Clin Rheumatol (2012) 31:251–257
DOI 10.1007/s10067-011-1810-6

ORIGINAL ARTICLE

Single-center, retrospective analysis of efficacy and safety of tacrolimus as a second-line DMARD in combination therapy and the risk factors contributing to adverse events in 115 patients with rheumatoid arthritis

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Received: 28 March 2011 / Revised: 1 July 2011 / Accepted: 8 July 2011 / Published online: 20 July 2011

Abstract To retrospectively evaluate the efficacy and safety of combination therapy with tacrolimus (TAC) and other disease-modifying antirheumatic drugs (DMARDs). One hundred fifteen rheumatoid arthritis (RA) patients treated with tacrolimus were enrolled in this retrospective analysis. We collected clinical information, including patient background, treatment efficacy (evaluated using the DAS score), and adverse events observed. Multiple logistic regression analysis was conducted to analyze factors contributing to clinical response and adverse effects. The disease activity score of 28 joints (DAS28) improved significantly at 24 weeks, and continuation rate at 1 year was 57.9%. There was no difference in continuation rate between different DMARD combinations, and not only methotrexate (MTX) but also bucillamine (BUC) and salazosulfapyridine (SSZ) were effective combination partners with TAC. No serious adverse events were observed, and no different inefficacy or safety was observed between non-elderly (<65 years old) and elderly (≥65 years old) RA patients. By conducting multiple logistic regression analysis, combination therapy with MTX and TAC, the number of baseline DMARDs (specifically, ≥3), and old age were identified as risk factors for adverse events. Our findings indicate that TAC is a valuable DMARD for second-line combination therapy in RA.

Keywords Combination therapy · Rheumatoid arthritis · Second-line DMARDs · Tacrolimus

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Introduction

Rheumatoid arthritis (RA) is a chronic, progressive inflammatory disease that requires early diagnosis and aggressive treatment to minimize bone destruction. Disease-modifying antirheumatic drugs (DMARDs) are used to reduce inflammation and decrease the progression of articular damage. With the use of methotrexate (MTX) and biologics, disease remission has recently become a realistic therapeutic goal. However, many patients cannot undergo aggressive treatment with biologics due to problems such as complications, possible infections, adverse effects, and economic limitations. Therefore, conventional DMARDs are still the mainstream of RA treatment, and they should be studied to find more suitable and effective applications.

Tacrolimus (TAC, Prograf® from Astellas Pharma Inc.) is an oral immunosuppressive agent commonly used in the area of transplantation. It exerts its immunosuppressive effects via inhibition of calcineurin, leading to interference with T-cell activation. In Japan, it became the newest orally administered DMARD available for RA in April 2005. A number of studies have reported the usefulness of TAC monotherapy for RA [1–8] and also in patients who have

demonstrated a lack of response to MTX therapy [1]. In dual-DMARD therapy, TAC has been reported to be a good combination partner for MTX [9, 10]; however, few reports to date have demonstrated the usefulness of TAC as a second-line DMARD in combination therapy.

We retrospectively evaluated the efficacy and safety of TAC as a second-line DMARD in combination therapy with not only MTX but also other DMARDs for the treatment of RA. Moreover, we investigated risk factors that may be related to the occurrence of adverse effects by conducting multiple logistic regression analysis.

Patients and methods

We retrospectively collected the clinical and laboratory data of 115 RA patients receiving TAC in addition to other DMARDs from April 2005 to August 2008 in Juntendo Hospital Tokyo, Japan. All patients who had used TAC in combination with DMARDs for at least 24 weeks, or had stopped TAC combination therapy due to adverse effects were retrospectively selected from the prescribed medicine database of the hospital. We analyzed the efficacy and safety of those combination therapies (Fig. 1). All enrolled patients met the American College of Rheumatology (ACR; formerly, the American Rheumatism Association) 1987 revised criteria for RA [11]. Patients were administered TAC at a dose of 1–3 mg once daily in the evening, and the dose assignments were determined by the physicians in charge. Corticosteroid dosage could be decreased when a patient showed treatment efficacy. Clinical status with disease activity was evaluated by the disease activity score of 28 joints (DAS28) using C-reactive protein (CRP) at 12 and 24 weeks, and clinical response was analyzed using the European League Against Rheumatism (EULAR) improvement criteria, both only in 69 of 115 enrolled patients whose DAS data were available. Continuation rate, which is a simple variable that reflects the effectiveness and the tolerability of the drug, was analyzed with the Kaplan–Meier method, and the log-rank test was performed for comparisons across groups in sub-analyses. We also analyzed the effect of different drug partners combined with TAC and age (ERA or NERA) on efficacy and continuation rate. Statistical significance was defined as a P value<0.05. All adverse events that occurred during combination therapy over 24 weeks were evaluated. We also estimated the factors related to the clinical response and the occurrence of adverse effects with multiple logistic regression analysis. The last observation carried forward method was used to handle missing data for calculation of the DAS28.

