1; Q3]	1.5 [0.6; 3]
CRP, mg/L, median, [Q1; Q3]	27 [8; 60]

Table 2. Histological features of the patients with IgAV included in the IGAVAS survey.

Histological features	
Skin biopsy, n (%)	222/260 (85)
Leukocytoclastic vasculitis	205/222 (92)
IgAdeposits	174/216 (81)
C3 deposits	47/222 (21)
Fibrinoid necrosis	59/222 (27)
Renalbiopsy	144/182 (79)
IgA mesangial deposits, n (%)	142/144 (99)
Extracapillaryproliferation, n (%)	59/144 (41)
Fibrinoid necrosis, n (%)	46/144 (32)
Glomerularsclerosis, n (%)	47/144 (33)
% of glomerular sclerosis, median [Q1; Q3]	11 [7; 20]
% of interstitial fibrosis, median [Q1; Q3]	15 [10; 21]
Tubulointerstitial nephritis, n (%)	44/144 (31)
Classification, n (%)	
Class 1	2/67 (3)
Class 2	33/67 (49)
Class 3a	18/67 (27)
Class 3b	9/67 (13)
Class 4	4/67 (6)
Class 5	1/67 (2)

Table 3. Characteristics of the patients according to treatment received

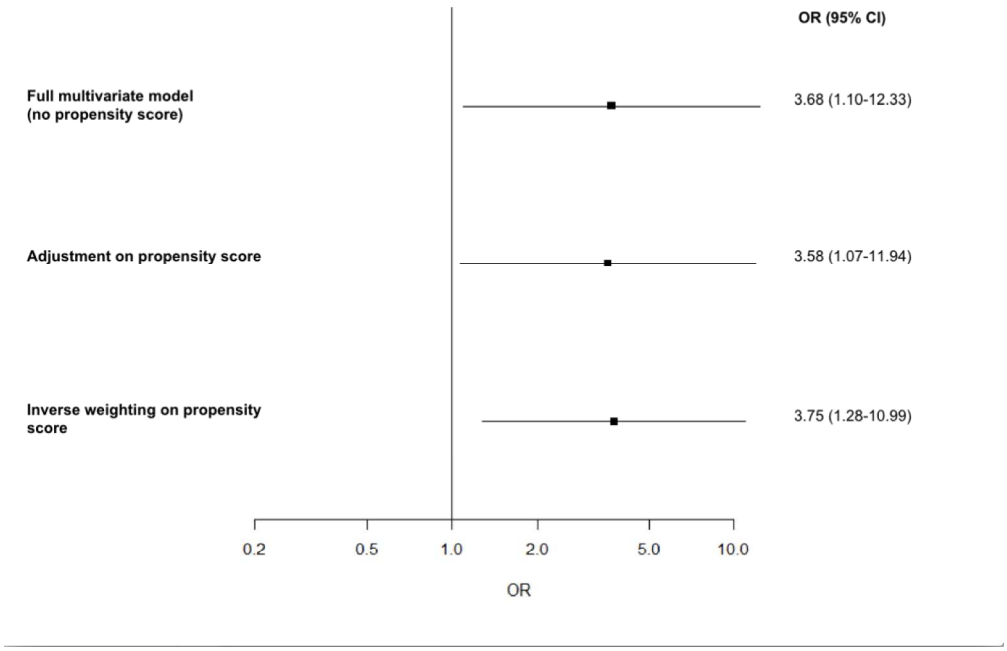
Characteristics	CS + CYC n=35	CS n=122	Colchicine only n=27	No therapy n=66	P
Age, mean (SD)	47 (18)	51 (20)	45 (16)	51 (18)	0.36
Gender, n (%)					**0.004**
Men	31 (89)	76 (62)	15 (56)	35 (53)	
Women	4 (11)	45 (38)	12 (44)	31 (47)	
Skin involvement, n (%)	35 (100)	122 (100)	27 (100)	66 (100)	-
Necrotic purpura	17 (49)	30 (25)	5 (19)	12 (18)	**0.006**
Fibrinoid necrosis at biopsy	9 (26)	33 (27)	4 (15)	11 (17)	0.28
Joint involvement, n (%)	23 (66)	79 (65)	16 (59)	32 (48)	0.15
Renal involvement, n (%)	30 (86)	93 (76)	11 (41)	39 (59)	**0.0001**
Proteinuria >1 g/d, n (%)	24 (69)	53 (43)	4 (15)	17 (26)	**<0.0001**
Proteinuria >3 g/d, n (%)	13 (37)	24 (20)	1 (4)	5 (7)	**0.0004**
Hematuria, n (%)	27 (77)	79 (65)	9 (33)	31 (47)	**0.0005**
Creatinine, median [Q1; Q3]	80 (70-117)	80 (66-111)	75 (66-85)	71 (62-86)	**0.02**
eGFR, median [Q1; Q3]	90 (50-112)	90 (61-108)	96 (87-105)	98 (80-111)	0.23
Biopsy performed, n (%)	29 (83)	69 (57)	8 (30)	29 (44)	**<0.0001**
Endocapillary GN, n (%)	18 (62)	33 (48)	3 (37)	9 (31)	
Extracapillary GN, n (%)	14 (48)	35 (51)	0 (0)	5 (17)	
GI involvement, n (%)	26 (74)	75 (61)	7 (26)	21 (32)	**<0.0001**
Ileus	3 (9)	8 (7)	0 (0)	2 (3)	0.38*
Bleeding	14 (40)	23 (19)	1 (4)	2 (3)	**<0.0001**
Surgical abdomen	3 (9)	2 (2)	0 (0)	0 (0)	0.054*

