Clinical Rheumatology (2018) 37:2789–2795
https://doi.org/10.1007/s10067-018-4094-2

ORIGINAL ARTICLE

Analysis of predictive factors for treatment resistance and disease relapse in Takayasu's arteritis

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Received: 6 November 2017 / Revised: 10 March 2018 / Accepted: 2 April 2018 / Published online: 23 April 2018

Abstract

The objective of the study was to investigate the long-term treatment effects and predictive factors for treatment response and disease relapse for Takayasu's arteritis (TA). Eighty-one patients were recruited from the Department of Rheumatology, Zhongshan Hospital, Fudan University, between January 2009 and January 2015. The follow-up duration ranged from 6 to 36 months. Patients were divided into three groups: clinical remission (CR; $n = 59$); treatment-resistant (TR; $n = 11$); and disease relapse (DR; $n = 11$). Signs/symptoms, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), and imaging items were recorded at baseline and at each visit. Kerr's criteria, physician's global assessment, and Indian Takayasu Clinical Activity Score (ITAS2010) were used to evaluate disease activity. Incipient disease was more common in CR patients compared with DR cases (69.49 vs. 36.36%, $p = 0.05$). Fewer patients aged < 40 years were in the CR group in comparison with the DR group (57.63 vs. 90.91%, $p = 0.04$). In TR patients, high CRP levels (63.74 vs. 23.73%, $p = 0.01$) and aortic arch involvement (70.00 vs. 24.14%, $p < 0.01$) were more common in comparison with CR cases. Patients with high CRP levels (> 25 mg/L) (OR = 1.61, $p = 0.03$) carried a higher risk for treatment resistance. Age > 40 years (OR = − 2.82, $p = 0.03$), incipient disease (OR = − 2.47, $p = 0.01$), and treatment with cyclophosphamide (OR = − 2.07, $p = 0.03$) and hydroxychloroquine (OR = − 1.91, $p = 0.05$) could prevent disease relapse. Patients with high CRP levels carry a high risk of treatment resistance. In patients with incipient disease, aged > 40 years, treatment with cyclophosphamide and hydroxychloroquine protects against disease relapse.

Keywords Clinical remission · Cyclophosphamide (CYC) · Disease relapse · Hydroxychloroquine (HCQ) · Takayasu's arteritis (TA) · Treatment resistance

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Introduction

Takayasu's arteritis (TA) is a rare, chronic vasculitis of the aorta and its major branches that appears commonly at a young age [1, 2]. TA is characterized by panarteritis with an inflammatory infiltrate that is predominantly lymphoblastic, with granuloma formation and giant cells involving the media and adventitia [3]. In general, TA has a prolonged, indolent course with constitutional features (fever, malaise, anorexia, weight loss), extremity pain/claudication, and light-headedness. Bruits, absent/diminished pulses, and absence of measurable blood pressure can be present depending on the location and extent of vessel involvement [4, 5]. Early diagnosis and effective treatments are essential to control disease progression and to prevent further organ dysfunction.

Widely accepted treatment guidelines or evidence for treatment to target TA is lacking. TA treatment is dependent primarily upon the experience of experts. Refractory cases and

disease relapses are seen frequently [6, 7]. Glucocorticoid (GC) with various immunosuppressants such as cyclophosphamide (CYC; i.v.) and high doses of methotrexate (MTX; p.o.), leflunomide (LEF; p.o.), or azathioprine (AZA; p.o.) can be used to induce TA remission [8–10]. In 2007, Setfano and colleagues found that induction treatment of CYC with prednisone for 3 months, with sequential use of MTX for 12 months, could control disease activity and improve the profile of inflammatory biomarkers, but that 50% of patients had disease relapse [11]. In 2012, Freitas et al. suggested that, in patients with initial treatment of prednisone and MTX, 75% developed new vascular lesions upon follow-up, and that 34.6% of patients needed to change immunosuppressive therapy due to treatment failure or drug toxicity [12]. In 2013, Schmidt et al. demonstrated that, through treatment of corticosteroids and additional immunosuppressants, 96% of patients experienced at least one remission of any duration at 5-year follow-up [3]. During recent years, the relative efficacy of treatments using biologic agents, anti-tumor necrosis factor (TNF)-α, anti-interleukin (IL)-6, or even B-cell depletion in TA patients has been shown [13–15]. However, evidence for standard treatments and prevention of disease relapse for TA is lacking.

