Rheumatol Int (2012) 32:2999–3005
DOI 10.1007/s00296-011-2136-z

ORIGINAL ARTICLE

Evaluation of weekly-reduction regimen of glucocorticoids in combination with cyclophosphamide for anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis in Japanese patients

Yoshinori Matsumoto · Ken-ei Sada · Fumio Otsuka · Mariko Takano · Noriko Toyota · Koichi Sugiyama · Hiroshi Wakabayashi · Tomoko Kawabata · Hirofumi Makino

Received: 8 May 2011 / Accepted: 22 August 2011 / Published online: 7 September 2011

Abstract The current therapeutic regimen recommended by the European League against Rheumatism (EULAR) for anti-neutrophil cytoplasmic antibody-associated vasculitis (AAV) is continuation of initially administered doses of glucocorticoids (GCs) in combination with cyclophosphamide (CYC) for 1 month followed by gradual tapering. Considering the adverse effects of GCs, another tapering regimen of GCs with CYC, which was characterized by tapering GCs weekly, was reported by the British Society of Rheumatology (weekly-reduction regimen). The aim of the present study is to evaluate the safety and efficacy of this weekly-reduction regimen for Japanese AAV patients in comparison with the monthly-reduction regimen recommended by the EULAR. We retrospectively reviewed medical records of adult patients newly diagnosed with AAV during the period from April 2000 to December 2010. The outcome measures were rates of remission, relapse, infection, and GC-induced diabetes mellitus during the first 12 months. Clinical data in the two groups and categorial variables with a possible relation to the outcomes were compared by using the *t* test and chi-square test, respectively. Twenty-four patients were enrolled in our study. All of the patients achieved remission, and the rates of relapse during the first 12 months were not statistically different between the two groups ($P = 0.16$). Patients treated with the weekly-reduction regimen were less liable to have infection ($P = 0.03$) and impaired glucose tolerance ($P = 0.017$), compared with those treated with the monthly-reduction regimen. A therapeutic strategy using the weekly-reduction regimen of GCs would be effective and would have fewer side effects than the monthly-reduction regimen.

Keywords Anti-neutrophil cytoplasmic antibody-associated vasculitis · Glucocorticoids · Cyclophosphamide · Retrospective studies

Y. Matsumoto (✉) · K. Sada · F. Otsuka · M. Takano · N. Toyota · K. Sugiyama · H. Wakabayashi · T. Kawabata · H. Makino
Department of Medicine and Clinical Science, Okayama University Graduate School of Medicine, Dentistry and Pharmaceutical Sciences, 2-5-1 Shikata-cho, Kitaku, Okayama City 700-8558, Japan
e-mail: yossy.m0629@nifty.com

Introduction

The current therapeutic regimen recommended by the European League against Rheumatism (EULAR) for anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV) is treatment with high-dose glucocorticoids (GCs) in combination with cyclophosphamide (CYC). According to the recommendation, initial dose of GCs (1 mg/kg/day of prednisolone) in combination with CYC should be continued for 1 month followed by gradual tapering [1]. However, the appropriate dose and duration of administration of GCs for the treatment of AAV have not yet been determined. Long-term use of high-dose GCs increases the risk of various complications including infection, which is one of the main causes of morbidity and mortality in patients with rheumatic diseases [2–9]. Moreover, high-dose GCs have been reported to be responsible for the progression of impaired glucose tolerance [10–13]. Considering the effects of GCs on morbidity and mortality, another tapering regimen of GCs in combination with CYC was reported in guidelines published by the British Society of Rheumatology (BSR) in 2007 [14]. This regimen is characterized by tapering GCs weekly. In recent randomized controlled studies by the EULAR and other European

researchers, this weekly-reduction regimen of GCs in combination with CYC has been used instead of 1-month continuation of initial high-dose GCs (monthly-reduction regimen) [15–19]. However, the efficacy and safety of this weekly-reduction regimen compared to the monthly-reduction regimen for AAV patients have yet to be elucidated.

The aim of the present study was to determine the safety and efficacy of the weekly-reduction regimen of GCs with CYC for AAV patients in Japan in comparison with the previous protocol, i.e., monthly-reduction regimen of GCs with CYC.