CS : corticosteroids ; CYC :cyclophosphamide ; GN :glomerulonephritis, GI :gastrointestinal
*Fisher exact test

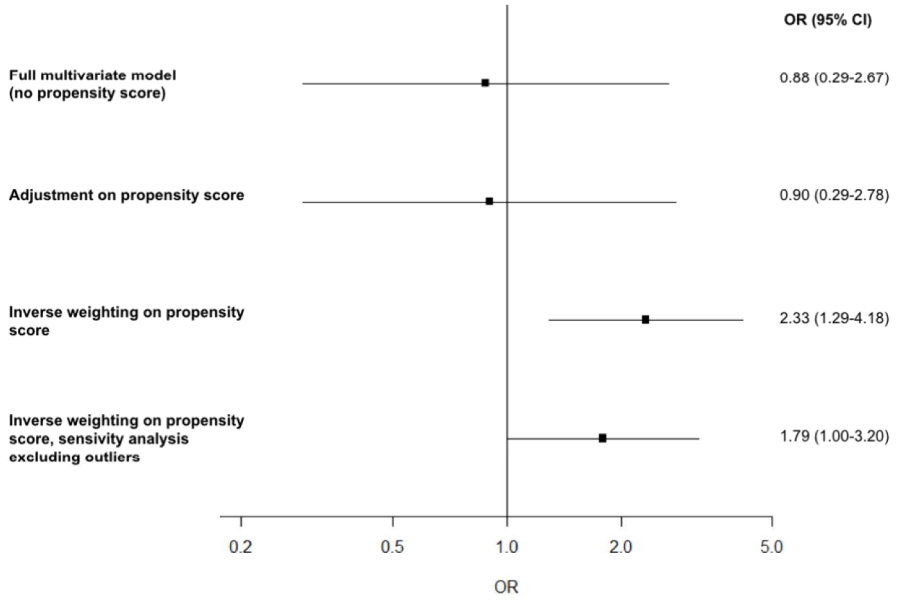
Table 4. Characteristics of patients according to the achievement of partial or complete response in comparison with those without any response.

Characteristics	Response n=97	No response n=30	p
Age, mean (SD)	49 (19)	48 (17)	0.72
Gender, n (%)			0.16
Men	61 (63)	23 (77)	
Women	36 (37)	7 (23)	
Skin involvement, n (%)	97 (100)	30 (100)	NA
Necrotic purpura	30 (31)	9 (30)	0.92
Fibrinoid necrosis at biopsy	25 (26)	8 (27)	0.92
Joint involvement, n (%)	65 (67)	16 (53)	0.17
Renal involvement, n (%)	69 (71)	21 (70)	0.90
Proteinuria >1 g/d, n (%)	46 (47)	16 (53)	0.57
Proteinuria >3 g/d, n (%)	22 (23)	9 (30)	0.41
Hematuria, n (%)	58 (60)	17 (57)	0.76
Creatinin, median [Q1; Q3]	76 (67-104)	88 (78-110)	0.31
eGFR, median [Q1; Q3]	95 (65-111)	86 (57-96)	0.14
Biopsy performed, n (%)	59 (61)	19 (63)	0.80
Endocapillary GN, n (%)	31 (53)	11 (58)	
Extracapillary GN, n (%)	30 (51)	8 (42)	
GI involvement, n (%)	55 (57)	15 (50)	0.52
Ileus	4 (4)	1 (3)	1*
Bleeding	28 (29)	4 (13)	0.09
Surgical abdomen	2 (2)	1 (3)	0.56*
First line treatment, n (%)			0.17
CS (n=80)	64 (66)	16 (53)	
CS + CYC (n=30)	23 (24)	7 (23)	
Colchicine (n=17)	10 (10)	7 (23)	

CS : corticosteroids ; CYC :cyclophosphamide ; GN :glomerulonephritis, GI :gastrointestinal
* Fisher exact test.



Efficacy of Corticosteroids or Cyclophosphamide versus Colchicine



Efficacy of Corticosteroids plus Cyclophosphamide versus Corticosteroids alone