We investigated the effects of long-term treatment of TA and if there are predictive factors for treatment response and disease relapse. To evaluate disease activity and treatment outcomes in a systematic manner, laboratory indices (erythrocyte sedimentation rate (ESR), C-reactive protein (CRP) level), release of inflammatory cytokines (IL-6, TNF-α), physician's global assessment (PGA), and Indian Takayasu Clinical Activity Score (ITAS2010) were used.

Methods

Ethical approval of the study protocol

The study protocol was approved by the Ethics Review Board of Zhongshan Hospital (Approval No. B2016-168, Fudan University, Shanghai, China). Written informed consent was obtained from all patients.

Subjects

Eighty-one patients were recruited from the Department of Rheumatology of Zhongshan Hospital between January 2009 and January 2015. Enrolled patients were aged at least 14 years and were diagnosed as TA by rheumatic specialists according to the criteria set by the American College of Rheumatology in1990 [16]. The whole-body contrast-enhanced magnetic resonance angiography (MRA) was used instead of angiography for the diagnosis.

Exclusion criteria were (i) heart failure (New York Heart Association grade IV); (ii) renal failure (creatinine clearance rate by the Modification of Diet in Renal Disease formula ≤ 30 mL/min); (iii) allergy or contraindication to therapeutic drugs; (iv) pregnancy planned within 2 years; and (v) cancer or chronic inflammatory disease (e.g., tuberculosis).

Treatments

The therapeutic procedure was divided into "induction treatment" and "maintenance treatment." During the induction phase, prednisone (0.8–1.0 mg/kg/day, p.o.) was started. If high disease activity with considerable organ dysfunction was present (e.g., involvement of the central nervous system, including epilepsy), methylprednisolone (≥ 2 mg/kg/day, i.v.; usually 80–240 mg/day) was given for 3–5 days and then prednisone (0.8 mg/kg/day, p.o.) was administered. After 4 weeks, the prednisone dose was tapered gradually to a maintenance dose of 0.1–0.2 mg/kg/day within the next 5 months. Meanwhile, one type of immunosuppressant (CYC, MTX, or AZA) was used according to the experience of the attending physician. CYC (0.5–0.75 g/m^2, i.v.; usually 0.8 g) was given every 4 weeks for ≥ 3 months. MTX (10–15 mg/week, p.o.) was administered initially and, if side effects were absent, the maximum dose could reach 25 mg/week. AZA (p.o.) was applied from a low dose (usually 25 mg/day) and 25 mg/day was added every 2 weeks until the final dose was ≤ 100 mg/day. The entire period of treatment induction using MTX or AZA was ≥ 6 months.

In the maintenance phase, application of CYC (i.v.) was stopped and was followed by MTX (10–15 mg/week, p.o.) or AZA (25–50 mg/day, p.o.) or LEF (10–20 mg/day, p.o.) as maintenance drugs. If MTX or AZA was the induction drug, the dose was reduced to 10–15 mg/week for MTX and 50–100 mg/day for AZA. If the induction treatment failed, the dose of GC would not be reduced.

Hydroxychloroquine (HCQ; 0.2 g/day, p.o.) was given as an immunomodulatory on the base of immunosuppressant (CYC, MTX, or AZA) according to the physician's experience. For patients with hypertension, one or more hypotensive agents (calcium channel blocker (CCB), angiotensin-converting enzyme inhibitor (ACEI), angiotensin receptor blocker (ARB), or diuretic) were given simultaneously.

