Resposta à corticoterapia na nefropatia da IgA primária

Corticotherapy response in primary IgA nephropathy

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Abstract

Introduction: Some beneficial effects from long-term use of corticosteroids have been reported in patients with IgA nephropathy. **Objective:** This retrospective study aimed to evaluate the outcome of proteinuria and renal function according to a protocol based on a 6-month course of steroid treatment. **Method:** Twelve patients were treated with 1 g/day intravenous methylprednisolone for 3 consecutive days at the beginning of months 1, 3, and 5 plus 0.5 mg/kg oral prednisone on alternate days for 6 months (treated group). The control group included 9 untreated patients. **Results:** Proteinuria (median and 25th and 75th percentiles) at baseline in the treated group was 1861 mg/24h (1518; 2417 mg/24h) and was 703 mg/24h (245; 983) and 684 mg/24h (266; 1023) at the 6th ($p < 0.05$ *vs.* baseline) and 12th months ($p < 0.05$ *vs.* baseline), respectively. In the control group the proteinuria was 1900 mg/24h (1620; 3197) at baseline and was 2290 mg/24h (1500; 2975) and 1600 mg/24h (1180; 2395) at the 6th and 12th months, respectively (not significant *vs.* baseline). When compared with the control group, the treated group showed lower proteinuria ($p < 0.05$) during the follow-up and a higher number of patients in remission ($p < 0.05$) at the 6th and 12th months. Renal function did not change during the follow-up and the adverse effects were mild in most of the patients. **Conclusion:** The 6-month course of steroid treatment was effective in reducing proteinuria during the 12 months of the follow-up, and was well-tolerated by most of the patients.

Keywords: glomerular filtration rate, glomerulonephritis, IgA, proteinuria, steroids.

Resumo

Introdução: Tem sido sugerido que tratamento mais prolongado com corticosteroides pode ser benéfico em pacientes com nefropatia da IgA primária. **Objetivo:** Neste estudo retrospectivo avaliamos os efeitos na proteinúria e na função renal após 12 meses do protocolo baseado no uso por 6 meses de corticosteroides. **Método:** Doze pacientes receberam pulsos de 1 g/dia de metilprednisolona intravenosa por 3 dias consecutivos no início dos meses 1, 3 e 5, seguidos por prednisona (0,5 mg/kg) por via oral em dias alternados após cada pulso durante 6 meses (grupo tratado). O grupo controle foi composto por nove pacientes não tratados. **Resultados:** A proteinúria (mg/24h; mediana; 25º; 75º percentis) no período basal no grupo tratado foi de 1861 (1518; 2417) e de 703 (245; 983) e de 684 (266; 1023) nos 6º ($p < 0,05$ *vs.* basal) e 12º ($p < 0,05$ *vs.* basal) meses, respectivamente. No grupo controle, a proteinúria foi de 1900 (1620; 3197) no período basal e de 2290 (1500; 2975) e de 1600 (1180; 2395) nos 6º e 12º meses, respectivamente (não significantes *vs.* basal). Comparado com o grupo controle, o grupo tratado teve menor proteinúria ($p < 0,05$) e número maior de pacientes em remissão ($p < 0,05$) nos 6º e 12º meses. A função renal não teve alteração significante e eventos adversos foram de pequena intensidade na maioria dos pacientes. **Conclusão:** O protocolo terapêutico baseado no uso por 6 meses de corticosteroides foi efetivo em reduzir a proteinúria durante os 12 meses de seguimento e foi bem tolerado pela maioria dos pacientes.

Palavras-chave: glomerulonefrite por IgA, glucocorticoides, proteinúria, taxa de filtração glomerular.