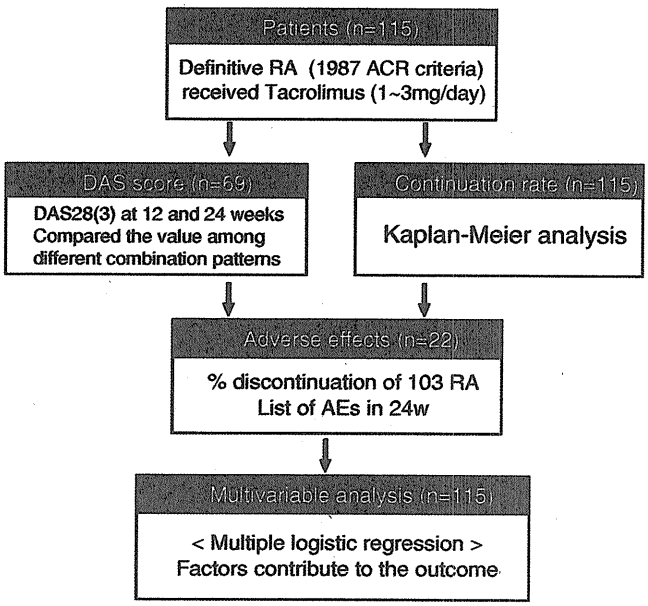

Fig. 1 Analysis scheme. One hundred fifteen RA patients were enrolled in this study. Of those, 69 patients were analyzed for treatment efficacy using DAS28 score. In the Kaplan–Meier analysis, all 115 RA patients were utilized to estimate the continuation rate

Results

Patients' background

Table 1 shows the characteristics of the patients who received combination treatment with TAC and other DMARDs. The average age was 60.4±12.5 years, and more than half the patients were over 65 years old. The mean duration of RA was 10.5±9.5 years. All patients were treated with MTX or other DMARDs for a minimum of 8 weeks before starting TAC. Based on DAS28-CRP

Table 1 Baseline characteristics of patients enrolled in this study (n=115)

Characteristic	Value (%)
No. of women	89 (77)
Age at entry (years)	60.4±12.5
STAGE	
I + II	24 (21)
III + IV	88 (76)
Undetermined	3 (3)
RA duration (years)	10.5±9.5
Previous DMARDs duration (years)	2.3±2.2
Use of nonbiologic DMARD	113/115
Use of biologic DMARD	2/115
Prednisolone (mg/day)	6.6±4.4

values, 93% of patients were considered to have high or moderate disease activity (Fig. 2b).

Efficacy

We analyzed changes from baseline values in CRP, tender joint count (TJC), swollen joint count (SJC), and DAS28-CRP in 69 of the 115 enrolled patients. TJC, SJC, CRP, and DAS28-CRP improved significantly after the start of TAC therapy. The mean DAS28-CRP value decreased from 4.1± 0.9 at baseline to 3.2±1.0 at 24 weeks (Fig. 2a). Before starting TAC therapy, 93% of patients were categorized as having high or moderate disease activity, and the percentage of those patients decreased to 65% at 6 months (Fig. 2b). Good and moderate response rates according to the EULAR improvement criteria were 38% at 12 weeks and 57% at