Assessment of TA activity

Detailed information regarding signs and symptoms was recorded at baseline and at each visit. Laboratory parameters (complete blood count, ESR, CRP, inflammatory cytokines) were tested according to standard protocols. Drug-related side events were recorded at each follow-up. Incipient disease was defined as cases that were diagnosed as TA for the first time

and had no treatment history before including glucocorticoid and immunosuppressant.

PGA is the "gold standard" method for assessment of disease activity. The PGA is a general evaluation according to new/worsen symptoms, new/worsen physical signs, evaluated inflammatory parameters (ESR, CRP), and positive imaging findings (magnetic resonance angiography, computed tomography angiography, positron emission tomography/computed tomography, vascular ultrasound) [17]. Patients, who satisfied ≥ 2 items and had no other infective and inflammatory conditions, were defined as active disease. Two rheumatologists performed the evaluation in a systematic and independent way; if the initial opinion differed, a consensus was achieved by discussion. The Kerr criteria and ITAS2010 were also used to assess disease activity [17].

Definition of treatment response

Treatment response was defined according to the following criteria: (i) the dose of GC was reduced to no more than 15 mg/day through the induction treatment; (ii) ESR levels were normal (≤ 40 mm/h); and (iii) no new/worsen symptoms and physical signs. Patients were divided into three groups according to treatment response: (i) clinical remission (CR): patients satisfied all the criteria and did not complain of active disease during the remainder of follow-up; (ii) treatment-resistant (TR): patients did not achieve all the criteria when treated by GC combined with an immunosuppressant for 6 months, and even through an induction treatment prolonged to 9 months; and (iii) disease relapse (DR): patients went into disease remission at the end of induction treatment but suffered active disease during the remainder of follow-up.

Follow-up

In the first year of the study, the frequency of visits was once per month. If clinical remission was achieved, this frequency was once per 3 months. For patients in the CR group, the end of the follow-up was July 30, 2015, and the longest follow-up was 3 years. For patients in the TR group or DR group, the end was when adverse outcomes were observed.

Statistical analyses

Demographic characteristics are presented as the mean ± standard error for continuous variables, and frequencies and percentages for categorical variables. Univariate associations of individual clinical features between different response groups were analyzed with Fisher's exact test or Wilcoxon rank sum test, as appropriate. ANOVA was used to analyze the changing tendencies of disease activity markers during follow-up. To create predictive models for treatment resistance and disease relapse, factors with obvious differences ($p < 0.10$) in comparison with the CR group at baseline were chosen as candidate indicators. Logistic regression was modeled backwards to select strong predictors ($p < 0.05$). All analyses used $p = 0.05$ (two-sided) and were undertaken using SAS v9.4 (SAS, Cary, NC, USA).

Results

Patient characteristics

Eighty-one TA patients (mean age, 35 ± 3 years; female:male ratio, 8.33:1; mean duration of disease, 60 ± 27 months) were enrolled. The CR group contained 59 patients, whereas the TR group and DR group contained 11 subjects apiece. Patient characteristics at baseline are shown in Table 1.

Comparisons between patients with different treatment responses at baseline

Incipient disease was seen more commonly in patients with clinical remission compared with those with disease relapse (69.49% (41/59) vs. 36.36% (4/11), $p = 0.05$), whereas fewer patients aged < 40 years were in the CR group compared with the DR group (57.63% (34/59) vs. 90.91% (10/11), $p = 0.04$) (Table 1).

In patients resistant to treatment, systemic symptoms (90.01% (10/11) vs. 45.76% (27/59), $p < 0.01$) and high CRP levels (63.74% (7/11) vs. 23.73% (14/59), $p = 0.01$) as well as involvement of the aortic arch (70.00% (8/11) vs. 24.14% (14/59), $p < 0.01$) were seen more frequently in comparison with those with remission. However, vascular bruits (31.36% (4/11) vs. 71.93% (43/59), $p = 0.04$) were seen less commonly in treatment-resistant patients. Indices of disease activity (PGA, ITAS, ITAS-ESR, ITAS-CRP) did not show significant differences at baseline between the groups (Table 1).