Introduction

Primary IgA nephropathy (IgAN) is considered to be the most common primary glomerulopathy worldwide and is a significant cause of chronic kidney disease (CKD).[1] Patients with IgA nephropathy presenting with normal renal function, persistent microscopic hematuria, and minimal or no proteinuria have excellent long-term prognosis.[2] However, sustained high proteinuria levels during follow-up in IgA nephropathy is accepted to be the most important predictor of the rate of renal function decline.[3] For these patients, rate of progression to CKD stage V is estimated nearly 15% at 10 years and 20% to 30% at 20 years.[4-7] On the other hand, patients with proteinuria higher than 3 g/24h at presentation who achieved proteinuria lower than 1 g/24h with treatment showed a similar clinical course to those patients who had proteinuria lower than 1 g/24h.[3] The real incidence of primary IgAN is unknown, but it was recently demonstrated to be at least 2.5/100,000/year in adults[8]. It is note-worthy that this disease can exist sub clinically, and it is therefore only detected by chance in some patients. In Brazil, the São Paulo Registry of Glomerulopathies reported that 17.8% of all biopsies of native kidneys were diagnosed as IgAN,[9] and one nephropathology center reported from a total of 4,619 renal biopsies with primary glomerulopathies, IgAN corresponded to 20.1%.[10]

Proteinuria is an important and independent predictor of adverse outcomes in patients with glomerulopathies, including IgAN.[3,11-13] While nephrotic range proteinuria levels are necessary to confirm a poor prognosis in most glomerular diseases, this seems to happen at much lower levels in primary IgAN.[3,11,12] The goal of any treatment of IgAN aims to decrease the proteinuria levels in order to provide a cure or at least achieve better long-term renal survival.

There is no established therapy for this disease, although some treatments according to specific classes of severity have been discussed.[14-16] Treatment based on low-dose corticosteroids has no effect on kidney survival.[17] However, the use of relatively higher doses of corticosteroids over several months has shown better results.[18,19] A 1999 controled and randomized study, by Pozzi *et al.*[20] investigated patients with proteinuria < 3.5 g/24h and a relatively well-preserved renal function. Patients were submitted to a 6-month course of steroid treatment, and the authors showed renal survival was significantly better in the steroid-treated group than in the untreated group after 5 years.

Although randomized controlled trials (RCTs) are the gold standard in evaluating the effects of IgAN treatment, results must be relevant to specific patient populations in different clinical settings. In this context, studies measuring the degree of beneficial effect of treatment under "real world" clinical settings could generate new hypothesis or confirm previously result obtained in RCT. The aim of the present study was to evaluate the outcome of proteinuria levels and renal function during treatment with Pozzi's protocol in patients with primary IgAN from a single nephrology center.

Methods

In this retrospective study, we reviewed the medical records of 165 patients (all at least 15 years old) with biopsy-proven IgAN from 1988 to 2010 at our Institution in order to select those who fulfilled the inclusion criteria. We assigned the patients to groups according to the period of diagnosis: the non-treated group (control group) consisted of patients diagnosed between 1988 and 2001, a period during which supportive therapy alone was used for patients with non-nephrotic proteinuria; and the treated group consisted of patients diagnosed between 2002 and 2010 and treated with steroids according to the Pozzi's protocol.[20] The supportive therapy was applied to both groups and was based mainly on ACE-inhibitors or angiotensin receptor blockers (ARB) in order to decrease proteinuria, arterial blood pressure control with other anti-hypertensive drugs and low salt diet, and statin therapy if necessary. The study was approved by the local Research Ethics Committee and it was performed in accordance with the ethical standards laid down in the 2000 Declaration of Helsinki as well as the Declaration of Istanbul 2008.

The inclusion criteria included: age 15 to 69 years, urinary protein excretion of 1,000 to 3,500 mg/24h, and serum creatinine concentrations of 1.5 mg/dL or less. Exclusion criteria were previous (within 12 months) treatment with steroids or cytotoxic drugs, pregnancy, or clinical or biological evidence of Henoch-Schönlein purpura, alcohol abuse, lupus erythematosus, diabetes mellitus,

neoplasia, active peptic-ulcer disease, viral hepatitis, or other infectious or inflammatory diseases.