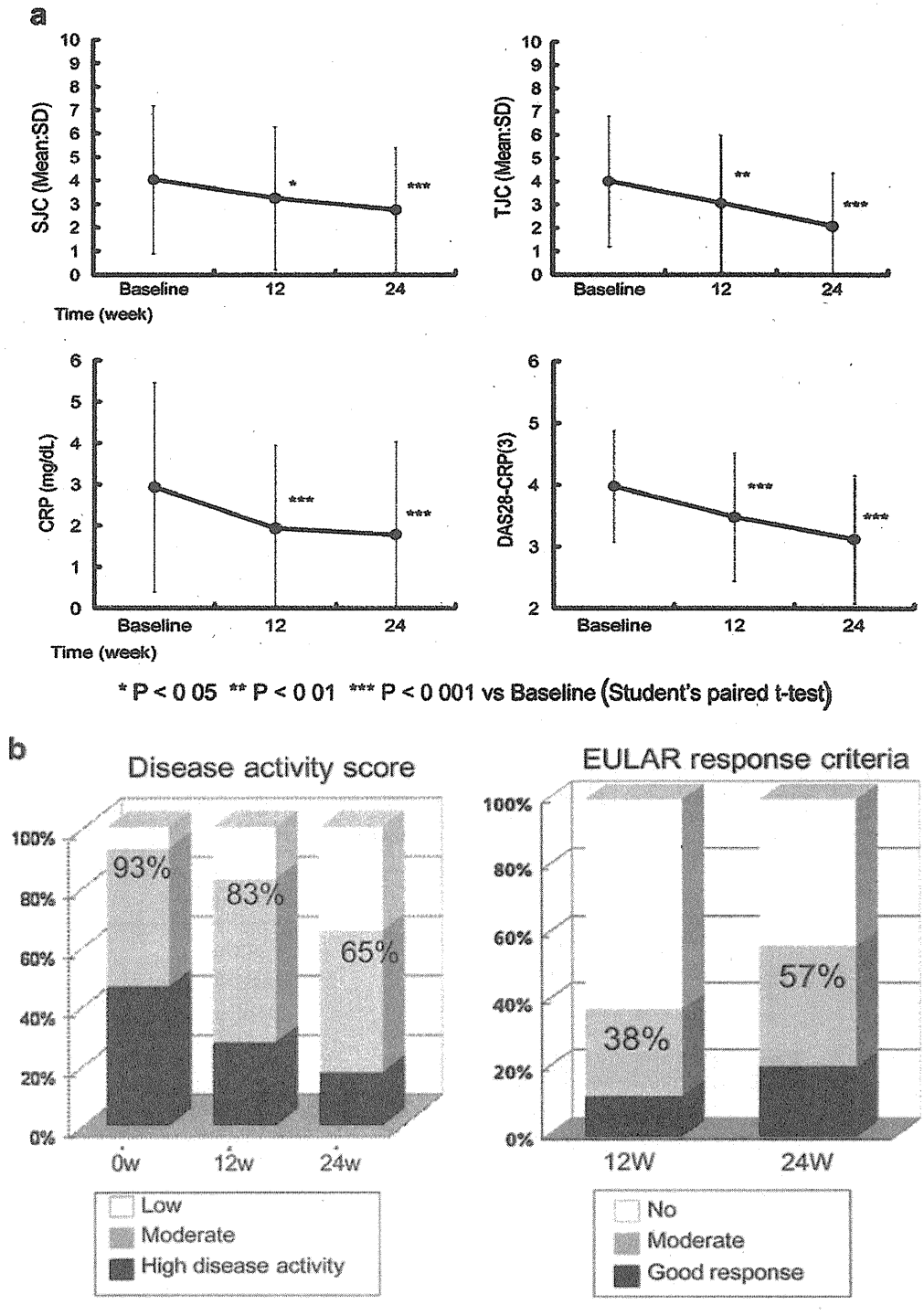

Fig. 2 **a** Serial changes in swollen joint count (0–28 joints), tender joint count (0–28 joints), C-reactive protein (CRP), and disease activity score of 28 joints (DAS28-CRP) in patients who received TAC in addition to other DMARDs. N=69. *P<0.05, **P<0.01, ***P<0.001 compared with baseline. **b** Disease activity state before 12 weeks, and 24 weeks after addition of TAC, evaluated with DAS28-CRP (*left*). Clinical response to the combination therapy with TAC and other DMARDs based on EULAR response criteria using DAS28-CRP (*right*)

24 weeks (Fig. 2b). Average dosage of prednisolone had decreased from 6.3±3.9 to 6.2±3.8 at 12 weeks (p=0.25) and 6.0±3.8 at 24 weeks (p=0.03).

To compare the clinical effect of different drug partners combined with TAC, we selected 37 from 69 patients who received monotherapy with single DMARD at the baseline resulting to dual-DMARDs treatment for the study duration (Table 2). Other patients treated with dual or more DMARDs partners at the baseline resulting to triple or more DMARDs combination therapy was excluded from this analysis. In 21 patients, MTX monotherapy was administered at baseline. Monotherapy with SSZ and BUC was used in ten and six patients, respectively. In those patients, the addition of TAC was clinically effective; moreover, the efficacy of combination therapy with TAC and MTX was significantly higher than that of other combinations (Fig. 3a). We also compared the efficacy of TAC between ERA (n=24) and NERA (n=45). The value of DAS28-CRP at baseline, 12 and 24 weeks was 4.0±0.7, 3.4±1.0, and 3.1±1.1, respectively for ERA, and 4.1±0.9, 3.7±1.0, and 3.2±1.0, respectively for NERA. No significant difference in the efficacy of TAC was observed between these two groups (Fig. 3b).

Continuation rate

The continuation rate of TAC in 115 RA patients was 57.9% and 48.9% at 1 and 2 years, respectively (Fig. 4a). No significant difference in continuation rate was observed in patients treated with different baseline drugs such as BUC, SSZ, and MTX (Fig. 4b), or between ERA and NERA (Fig. 4c).