CYC (i.v.) was given to 62.71% (37/59) of patients in the CR group, whereas 72.73% (8/11) of patients in the TR group received CYC. There were no significant differences in the prevalence of CYC administration and dose between these two groups. Prevalence of CYC administration was significantly lower in the DR group compared with the CR group ($p < 0.01$). HCQ was administered to 57.63% (34/59), 36.36% (4/11), and 27.27% (3/11) of patients in the CR, TR, and DR groups, respectively (CR vs. TR group, $p = 0.19$; CR vs. DR group, $p = 0.06$) (Table 1).

Changes in laboratory parameters and disease activity during follow-up

In the DR group throughout treatment, mean levels of ESR decreased significantly from 47.18 ± 33.37 to 7.60 ± 6.95 mm/h

Table 1 Patient characteristics at baseline (mean ± SE)

Groups	CR ($n = 59$)	TR ($n = 11$)	DR ($n = 11$)	P	P^*
Demographic data					
Incipient cases (%)	41 (69.49)	9 (81.82%)	4 (36.36)	0.41	0.05
Age (years)	37 ± 2	31 ± 4	32 ± 3	0.14	0.24
Age (< 40 years, %)	57.63	81.82	90.91	0.18	0.04
Symptoms					
Systemic symptoms (fatigue, fever, etc.) (%)	27 (45.76)	10 (90.91)	3 (27.27)	0.006	0.33
Nervous system symptoms (headache, dizziness, etc.) (%)	27 (45.76)	7 (63.63)	2 (18.18)	0.28	0.11
Cardiovascular symptoms	59 (100)	11 (100)	11 (100)	–	–
Increasing DBP (%)	22 (36.84)	1 (9.09)	3 (27.27)	0.09	0.70
Increasing SBP (%)	26 (43.86)	3 (27.27)	4 (36.36)	0.50	1.00
Claudication (%)	12 (20.34)	4 (36.36)	2 (18.18)	0.27	1.00
Carotidodynia (%)	14 (23.73)	1 (9.09)	0 (0.00)	0.43	0.18
Aortic incompetence (%)	14 (23.73)	0 (0.00)	3 (27.27)	0.10	1.00
Ischemic cardiac pain (%)	1 (1.75)	2 (18.18)	0 (0.00)	0.07	1.00
Physical signs					
Asymmetric pulse (%)	26 (45.61)	7 (63.64)	4 (36.36)	0.27	0.72
Absence of pulse (%)	21 (35.09)	6 (54.55)	2 (12.5)	0.31	0.26
Asymmetric blood pressure (%)	21 (35.09)	6 (54.55)	4 (36.36)	0.31	1.00
Bruits (%)	43 (71.93)	4 (31.36)	5 (50.00)	0.04	0.24
Laboratory data					
Hb < 90 g/L (%)	8 (13.56)	2 (18.18)	3 (27.27)	0.65	0.36
WBC < 4×10^9/L (%)	7 (11.86)	1 (9.09)	4 (36.36)	1.00	0.06
PLT > 300×10^9/L (%)	16 (27.12)	6 (54.55)	3 (27.27)	0.08	1.00
ESR > 40 mm/h (%)	28 (47.46)	7 (63.64)	4 (36.36)	0.32	0.49
CRP > 25 mg/L (%)	14 (23.73)	7 (63.64)	2 (18.18)	0.01	1.00
IL-6 > 3.4 ng/mL (%)	15 (25.42)	2 (18.18)	0	1.00	0.11
TNF-α > 8.1 pg/mL (%)	16 (27.12)	4 (36.36)	2 (18.18)	0.72	0.72
Imaging data					
Involved location > 4 (%)	29 (49.15)	7 (63.64)	5 (45.45)	0.38	0.82
Aortic arch involvement (%)	14 (24.14)	8 (70.00)	4 (33.33)	< 0.01	0.68
Type I (%)	6 (10.17)	1 (9.09)	2 (18.18)	1.00	0.21
Type IIa (%)	5 (8.47)	1 (9.09)	1 (9.09)	0.32	1.00
Type IIb (%)	3 (5.08)	1 (9.09)	1 (9.09)	0.12	1.00
Type III (%)	7 (11.86)	2 (18.18)	2 (18.18)	0.34	0.23
Type IV (%)	6 (10.17)	1 (9.09)	1 (9.09)	0.57	1.00
Type V (%)	32 (54.24)	5 (54.55)	4 (33.36)	0.72	0.23
Disease activity					
PGA (%)	48 (81.36)	11 (100.00)	9 (81.82)	0.19	1.00
Kerr criteria	3.38 ± 0.08	3.90 ± 0.10	3.13 ± 0.23	0.01	0.28
ITAS	9.58 ± 0.64	10.64 ± 2.15	6.38 ± 1.48	0.54	0.08
ITAS_ESR	11.09 ± 0.66	12.45 ± 2.06	7.63 ± 1.46	0.43	0.06
ITAS_CRP	10.96 ± 0.65	12.73 ± 1.87	8.00 ± 3.63	0.30	0.11
Treatment					
Methylprenisolone (%)	6 (10.17)	2 (18.18)	0	0.61	0.58
CYC (%)	37 (62.71)	8 (72.73)	2 (18.18)	0.73	< 0.01
CYC dose (g)	4.31 ± 0.38	4.15 ± 0.86	2.9 ± 1.7	0.85	0.40
MTX (%)	4 (6.78)	1 (9.09)	3 (27.27)	1.00	0.07
AZA (%)	5 (8.47)	0	3 (27.27)	1.00	0.11
HCQ (%)	34 (57.63)	4 (36.36)	3 (27.27)	0.19	0.06