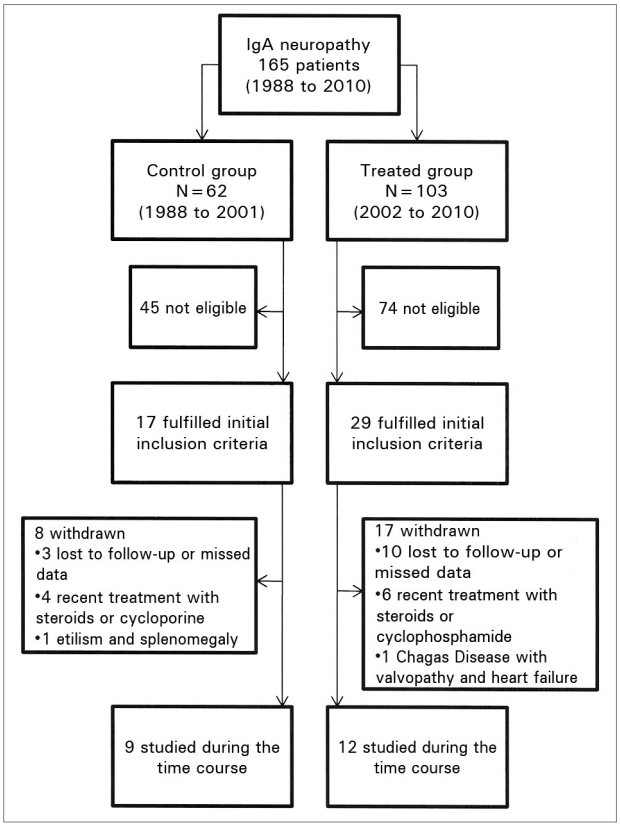
The onset of IgA nephropathy was arbitrarily defined as the first macroscopic hematuria episode or the detection of urinalysis abnormalities by chance or edema noticed by the patient. The glomerular filtration rate was estimated by the abbreviated MDRD formula[21] (eGFR). All of the diagnoses of IgA nephropathy were confirmed by the presence of typical predominant or codominant mesangial deposits of IgA by immunofluorescence microscopy. Histologic grading of the renal biopsy samples was performed by a central pathologist in accordance with the classification published by Haas.[22] One non-treated patient's renal biopsy specimen for histologic grading was unavailable. However, this 25-year-old patient had the typical mesangial IgA deposition upon immunofluorescent microscopy, recurrent macroscopic hematuria as clinical presentation of IgA nephropathy, and a serum creatinine concentration of 0.8 mg/dL.

Of the 17 eligible patients in the control group, nine were studied and eight were withdrawn; of the 29 eligible patients in the treated group, 12 were studied and 17 were withdrawn (Figure 1). Baseline levels of the control group were those at the time of biopsy. For the treated group, baseline levels were those at the beginning of the steroid treatment that was no longer than 3 months from the biopsy in 10 patients and 6 months and 36 months in the remaining two patients, respectively.

The treatment protocol was based on 1 g intravenous methylprednisolone per day for three consecutive days at the beginning of months 1, 3, and 5 plus 0.5 mg/kg oral prednisone on alternate days for 6 months according to Pozzi's protocol.[20]

The primary objective was to assess whether the 6-month course of corticosteroids improved proteinuria at the 6th and 12th months after the beginning of the steroid treatment. Remission was defined by the presence of both proteinuria less than 1000 mg/24h and reduction of proteinuria to at least 50% of the baseline level. The secondary objective was to assess whether the steroid treatment preserved renal function (measured by serum creatinine levels and eGFR). The systolic and diastolic blood pressure and the total and relative (percentage) body weight increase from baseline to the 6th month was evaluated.

Figure 1. Trial profile of patients with primary IgA nephropathy.



Once the statistical tests do not have enough power to assure Gaussian distribution of the samples, we used only non-parametric statistical tests. The Mann-Whitney U test was employed to evaluate the variables at the baseline. The Kruskal-Wallis test was employed to evaluate the proteinuria, serum creatinine, eGFR, and systolic and diastolic blood pressure during follow-up. Changes in proteinuria and eGFR over time between the two groups were also compared using Friedman test for repeated measures. Categorical variables (gender and number of remissions at different time points between the two groups) were compared using a Fisher's exact test. Data are expressed as median and 25th and 75th percentiles. All p values were two-tailed and $p < 0.05$ was considered statistically significant.