Adverse effects

One hundred three patients were observed for more than 24 weeks. In those patients, adverse events resulting in discontinuation of TAC were observed in 22 patients (21.4%) within 24 weeks (Table 3). Although one patient developed infectious endocarditis and needed antibiotic therapy, all adverse events were mild or moderate, and those symptoms were resolved by stopping TAC treatment and subsequent proper management.

Table 2 Combined DMARDs that were already prescribed at the start of TAC

Combination partner	No. of patients	Mean dosage	TAC dosage (mg)
MTX	21	5.88±1.99 (mg/week)	1.17±0.51
SSZ	10	900±207 (mg/day)	1.33±0.62
BUC	6	200±63.2 (mg/day)	1.23±0.4

Analysis of factors contributing to clinical response and adverse effects

We analyzed variables including sex, X-ray progression according to Steinblocker's stage [12], disease duration, age, baseline DMARDs, number of previously used DMARDs, and complications to identify factors contributing to clinical response and adverse effects. By conducting multiple logistic regression analysis, three factors, combination therapy with MTX, the number of baseline DMARDs (specifically, ≥3 DMARDS), and old age, were found to contribute to the occurrence of adverse effects. We did not identify any factors contributing to clinical response to TAC (Table 4).

Discussion

This study has demonstrated the efficacy and safety of TAC as a second-line DMARD in combination with other DMARDs. In all patients in this study, TAC was added to baseline treatment with other DMARDs. This design reflects the real situation in which TAC is often used in combination therapy in clinical practice. TAC has been previously demonstrated to be safe and effective for the treatment of patients with RA in combination with MTX [9, 10]. Our results suggest that addition of TAC may be effective not only with MTX but also with SSZ or BUC.

Based on the successful efficacy results, the continuation rates of all TAC combination therapies were acceptably high, and we observed no statistically significant differences between them (Fig. 4b). ERA generally experience more complications and problems due to the effects of age-dependent changes in body composition and function on drug pharmacokinetics and pharmacodynamics, and therefore, these patients are more difficult to treat with appropriate DMARDs. However, our sub-analysis comparing ERA and NERA indicated nearly equal efficacy and continuation rates. Thus, TAC is a valuable DMARD in the treatment of ERA as well as NERA. All these results indicate that TAC is a useful second-line DMARD in combination therapy with good efficacy and long continuation rate.

Of the patients treated with TAC in this study, 22 developed adverse effects that led to discontinuation of TAC. As TAC is an immunosuppressant, the occurrence of infectious diseases was a concern. However, infectious disease was observed in only three patients (pneumonia, infectious endocarditis, and herpes zoster virus infection), and these patients recovered from the infectious episodes with appropriate management. The dosage of TAC used for RA is much lower than that used in transplant procedures, and this appears to be one reason for the low incidence of adverse events in RA patients. The frequently observed