P comparison between the CR group and TR group; P^* comparison between the CR group and DR group. The imaging findings were grouped into five types according to the 1996 Numano's classification: type I, involvement of the primary branches of aortic arch; type IIa, involvement of the ascending aorta, aortic arch, and its branches; type IIb, involvement of the ascending aorta, aortic arch with its branches, and thoracic descending aorta; type III, involvement of the thoracic descending aorta, abdominal aorta, and/or renal arteries; type IV, involvement of only abdominal aorta and/or renal arteries; and type V, combined features of both type IIb and IV

CR clinical remission, *TR* treatment-resistant, *DR* disease relapse, *Hb* hemoglobin, *WBC* white blood cell count, *PLT* platelet count, *ESR* erythrocyte sedimentation rate, *CRP* C-reactive protein, *IL-6* interleukin-6, *TNF-α* tumor necrosis factor-α, *SBP* systolic blood pressure, *DBP* diastolic blood pressure, *ITAS* Indian Takayasu Clinical Activity Score, *CYC* cyclophosphamide, *MTX* methotrexate, *AZA* azathioprine, *HCQ* hydroxychloroquine

($p < 0.01$), as did CRP levels (19.03 ± 22.27 to 1.03 ± 0.73 mg/L, $p < 0.01$). Indices of disease activity such as ITAS (baseline vs. last visit, 9.58 ± 4.81 vs. 0.14 ± 0.38, $p < 0.01$), ITAS-ESR (11.24 ± 4.80 vs. 0, $p < 0.01$), and ITAS-CRP (11.25 ± 4.78 vs. 0, $p < 0.01$) were improved significantly during follow-up (Fig. 1).

In the TR group, 11 patients did not reach disease remission through 9-month treatment, so alternative treatments were given. Seven cases (63.64%) had initial treatment of a GC with CYC, and then treatment was switched for each of these 7 patients: MTX (15 mg/week) with AZA (50 mg/day); MTX (15 mg/week) with LEF (20 mg/day); AZA (50 mg/day); MTX (15 mg/week) with LEF (10 mg/day); adalimumab (40 mg twice a month for 3 months); mycophenolate mofetil (MMF; 1 g/day); and tocilizumab (400 mg/month for 3 months). Two patients had initial treatment of GC, and then MTX (15 mg/week) was given to 1 case and MMF (1.5 g/day) to the other patient. One patient had initial treatment of a GC with AZA (50 mg/day) and treatment was changed to MTX (15 mg/week). One patient had initial treatment of a GC with MTX (15 mg/week) and then switched to tocilizumab (400 mg/month) for 6 months.