Results

As shown in Table 1, the control and treated groups at the baseline had no statistically significant differences related to age and gender distributions, duration of IgA nephropathy from clinical presentation to renal biopsy, systolic and diastolic blood

Table 1 Baseline demographic and clinical features of the control (untreated) and treated (corticosteroids) groups of patients with primary IgA nephropathy

Clinical features	Control group (n = 9)	Treated group (n = 12)	*p*
Gender (male/female)	7/2	4/8	0.085
Age (years)	32.0 (21.0; 34.0)	35.0 (30.0; 38.0)	0.188
Time from clinical presentation to biopsy (months)	36.0 (27.0; 56.0)	24.0 (7.5; 57.0)	0.372
Systolic blood pressure (mmHg)	130.0 (120.0; 140.0)	128.0 (112.5; 137.5)	0.490
Diastolic blood pressure (mmHg)	80.0 (75.0; 90.0)	80.0 (70.0; 90.0)	0.825
Body weight (kg)	75.0 (72.4; 81.25)	74.5 (63.7; 87.8)	0.859
Proteinuria (mg/24h)	1900 (1620; 3197)	1861 (1518; 2417)	0.374
Serum creatinine (mg/dL)	0.90 (0.80; 1.05)	1.20 (1.00; 1.30)	0.057
Estimated GFR* (mL/min/1.73 m^2)	114.3 (72.5; 126.8)	66.2 (55.6; 76.3)	0.009
Serum albumin (g/dL)	4.1 (3.9; 4.7)	3.8 (3.5; 4.1)	0.123
Grade of histologic classification [1]	2.5 (2.0; 3.0)	2.0 (2.0; 2.7)	0.298

* Estimated GFR: glomerular filtration rate evaluated by abbreviated MDRD formula[2]; Mann-Whitney U test; data are presented as median (25th percentile; 75th percentile).

pressure, body weight, serum albumin concentration, proteinuria, and grade of renal histology.[22] However, the treated group showed a statistical tendency of increased serum creatinine levels and a statistically significant lower levels of the eGFR ($p = 0.009$).

The most common clinical presentation of the primary IgAN was recurrent visible hematuria in six patients of the control group (associated with upper respiratory tract infection in two patients and diarrhea in one patient) and in six patients of the treated group (also associated with upper respiratory tract infection in two patients and diarrhea in one patient). Other clinical presentation patterns included: microscopic hematuria associated with asymptomatic proteinuria, which was identified by chance in a urine screening of one patient in the control group and four in the treated group, followed by edema in two patients in the control group, and isolated foamy urine in two patients in the treated group.

Seven patients in the control group were treated with a low dose ACE-inhibitor, and two received no drugs. In the treated group, all patients were treated with either an ACE-inhibitor or ARB, five of them at low dose and seven at high dose. Only one patient was treated with an ACE-inhibitor and ARB in combination. No patient in the control group and only one patient in the treated group had previously received a course of oral prednisone up to two years before beginning the current 6-month course of steroid treatment.

As shown in Table 2 and Figure 2A, the proteinuria level in the treated group was significantly lower at the 6th and 12th months compared to baseline, while the control group showed no statistical differences at these same time points. Proteinuria was significantly lower in the treated group when compared to control group at the 6th and the 12th months (Table 2 and Figure 2A). Remission occurred in nine patients of the treated group *vs*. none in the control group at the 6th month ($p < 0.01$), and in nive patients *vs*. one ($p < 0.01$) at the 12th month in the treated and control groups, respectively.

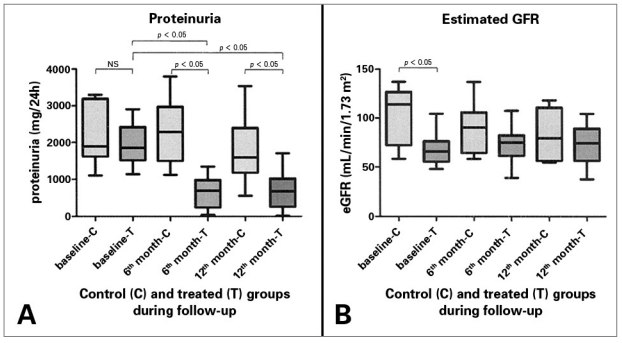
Table 2 Proteinuria of the control (untreated) and treated (corticosteroid) groups of patients with primary IgA nephropathy at baseline and during the 12 months of follow-up

	Proteinuria (mg/24h; median and 25th and 75th percentiles)		
Groups	Baseline	6th month	12th month
Control (n = 9)	1900 (1620; 3197)	2290 (1500; 2975)	1600 (1180; 2395)
Treated (n = 12)	1861 (1518; 2417)	703*,** (245; 983)	684*,** (266; 1023)

* $p < 0.05$ *versus* baseline; ** $p < 0.05$ control *versus* treated groups at the same occasion; (Kruskal-Wallis test); data are presented as median (25th percentile; 75th percentile).