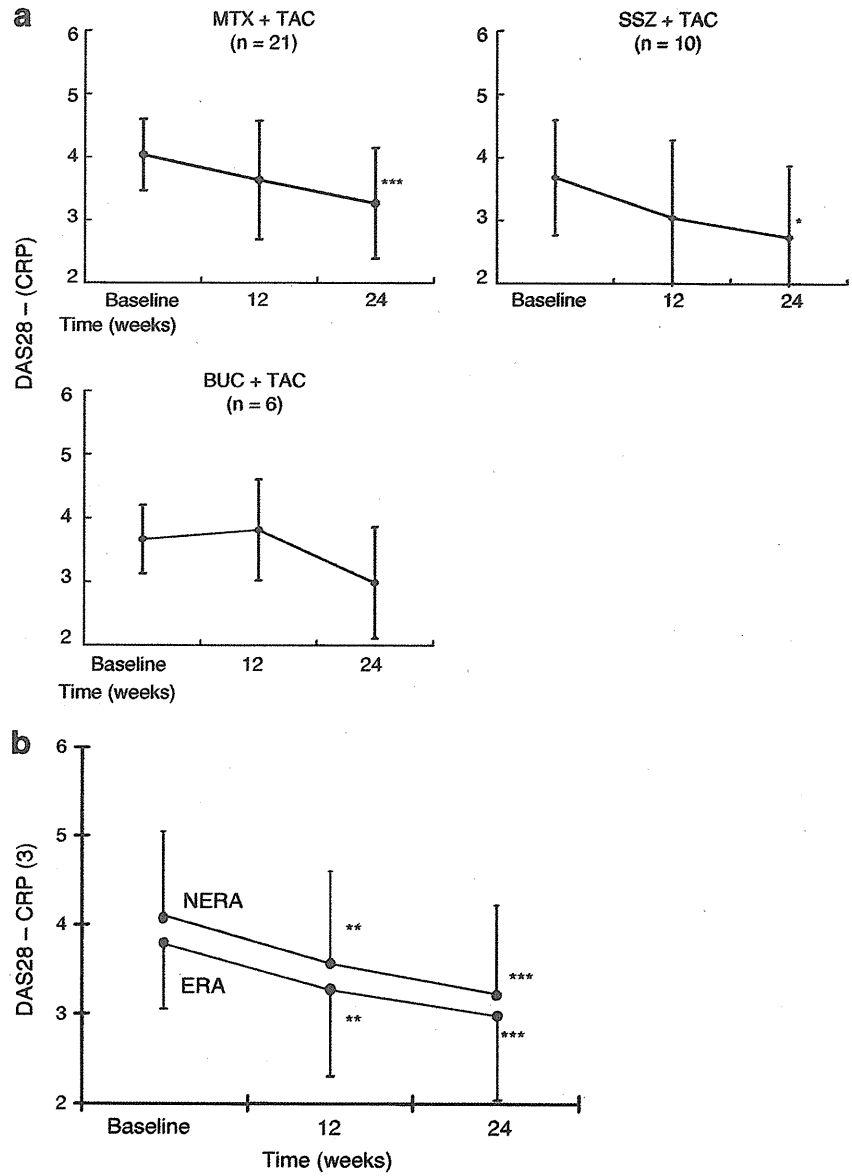

Fig. 3 a Changes in disease activity score of 28 joints (DAS28-CRP) in each drug combination, MTX + TAC (n=21), SSZ + TAC (n=10), and BUC + TAC (n=6). *P<0.05, **P<0.01, ***P<0.001 compared with baseline. b Changes in disease activity score of 28 joints (DAS28-CRP) in non-elderly (NERA) and elderly RA patients (ERA). *P<0.05, **P<0.01, ***P<0.001 compared with baseline

adverse events were allergic symptoms and abnormal glucose tolerance (increased glucose and increased HbA1c). These are all known adverse events of TAC, and no events specifically related to long-term therapy were detected. Most of the adverse events resolved or improved. TAC was generally safe and well tolerated by the patients of this study. These results are consistent with previous safety findings obtained from a non-controlled study in ERA [5] and a randomized controlled study in NERA [4], although TAC was administered alone as a DMARD in these studies.

According to the results of analysis for risk factors related to adverse events, three factors—combination with MTX, a larger number of combined DMARDs (specifically, ≥3 DMARDs), and old age—were detected. This finding suggests that we should be careful in prescribing TAC to older patients treated with MTX. Moreover, if patients are treated with three or more DMARDs, we should consider stopping the use of one when TAC is added, and we also have to consider the risk and benefit of combination with MTX.

This study may have some limitations arising from its retrospective design, small sample size, and short observation period. However, these results may be helpful in the use of TAC in addition to other DMARDs. Many clinical studies have been performed to investigate combination therapy with DMARDs for RA, and combinations of MTX/hydroxychloroquine/SSZ have exhibited more effectiveness than DMARD monotherapy [13]. Patients who fail to respond to one or more DMARDs are left with a decreasing list of other DMARD options. Thus, we need new DMARDs and DMARD combination patterns that can provide more effective treatment options for RA. TAC has been expected to have some appropriate combination