At the end of follow-up, mean levels of ESR (61.70.18 ± 35.77 vs. 42.57 ± 42.79 mm/h, $p < 0.01$) and CRP (36.90 ± 30.13 vs.29.00 ± 22.46 mg/L, $p = 0.025$) decreased significantly during treatment. ITAS (10.64 ± 7.12 vs. 1.29 ± 1.49, $p < 0.01$), ITAS-ESR (12.60 ± 7.17 vs. 3 ± 1.15, $p < 0.01$), and ITAS-CRP (12.73 ± 6.21 vs. 3.71 ± 1.49, $p < 0.01$) were improved significantly during follow-up (Fig. 1).

In patients with disease relapse, in the first 3 months of the treatment, noticeable reductions in the ESR and CRP levels, as well as indices of disease activity (PGA, ITAS, ITAS-ESR, ITAS-CRP), were observed. The mean time from initial treatment to disease relapse was 22.09 ± 8.79 (10–36) months with a prednisone dose of 7.5–15 mg/day at the time of relapse. Significant improvements were not demonstrated at the end of follow-up ($p > 0.05$) (Fig. 1).

Predictive models for treatment response and disease relapse

Further analyses were done to define potential predictive factors for treatment resistance and disease relapse. Factors with obvious differences ($p < 0.01$) in comparison with the CR group at baseline were chosen as candidate indicators: incipient disease; age < 40 years; CRP > 25 mg/L; globulin > 30 mg/L; systemic symptoms; vascular murmur; coronary artery disease; ITAS; ITAS-ESR; CTX treatment; HCQ treatment; CCB treatment; and involvement of the right subclavian artery, ascending aorta, aortic arch, or arteries in the right lower extremity.

Patients with high CRP levels (> 25 mg/L) (OR = 1.61, $p = 0.03$) carried a higher risk for treatment resistance. Age > 40 years (OR = − 2.82, $p = 0.03$), incipient disease (OR = − 2.47, $p = 0.01$), and treatment with cyclophosphamide (OR = − 2.07, $p = 0.03$) and hydroxychloroquine (OR = − 1.91, $p = 0.05$) could prevent disease relapse (Table 2).

Discussion

Until now, the choice of treatment strategy for TA has been based on the personal experience of the attending physician, and standard guidelines have been lacking. Various immunosuppressants and biologic agents have been demonstrated to be effective for inducing disease remission [3, 8–15], but large-sample studies to assess long-term treatment responses and disease outcomes in TA have not been undertaken. Treatment resistance and disease relapse are commonly seen in TA, so definition of predictive factors for treatment response and disease relapse is important.

In this study, we demonstrated that, through treatment of GC with CYC and/or other immunosuppressants, laboratory parameters (ESR, CRP levels) and disease activity indices (ITAS, ITAS-ESR, ITAS-CRP) were improved significantly in the CR and TR groups. These findings are in accordance with other studies [8–10]. These improvements were more pronounced in the first 3 months of treatment, but unremarkable (or even progressive) at final follow-up (Fig. 1). Hence, early treatment was effective but long-term outcomes of treatments differed and could have been affected by various factors. In patients with disease relapse, the mean time from initial treatment to disease relapse was 22.09 ± 8.79 (10–36) months with a prednisone dose of 7.5–15 mg/day at the time of relapse. This finding suggests that disease relapse often appeared in the late phase of treatment with a low dose of prednisone. Thus, for better outcomes, long-term monitoring and recognition of the risk factors associated with disease relapse are crucial.