In the control group, serum creatinine levels were 0.90 mg/dL (0.80; 1.05 mg/dL) at baseline (Table 1) and 1.00 mg/dL (0.90; 1.10 mg/dL), and 1.20 mg/dL (0.90; 1.20 mg/dL) at the 6th and 12th months, respectively. No statistical difference was found during the follow-up compared to baseline.

Figure 2. Graphics depict the (A) proteinuria levels and (B) estimated glomerular filtration rate during the 12 months of follow-up of patients with primary IgA nephropathy who were untreated (control) or treated with corticosteroids. The lines in the middle and those limiting the boxes indicate the median and 25th and 75th percentile values, respectively. Whiskers show the largest and smallest observed values. NS: not significant difference.



In the treated group, serum creatinine levels were 1.20 mg/dL (1.00; 1.30 mg/dL) at baseline (Table 1) and 1.15 mg/dL (0.82; 1.35 mg/dL) and 1.05 mg/dL (0.80; 1.40 mg/dL) at the 6th and 12th months, respectively, and no statistical difference was observed during the follow-up compared to baseline. Serum creatinine levels of the control *vs.* treated groups at the 6th and 12th months also showed no statistical difference. Estimated GFR was lower at baseline in the treated group [66.2 mL/min/1.73 m^2 (55.6; 76.3)] compared to the control group [114.3 mL/min/1.73 m^2 (72.5; 126.8)] (Table 1 and Figure 2B). However, eGFR (mL/min/1.73 m^2) in the treated group was 75.2 (61.5; 82.3) and 74.7 (56.7; 89.3) at 6th and 12th months, respectively, which did not reach statistical significance (Figure 2B). The eGFR in the control group was 75.8 (58.9; 125.5) and 77.1 (55.7; 112.0) at the 6th and 12th months, respectively, and also showed no statistically significant difference (Figure 2B). During the follow-up, eGRF did not show statistically significant differences between control and treated groups at the 6th and 12th months.

Most patients of the treated group showed good tolerance to steroid treatment after the 6-month course of steroid therapy. Two patients showed mild hypertension in the treated group, but there was no statistical difference in systolic and diastolic blood pressures between groups. Only one patient presented cushingoid facies, acne and striae rubrae, and another one presented moderate cutaneous mycosis. Most patients in the treated group presented weight gain with a median of 4.55 kg (0.62; 7.12 kg), but it was not statistically different compared with the control group, which had a weight gain of 3.55 kg (2.75; 3.55 kg). The relative weight gain was 6.0% (3.1%; 8.7%) in the treated group and 4.6% (2.6; 4.8%) in the control group (not statistically significant).

Discussion

In the present study, a 6-month course of steroid treatment caused a significant reduction in the proteinuria levels and higher frequency of remission during the first year compared to control group. These results are similar to the original study by Pozzi *et al.*,[20] who showed proteinuria excretion decreases in the steroid-treated group and remains unchanged in the control group. Later, the same researchers demonstrated that after a median follow-up of 7 years, proteinuria remains lower in the steroid group.[23] Moreover, this 6-month course of steroid treatment protects against deterioration in renal function after 5 and 10 years of follow-up.[20,23] Patients in the present study were followed-up for only 12 months, which is not long enough to detect changes in glomerular filtration rate.

Although uncommon, spontaneous remission can also happen in the non-treated patients. However, the 6-month steroid course used in the present study was much more effective to induce remission. Since relapses are expected, other strategies must be defined. In an attempt to reduce the loss of renal function in high-risk-adult patients with IgAN, Pozzi *et al.*[24] added a 6-month course of azathioprine to a 6-month corticosteroid treatment. No difference between the two treatment groups was found concerning maintaining renal function or decrease in proteinuria, and adverse effects were significantly more common in the combined corticosteroid and azathioprine group.[24]

In this study, the treated group showed a lower estimated GFR at baseline compared to control group. However, the treated group that was expected to have the worst prognosis,[25-27] had a significant reduction of proteinuria levels.