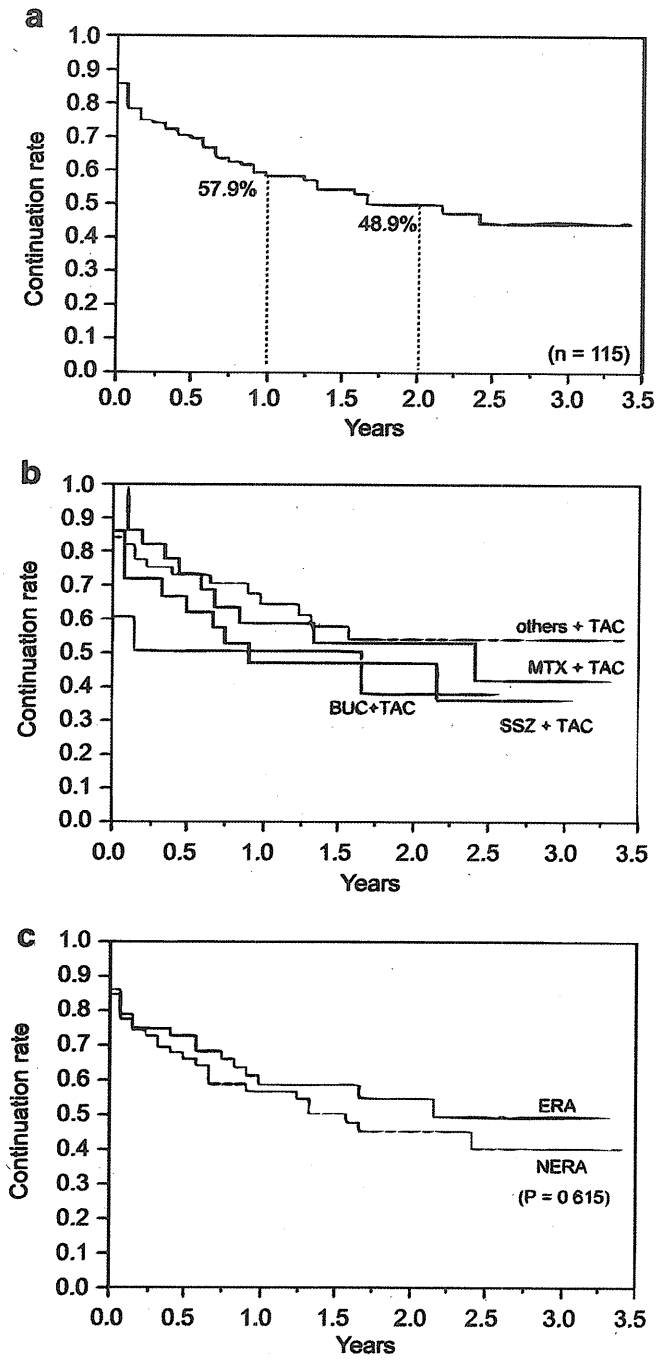

Fig. 4 a Continuation rate of TAC. The continuation rate was 57.9% at 1 year and 48.9% at 2 years. b Continuation rate of TAC with other DMARDs. No difference of the continuation rate was observed across those combination patterns. c Continuation rate compared in non-elderly (NERA) and elderly RA patients (ERA). No difference in continuation rate was observed between those two groups

partners, and two previous reports have described the usefulness of TAC + MTX combination therapy [9, 10]. Our results regarding the efficacy and continuation rate of TAC + MTX combination further support those prior reports. Moreover, our study shows that other combination patterns TAC + SSZ and TAC + BUC may also be useful, and could be novel appropriate options to use with TAC in combination therapy.

In summary, the results of this study demonstrate that TAC can be safely used in combination with MTX/BUC/SSZ for the treatment of RA, and suggest that the combination is an effective alternative for patients who attain only a partial response to MTX/BUC/SSZ. However, due to the limited data, further prospective large-scale studies are required for the assessment of TAC in combination therapy for RA.

Table 3 Adverse events observed over 24 weeks resulting in TAC discontinuation

Adverse events		
		Value (%)
Allergy		4/103 (3.8)
Glucose or HbA1C elevation		3/103 (2.9)
Infection	Pneumonia Infectious encarditis HZV infection	3/103 (2.9)
Cre or BUN elevation		2/103 (1.9)
Nausea or diarrhea		2/103 (1.9)
Other minor events		8/103 (7.8)
Total		22/103 (21.4)

Table 4 Multiple logistic regression analysis for factors contributing to clinical response and adverse effects

Variable	Good or Moderate response		Adverse effect	
	RR	*P*	RR	*P*
Sex (woman vs. men)	0.03	0.1	0.002	0.64
Stage	0.12	0.14	0.04	0.37
RA duration (≥5 vs. <5 years)	–	–	0.0004	0.85
Age (years)	0.002	0.69	0.07	0.01*
ERA vs. NERA	0.002	0.74	0.04	0.04*
Combined DMARDs				
MTX + α vs. others	–	–	0.14	0.0003*
MTX only vs. others	0.001	0.76	0.095	0.003*
BUC only vs. others	0.02	0.19	0.03	0.1
SAS_only vs. others	0.002	0.69	0.007	0.41
Number of DMARDs	0.03	0.58	0.11	0.04*
≥3 vs. <3	–	–	0.05	0.03*
≥2 vs. <2	–	–	0	0.99
Complication (+) or none	–	–	0.0003	0.9
(Higher age)×(DMARDs' number≥3)×(combined with MTX)	–	–	0.28	<0.0001*

*$P<0.05$

Disclosures None.