Patients and methods

Subjects

We retrospectively reviewed medical records of adult patients with AAV who were admitted to Okayama University Hospital during the period from April 2000 to December 2010. Patients newly diagnosed with microscopic polyangiitis (MPA) or Wegener's granulomatosis (WG) who were treated with GCs in combination with intravenous CYC (IVCY) were enrolled in our study. Patients were classified as MPA or WG with the European Medicines Agency (EMEA) algorithm (2007) [20]. Since the purpose of our study was to compare two regimens with a focus on how to taper GCs in combination with IVCY, patients who were administered IVCY more than three times were enrolled in our study. This study was approved by the Ethics Committee of Okayama University Hospital.

Study protocol

Both regimens consisted of oral prednisolone and monthly IVCY. As recommended by the EULAR in 2009, the dose of CYC was reduced in patients with impaired renal function and in patients older than 60 years of age. In the weekly group (treated with the weekly-reduction regimen), prednisolone was tapered according to the BSR guideline (Table 1). Initial dose of prednisolone in the monthly group (treated with the monthly-reduction regimen) was maintained for at least 1 month and then tapered gradually. Administration of IVCY was continued for 3 months after disease remission in both groups. We used prophylaxis for *Pneumocystis jiroveci* and fungal infection in patients enrolled in our study.

Study endpoints

The primary endpoints were the rates of remission and relapse during the first 12 months after commencement of treatment, and the secondary endpoints were the rate of infection during the first 12 months, and the proportion of patients who had developed and required treatment intervention for GC-induced diabetes mellitus (GC-induced DM) during the first 12 months. The Vasculitis Damage Index (VDI), which scores cumulative damage from any cause since disease onset, was also assessed at 6 and 12 months after commencement of treatment.

Table 1 Oral prednisolone dose for AAV in combination with CYC recommended by the BSR

Time from the commencement of treatment	Prednisolone dose	Prednisolone dose in case of 60 kg (mg/day)
0–1 week	1 (mg/kg/day)	60
1–2 weeks	0.75 (mg/kg/day)	45
2–3 weeks	0.5 (mg/kg/day)	30
3–6 weeks	0.4 (mg/kg/day)	25
6–8 weeks	0.33 (mg/kg/day)	20
8–12 weeks	15 (mg/day)	15
12–16 weeks	12.5 (mg/day)	12.5
16 weeks–6 months	10 (mg/day)	10
6–12 months	7.5 (mg/day)	7.5

AAV anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis, *CYC* cyclophosphamide, *BSR* British Society of Rheumatology

Study definitions

We defined disease remission as the absence of new or worse signs of disease activity, with the Birmingham Vasculitis Activity Score (BVAS) index of 0. BVAS indicates manifestations of vasculitis activity during a period of 4 weeks before the date of assessment [21]. We also defined relapse as the recurrence or first appearance of at least one BVAS item.

As in previous studies, infections were confirmed by the existence of supportive clinical features, laboratory findings, positive cultures, and radiographic evidence. When causal organisms were not identified, diagnosis of infections was made on the basis of clinical findings in combination with improvement following antimicrobial therapy [4, 22].

GC-induced DM was defined as hyperglycemia described in the guidelines of the World Health Organization being detected continuously and requiring treatment [23]. Continuous elevation of blood glucose levels (fasting glucose levels $\geqq$126 mg/dl and/or random glucose levels $\geqq$200 mg/dl) was regarded as hyperglycemia.

Statistical analysis

Statistical analysis was performed with JMP® 7 (SAS Institute Inc, USA). Clinical data in the two groups were compared by using the *t* test, and categorial variables with a