One of the limitations of this study is the sample size of each group. In fact, we selected the patients available at our institution according to the inclusion and exclusion criteria. Even so, these sample sizes show very consistent results,

and we believed there were enough patients to show the beneficial effects of this treatment. Another limitation is that this is a retrospective and non-randomized study. However, prospective, randomized controlled trials to evaluate treatment of primary IgA nephropathy are few, and most studies have used approaches similar to the present study.[27] Finally, the present study focused on the effects during the first 12 months of treatment, and this time is not long enough to study the efficiency of this treatment to preserve renal function. For this effect would be necessary 5 to 10 years of follow-up.

There is a consensus that the three major independent consensual risk factors predictive of progression toward CKD stage V are arterial hypertension, proteinuria with a usual cut-off over 1 g/24h, and the presence of severe lesions on initial renal biopsy such as crescents, abundant obsolescent glomeruli, segmental hyalinosis, and tubulointerstitial fibrosis.[28,29] In our study, the use of an ACE-inhibitor or ARB seemed to be more intensive in the treated group compared to the control group. This difference could have some effect on the proteinuria levels observed in this group. Indeed, a retrospective study found patients followed-up from 1996 through 2006 had higher renal survival rates than those followed-up before 1995.[27] This difference was attributed to the more intensive use of the renin-angiotensin inhibitors and corticosteroid therapy in the more recently followed-up group. Using a multivariate model, it has been demonstrated that proteinuria together with high serum creatinine and histological severity at clinical presentation are independent risk factors.[27] During analysis of another study of Pozzi *et al*.,[24] which reported that the addition of azathioprine does not improve long-term renal survival in patients treated with the 6-month course of corticosteroid therapy, an editorial[16] considered it a limitation of the study that fewer than half of the patients received an ACE-inhibitor or ARB at baseline. According to the 2011 Kidney Disease: Improving Global Outcomes (KDIGO) Clinical Practice Guideline for Glomerulonephritis, optimization of supportive care before considering steroids or other immunosupressive agents is recommended unless the patient shows a rapidly progressive disease course.[30] We also agree that a reduction in proteinuria with ACE-inhibitors or ARB in renal diseases, including IgAN, improves the renal survival.[3,13,31] However, it has also been demonstrated that combining corticosteroid and ACE-inhibitors is superior to ACE-inhibitors alone in preventing the progression of renal disease in proteinuric IgAN patients.[32,33]

Most patients in the treated group showed good tolerance to steroid treatment after a 6-month course of therapy. Even the weight gain and change in the blood pressure were not statistically higher compared to the control group. This good tolerance to steroids is similar to the study of Pozzi *et al*., which used the same corticosteroid protocol.[20]

The pathogenesis of IgA nephropathy has been recently reviewed,[34,35] and the several cells such as macrophages,[36] myofibroblasts, and mast cells[37] and several mediators including monocyte chemoattractant protein-1[38] and nuclear factor κ-B[39] have been shown to participate in the inflammatory response. The effects of corticosteroids on this disease remain to be clarified, but some may be related to its action on the inflammatory response and cellular signaling. One question that arises is whether it is necessary to use intravenous pulse of methylprednisolone or whether oral corticosteroids are sufficient. One study suggests that pulse steroid therapy decreases the risk of CKD stage V compared to oral steroid therapy;[40] however, this study used different schedules than Pozzi *et al*.[20,23] and that used in the present study. In spite of our choice to use Pozzi's protocol, other treatment regiments with oral corticosteroids have been successful.[18,19,32,33] A recent meta-analysis concluded that steroid therapy was associated with a decrease in proteinuria and with a statistically significant reduction of the risk in CKD stage V.[41] Furthermore, the 2011 Kidney Disease: Improving Global Outcomes (KDIGO) Clinical Practice Guideline for Glomerulonephritis[30] suggests that corticosteroid regimens based on either Pozzi's protocol or a 6-month regime of oral prednisone should be used.

In conclusion, in patients with IgAN and non-nephrotic proteinuria and relatively well-preserved renal function, the 6-month course of steroid treatment based on Pozzi's protocol is able to reduce the level of proteinuria and to cause at least partial remission in most patients during the first 12 months, an outcome uncommon in untreated patients. This treatment

was well-tolerated and resulted only in mild adverse effects in most of the patients.

Conflicts of interest

The authors declare that have no potential conflicts of interest related with the content of this study.

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