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Mod Rheumatol
DOI 10.1007/s10165-011-0502-z

ORIGINAL ARTICLE

Diffuse alveolar damage in patients with dermatomyositis: a six-case series

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Received: 1 February 2011 / Accepted: 6 July 2011

Abstract The clinical course of diffuse alveolar damage (DAD) was studied in six consecutive cases of dermatomyositis (DM) based on our hospital records over 8 years. Three patients had severe myopathy at presentation, and the other three patients showed clinically amyopathic DM (CADM). Interstitial pneumonia in all patients developed shortly after they manifested DM. DAD in five deceased patients, which was proven pathologically, did not respond to steroid therapy combined with cyclosporine or tacrolimus. Of these, two patients began receiving combination therapy before suffering respiratory symptoms, and one of them had elevated serum Krebs von der Lungen-6 (KL-6) levels before visible abnormalities appeared on a plain chest X-ray. Only one patient with CADM survived; this patient received intravenously administered pulse cyclophosphamide (IVCY) therapy intravenously for DAD from the early stage. Delayed adjunctive IVCY was ineffective for progressed DAD in the remaining five patients. Elevated serum ferritin levels were observed in all four patients examined and might have predicted the lethal DAD, as in a previous report. In conclusion, promptly beginning IVCY therapy may be beneficial for patients with DM and interstitial pneumonia who show elevated serum levels of ferritin or KL-6 with minimal pulmonary abnormalities.

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Published online: 09 September 2011

Keywords Interstitial pneumonia · Dermatomyositis · Amyopathic dermatomyositis · Diffuse alveolar damage

Introduction

Interstitial pneumonia (IP) is a relatively frequent complication in patients with dermatomyositis (DM) [1]. The histopathology of IP in patients with DM is mostly nonspecific interstitial pneumonia (NSIP) [2]. Occasionally, the disease may present as acute IP with diffuse alveolar damage (DAD), with a rapid progression to respiratory failure or organizing pneumonia (OP). As patients with DM and DAD have a poorer prognosis compared with those with other histological patterns, effective therapeutic intervention based on early evaluation of the pathological types is important. Several studies have demonstrated that rapidly progressive IP with a poor prognosis develops in patients with amyopathic or hypomyopathic DM, both of which have been called clinically amyopathic dermatomyositis (CADM) [3]. However, DAD may develop in patients with DM other than CADM, and patients with CADM do not always develop from IP. In this study, we describe the clinical courses and therapeutic responses of DAD in six patents with DM.

Methods

Six patients with DAD and DM in our Division of Rheumatic Diseases between 2002 and 2009 were sequentially enrolled in this study. During the study period, 112 patients were diagnosed with DM (13 with CADM), and the frequency of progressive IP in DM patients was 40.2% ($n = 45$), whereas that in the CADM patients was 30.8%

($n = 4$). Three of the four CADM patients (75%) progressed to DAD. A chart review for all cases of IP during the study period showed that DAD occurred only in patients with DM, except for leflunomide-related DAD in a patient with rheumatoid arthritis. DM was diagnosed according to the criteria of Bohan and Peter [4] or by the cutaneous manifestation of CADM [3, 5]. The clinical diagnosis of DAD was made based on acutely progressed IP on chest computed tomography (CT) with diffuse ground-glass opacity (GGO), multiple patchy consolidations, and traction bronchiectasis after ruling out drug-induced pneumonia, infections, infection-induced exacerbation of IP, and IP with characteristic radiological findings other than DAD, i.e., usual IP, NSIP, and OP. Of the six patients with DM and DAD, three had symptomatic myopathy with severe muscle weakness, and the other three were diagnosed with CADM. Five of the six patients died of respiratory failure. Histological confirmation was obtained in all five deceased patients by lung biopsy or autopsy. Those patients fulfilled the clinical and pathological criteria of DAD as described by Katzenstein et al. [6]; i.e., symptoms of acute respiratory failure, pathological findings of diffuse alveolar damage with thickening of the alveolar walls attributable to edema, inflammatory cells, and active fibroblast proliferation.

This retrospective study was approved by the ethics committee of our hospital.

Case descriptions

Patient 1

A 60-year-old woman was admitted to our hospital after developing eyelid erythema and Gottron's papules. Based on a normal serum creatine kinase (CK) level and no muscular symptoms, she was diagnosed with ADM. Although she had no respiratory symptoms on admission, slight GGO was seen in the inferior lobe of the right lung on the chest CT (Fig. 1a), and the only abnormalities in the blood examination were an elevated serum Krebs von der Lungen-6 (KL-6) level at 886 U/ml (normal < 500) and a serum lactate dehydrogenase (LDH) level at 350 U/ml (normal < 230). The serum C-reactive protein (CRP) was negative, and arterial blood oxygen pressure (PaO_2) was 87 mmHg. Immunosuppressive therapy was started with 40 mg/day of prednisolone combined with 200 mg/day of cyclosporine A (CyA) to prevent IP progression. After 2 months, during which the cutaneous lesions resolved, she began to experience dyspnea, and the GGO on the chest CT deteriorated despite therapy. A bronchoalveolar lavage and transbronchial lung biopsy showed mild inflammatory changes without any findings, suggesting DAD (Fig. 1b). Thereafter, lethal IP progressed (Fig. 1a), for which therapy with high-dose steroid and cyclophosphamide (IVCY) intravenously was ineffective, and serum KL-6 level increased to 4,000 U/ml. DAD was proven at autopsy (Fig. 1b, right).