Table 2 Patient profile and comparability of the two treatment groups

	Monthly-reduction regimen ($N = 15$)	Weekly-reduction regimen ($N = 9$)	P value
Sex (M/F)	3:12	2:7	0.90
Age (years)	72.3 ± 1.9	71.4 ± 1.3	0.75
Body weight (kg)	48.3 ± 2.9	55.0 ± 3.7	0.17
BMI (kg/m^2)	21.7 ± 0.8	22.7 ± 1.9	0.61
Frequency and types of AAV (MPA/WG)	15:0	6:3	0.01*
BVAS	17.6 ± 1.6	15.0 ± 2.1	0.34
Presence of diabetes mellitus (yes)	1	3	0.37
Fasting blood glucose levels before treatment, mean ± SEM (mg/dl)	93 ± 4.3	93 ± 6.9	1.00
Postprandial blood glucose levels before treatment, mean ± SEM (mg/dl)	128 ± 8.7	140 ± 12.9	0.46
HbA1c before treatment, mean ± SEM (%)	5.4 ± 0.1	5.9 ± 0.2	0.04*
Use of methylprednisolone pulse (yes/no)	12 : 3	3 : 6	0.02*
Initial dose of prednisolone (mg/day)	32.0 ± 1.8	51.7 ± 2.3	<0.0001*
Cumulative dose of prednisolone during the first 12 months (mg)	4,815 ± 186	4,171 ± 240	0.045*
Cumulative dose of CYC during the first 12 months (mg)	2,523 ± 185	3,189 ± 239	0.038*

Data are expressed as numbers and means ± SEM

BMI body mass index, *AAV* anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis, *MPA* microscopic polyangiitis, *WG* Wegener's granulomatosis, *BVAS* Birmingham Vasculitis Activity Score, *CYC* cyclophosphamide

* P value <0.05

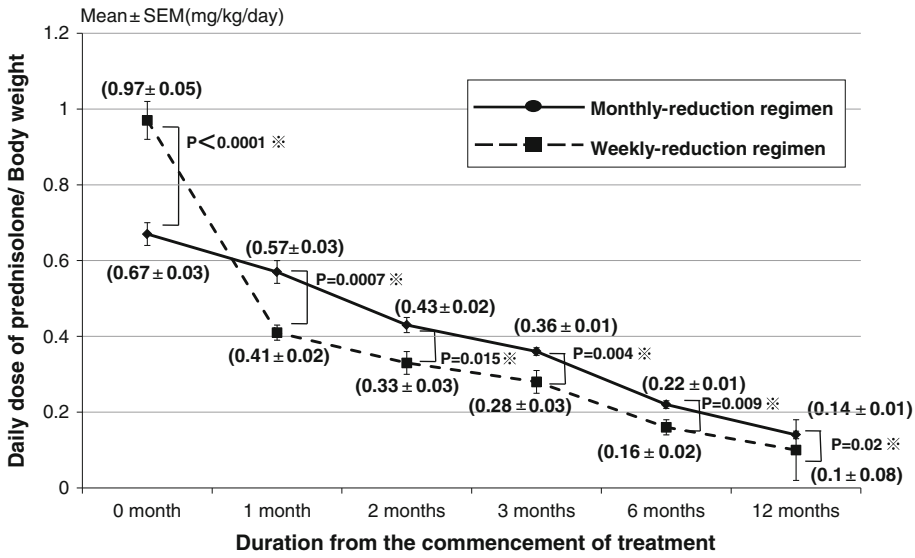

Fig. 1 Daily doses of prednisolone in the two groups. Data are expressed as means ± SEM. *P value <0.05

possible relation to the outcomes were compared by using the nonparametric chi-square test. Statistical significance was defined as a P value of less than 0.05, two-tailed.

Results

Baseline characteristics

In the period from April 2000 to December 2010, 24 patients were enrolled in our study. Baseline characteristics of the patients in each group are shown in Table 2. The mean ± SEM ages at diagnosis were 72.3 ± 1.9 years in the monthly group and 71.4 ± 1.3 years in the weekly group ($P = 0.75$). Except for the frequency and types of AAV, the differences between the two groups were not statistically significant. The numbers of patients with diabetes mellitus before treatment were 1 (6.7%) in the monthly group and 3 (33.3%) in the weekly group. Fasting glucose levels and postprandial glucose levels before treatment were similar in the two groups, but HbA1c level before treatment was higher in the weekly group.