Our study also demonstrated that high CPR levels (> 25 mg/L) could be predictive factors for treatment resistance. It may be because that high CPR reflected more intensive active inflammation status, which may relate to treatment resistance despite of immunosuppression. However, it should not be ignored that high CRP levels alone could not be considered equal to active disease. High levels of CRP might reflect inflammation status, but it lacked sensitivity and specificity for TA. In a substantial number of patients who had signs and symptoms of active disease, serum levels of acute-phase reactants are not increased, whereas in some others who appear to have silent disease, there is evidence of laboratory or radiologic inflammation. Thus, for patients with high CRP levels (> 25 mg/L), more intensive treatment and more effective monitoring should be undertaken to obtain better treatment responses at long-term follow-up. We further defined predictive factors for disease relapse. Patients with incipient disease, aged > 40 years, treated with CYC and HCQ may carry a lower risk of disease relapse. Patients with incipient disease might have better treatment responses than patients with disease recurrence, and older patients may have better compliance for treatment. In addition, for patients > 40 years, longer disease duration may exist and this subset may have lower activity though having active disease. Hence, these factors may prevent disease relapse.

CYC is a non-specific cell cycle inhibitor that can inhibit inflammation and immune responses by blocking the

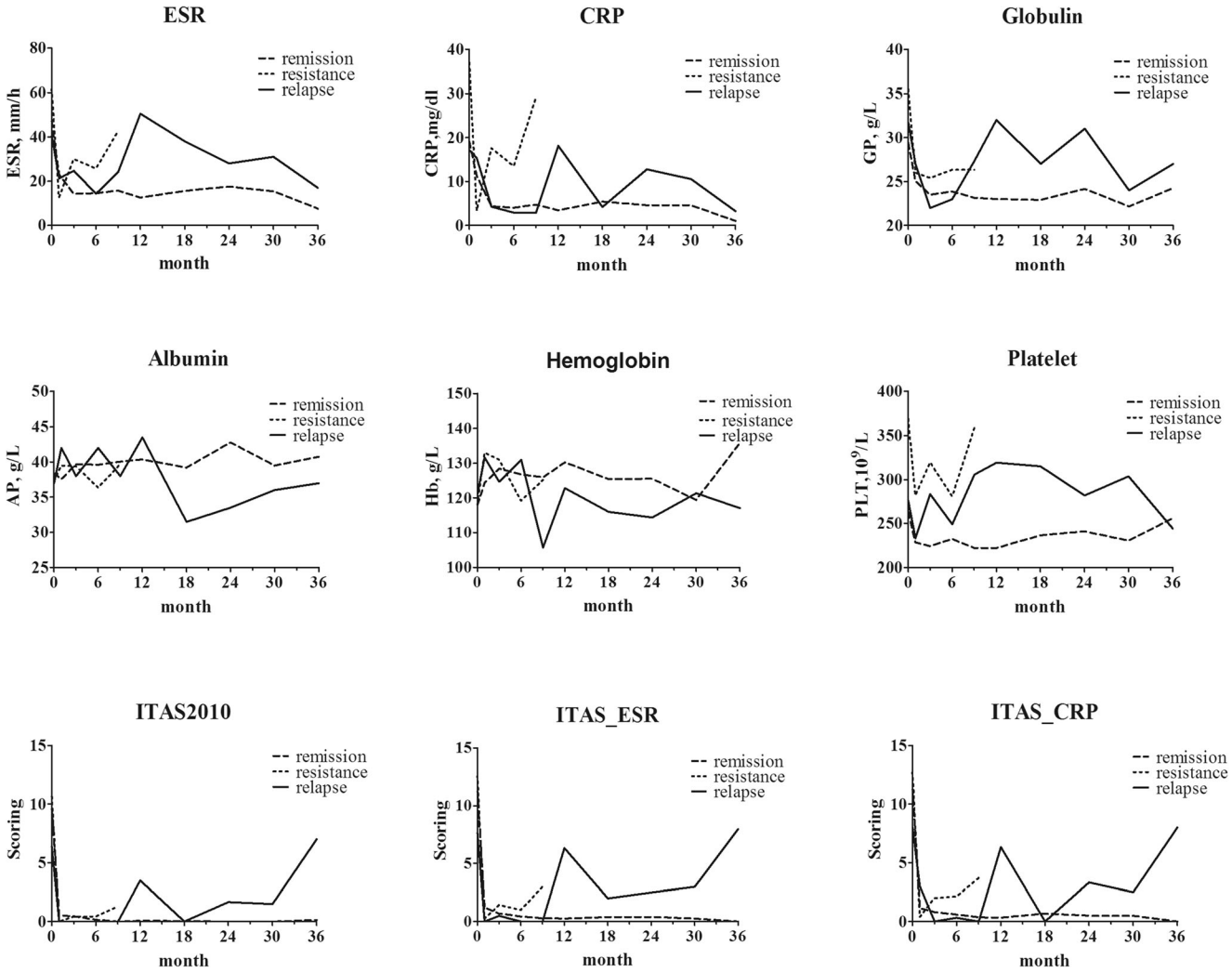

Fig. 1 Changes of levels of CRP, ESR, globulin, albumin, hemoglobin, and platelet as well as ITAS during the treatment

proliferation of lymphocytes. The latest data from our questionnaire survey of Chinese experts indicated that the combination of GC and CYC was the most commonly used regimen (63–78%) for inducing disease remission in TA. In 2014, one case analysis study demonstrated that in 15 patients treated with CYC and GC, the disease remission rate was 40% [11]. In our previous study, it demonstrated that CYC was more preferentially used in patients with higher disease activity and worse disease condition, and the 6-month clinical remission rate was 71.7% in patients treated with CYC and GC.