Table 3 Characteristics of infectious complications

	Monthly-reduction regimen ($N = 15$)	Weekly-reduction regimen ($N = 9$)	P value
Patients who developed infectious episodes during the first 12 months (n)	10	2	0.03*
Severe or life-threatening	4	2	
Respiratory infection	3	1	
Infection secondary to neutropenia	1	0	
Herpes retinitis with ulcer formation	0	1	
Mild or moderate	6	0	
Respiratory infection	2	0	
Infectious colitis	1	0	
Urinary tract infection	1	0	
Herpes zoster infection	1	0	
Fever and elevation of CRP with improvement following antimicrobial therapy	1	0	

Data are expressed as numbers

* P value <0.05

Treatment in the two groups

The initial dose of prednisolone in the weekly group was higher than that in the monthly group (0.97 ± 0.05 mg/kg/day vs. 0.67 ± 0.03 mg/kg/day, $P < 0.0001$), while the daily dose of prednisolone 1 month after the commencement of treatment in the weekly group was lower than that in the monthly group (0.41 ± 0.02 mg/kg/day vs. 0.57 ± 0.03 mg/kg/day, $P = 0.0007$) (Fig. 1). In addition, the cumulative dose of prednisolone during the first 12 months in the weekly group was lower than that in the monthly group, whereas the cumulative dose of CYC during the first 12 months in the weekly group was higher than that in the monthly group (Table 2).

Disease remission and relapse

All of our patients achieved remission within the first 6 months. During the first 12 months, 13.3% in the monthly group and none in the weekly group had relapse ($P = 0.16$). VDIs at 6 months (2.7 ± 0.4 in the monthly group and 2.4 ± 0.5 in the weekly group, $P = 0.72$) and those at 12 months (2.6 ± 0.4 in the monthly group and 2.3 ± 0.6 in the weekly group, $P = 0.71$) were not statistically different.

Infectious complications

The rate of infectious episodes during the first 12 months in the weekly group was lower than that in the monthly group (10 of the 15 patients in the monthly group and 2 of the 9 patients in the weekly group, $P = 0.03$) (Table 3). About half of the infections were severe or life-threatening (in 4 of the 10 patients in the monthly group and in both of the 2 patients in the weekly group). The most frequent infection in our study was respiratory infection. No patient died from infectious complications.

Glucocorticoid-induced diabetes mellitus (GC-induced DM)

Comparison of patients who developed GC-induced DM in the two groups is shown in Table 4. During the first 12 months, 13 of 14 patients in the monthly group and 2 of 6 patients in the weekly group without DM before treatment developed GC-induced DM (92.9% in the monthly group and 33.3% in the weekly group, $P = 0.017$). Interestingly, all of these patients were diagnosed as having GC-induced DM by elevation of postprandial glucose levels ≧200 mg/dl, not by fasting glucose levels ≧126 mg/dl, and GC-induced DM occurred in all patients within the first month (20.3 ± 4.6 days in the monthly group and 10.5 ± 11.8 days in the weekly group) (Table 4). Glucose levels after lunch were drastically elevated by treatment with prednisolone, while fasting glucose and HbA1c levels were not changed (data not shown). Three patients in the monthly group, but none in the weekly group, with GC-induced DM were treated with insulin. Notably, about 50% of the patients with GC-induced DM were treated with anti-diabetic drugs continuously at the end of the observation period.

Discussion

In the present study, all of the patients achieved remission during the first 6 months. In addition, the rates of relapse during the first 12 months and the VDIs at 6 and 12 months after the commencement of treatment were not statistically different between the two groups. In six previous studies,

Table 4 Comparison of patients who developed GCs-induced DM in the two groups

	Monthly-reduction regimen ($N = 15$)	Weekly-reduction regimen ($N = 9$)	P value
Patients without DM before treatment, n1	14	6	0.37
Patients who had developed GCs-induced DM after treatment with prednisolone, n2 (n2/n1%)	13 (92.9%)	2 (33.3%)	0.017*
Duration from the commencement of treatment to diagnosis of DM, mean ± SEM (days)	20.3 ± 4.6	10.5 ± 11.8	0.45
Treatments			
Insulin + diet therapy	3	0	
α-glucosidase inhibitor + diet therapy	7	2	
Diet therapy only	3	0	
Patients treated with anti-diabetic drugs at the end of the observation period, n3 (n3/n2%)	6 (46.2%)	1 (50%)	
HbA1c at the end of the observation period, mean ± SEM (%)	5.4 ± 0.1	5.5 ± 0.2	0.43

Data are expressed as numbers and means ± SEM

GC-induced DM, glucocorticoid-induced diabetes mellitus

* P value < 0.05

the mean rate of remission induction during the first 6 months was 87% (range, 68–93%) [15–19, 24] and the rate of relapse during the first 12 months was approximately 10% [16]. Although the mean BVAS in our weekly group was almost the same as that in our monthly group and in the six previous studies (17.6 ± 1.6 in the monthly group, 15.0 ± 2.1 in the weekly group, and 18.9 in the CYCAZAREM study group) [16], the rates of remission and relapse in the weekly group were not inferior to those in the monthly group or those in the previous studies. Thus, the efficacy of the weekly-reduction regimen was not inferior to that of the monthly-reduction regimen.

The rate of infectious episodes during the first 12 months in the weekly group was significantly lower than that in the monthly group (Table 3). A review of patients in the European Vasculitis Study Group (EUVAS) trials showed that infection occurred during the first 12 months in 24% of the patients [25], almost the same rate as that in our weekly group, and that 50% of deaths within the first year were caused by infection [25, 26]. Another study showed that a high cumulative dose of CYC increases the risk of infection in AAV patients [27]. Although the cumulative dose of CYC during the first 12 months in the weekly group was high compared to that in the monthly group, the rate of infection in the weekly group was not higher than that in the monthly group. Lower rate of infectious episodes in the weekly group indicated that early reduction in the doses of GCs might reduce infection-related mortality.

We also investigated the safety of the weekly-reduction regimen with a focus on GC-induced DM. The number of patients with GC-induced DM during the first 12 months in the weekly group was smaller than that in the monthly group (Table 4). In previous studies, the rates of GC-induced DM in patients with connective tissue diseases were between 0.4 and 54% [28–33], almost the same as that in our weekly group but lower than that in our monthly group. The large variability in the rate of GC-induced DM may be due to differences in study populations, observation periods, and other factors, including doses of GCs and age, which are known to influence the risk of GG-induced DM [30, 33–40]. The mean age of patients in our study (over 65 years) was more advanced than that of patients in previous studies [16, 41], and our patients were therefore more liable to have impaired glucose tolerance when treated with GCs. Nevertheless, the rate of GC-induced DM in the weekly group was not larger than that in previous studies, suggesting that early reduction in the doses of GCs may reduce GC-induced DM.

Second, all of our patients who had developed GC-induced DM were diagnosed by postprandial glucose levels ≧200 mg/dl within the first month. Iwamoto et al. reported that GC-induced DM was diagnosed in most patients by elevation of postprandial glucose levels, not by fasting glucose and HbA1c levels [33]. The results of their study suggested that measuring only fasting glucose and HbA1c levels is not sufficient to diagnose GC-induced DM, particularly in the early phase of the treatment. Postprandial hyperglycemia is a risk factor for acute inflammation and endothelial dysfunction, leading to cardiovascular diseases [42–45]. However, a clear definition of GC-induced DM was not given in most previous reports on the use of high-dose GCs, and the proportion of patients with GC-induced DM, which should be diagnosed by postprandial hyperglycemia, might have been underestimated. Continuous measurement with a focus on postprandial hyperglycemia is necessary in order not to overlook occult GC-induced DM.

This is the first report on evaluation of a weekly-reduction regimen of GCs compared to a monthly-reduction regimen in combination with CYC for AAV in Japanese patients. The weekly-reduction regimen may be as effective as the monthly-reduction regimen in inducing remission without increase in relapse. In addition, earlier reduction in the doses of GCs is beneficial for reducing onset of infection

and diabetes due to decreases in both daily dose and cumulative dose of GCs. Our findings indicate that a therapeutic strategy using the weekly-reduction regimen of GCs would be effective and would have fewer side effects than the monthly-reduction regimen due to decreased risks of infection and diabetes. However, our retrospective study has limitations including selection bias, incompleteness of medical records, and short observation period. A future prospective study with a larger number of AAV patients is needed to confirm our findings and to determine the ideal and cost-beneficial therapeutic regimen for patients suffering from disease activity and adverse effects.

Acknowledgments This work was supported in part by grants from the Ministry of Health, Labour and Welfare, Japan.

Conflict of interest The authors declare that they have no conflict of interest.

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