HCQ is an antimalarial agent that can regulate inflammatory and immune responses. HCQ has become an important immunomodulator used against rheumatic diseases [18, 19]. Studies have demonstrated that HCQ has synergistic effects, helps to reduce the GC dose, prolongs remission of renal disease, and improves the quality of life in patients with systemic lupus erythematosus (SLE) [20–22]. Use of HCQ combined with MTX can reduce the risk of liver dysfunction and prevent cardiovascular events in SLE [19, 20]. However, there is no evidence for the use of HCQ in TA. Recently, some researches have demonstrated that HCQ had effects on the activation and differentiation of T cells and cell autophagy [23–26], which was also involved the pathogenesis of TA. So, it might be an effective drug for TA. Our research indicated a protective effect of treatment with CYC and HCQ together instead of CYC alone in patients with incipient

Table 2 Logistic regression results for factors affecting treatment response and relapse

	OR	95% CI	*p* value
Treatment resistance			
CRP > 25 mg/L	1.61	1.21 20.64	0.03
Disease relapse			
Age > 40 years	− 2.82	− 1.31 − 4.67	0.03
Incipient disease	− 2.47	− 0.98 − 6.37	0.01
CYC treatment	− 2.07	− 0.95 − 4.82	0.03
HCQ treatment	− 1.91	− 0.97 − 3.87	0.05

Incipient disease was defined as cases that were diagnosed as TA for the first time and had no treatment history before including glucocorticoid and immunosuppressant

CYC cyclophosphamide, *HCQ* hydroxychloroquine

disease aged > 40 years. So, it was speculated that HCQ might play a role in protecting against disease relapse. This was the first study to show the benefits of HCQ in TA treatment.

Our investigation has some limitations. First, the small number of patients in the MTX or AZA group may hamper conclusions. To our knowledge, there were still no large-sample study to investigate the effects and safety of different immunosuppressants in TA long-term management. A further study with larger sample is being carried out to evaluate the treatment strategy in our center and more data would be provided in the future. On the other hand, the exact effects of HCQ on the long-term outcomes in TA also need to be confirmed in the further investigation.

In summary, we found that patients with high CRP levels carry a high risk of resistance to TA treatment. Treatment with CYC + HCQ for patients with incipient TA or aged > 40 years protects against disease relapse.

Funding This research was funded by the National Natural Science Funds of China (No. 81571571).

Compliance with ethical standards

The study protocol was approved by the Ethics Review Board of Zhongshan Hospital (Approval No. B2016-168, Fudan University, Shanghai, China). Written informed consent was obtained from all patients.

Disclosures None.

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