Patient 2

A 50-year-old man developed Gottron's papules and progressive IP. He was diagnosed with DM and IP at another hospital, and bilateral GGO and lateral consolidation were found on chest CT. He was moved to our hospital 1 month after initiation of therapy because of respiratory failure despite pulse therapy with methylprednisolone and CyA. We changed the CyA to tacrolimus and added intravenously administered pulse cyclophosphamide (IVCY), which was ineffective, and he died within 1 week of referral.

Patient 3

A 53-year-old man was admitted to our hospital because of cough and dyspnea. He presented with hypoxemia and a PaO_2 of 58.9 mmHg. He was diagnosed with ADM accompanied by IP based on eyelid erythema, Gottron's papules, a normal serum CK level, no muscle symptoms, and GGO on chest CT. A skin eruption developed 2 weeks before the onset of the dyspnea. Diffuse GGO and consolidation were seen (Fig. 2). High-dose steroid therapy combined with biweekly 500 mg IVCY for a six-session course was initiated immediately upon diagnosis. After 1 month, pulse methylprednisolone was added and orally administered CyA therapy started. IP improved during these therapies (Fig. 2).

Patient 4

A 71-year-old woman presented to our hospital with fever and sore throat. Erythema on the back and eyelid and muscle weakness occurred prior to symptoms. Methylprednisolone pulse therapy was started, as GGO close to the pleura in both lobes and consolidation in the middle lobe were seen on chest CT. Although the IP responded transiently to therapy, respiratory symptoms became exacerbated during oral steroid therapy. Neither adding pulse methylprednisolone nor CyA and IVCY combination therapy was effective, and the IP progressed to lethal DAD.

Patient 5

A 68-year-old woman with characteristic DM skin rashes, including eyelid erythema and Gottron's papules, was diagnosed with DM at another hospital. An OP-like shadow was found just under the pleura of the left lower lobe on a chest CT. Despite the fact that the OP-like change

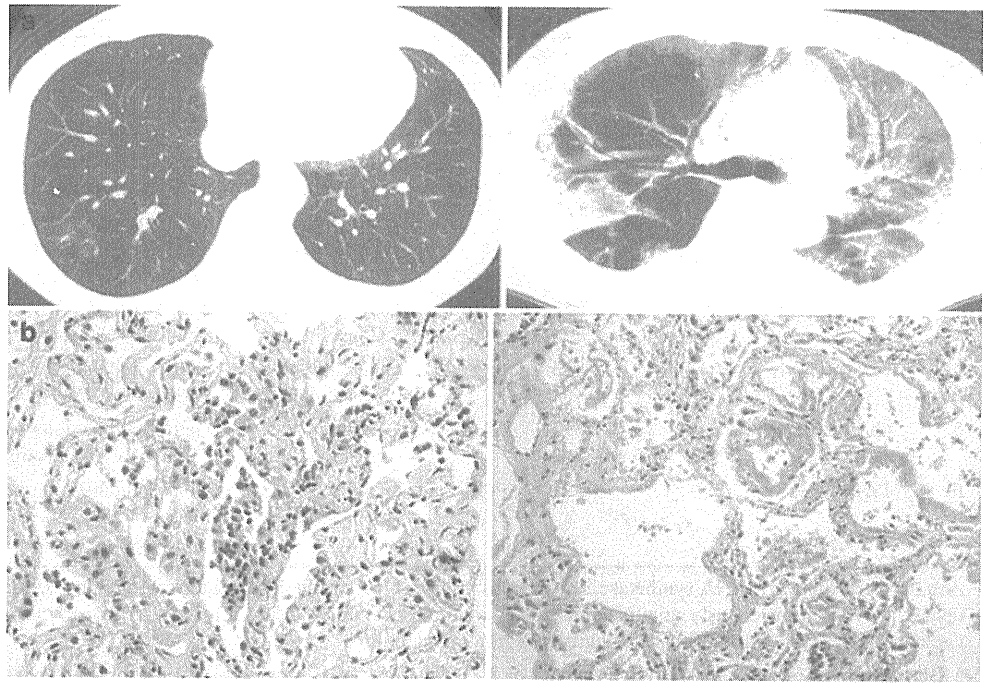

Fig. 1 **a** Change in the chest computed tomography (CT) findings in patient 1. At the time of diagnosis, only slight ground-glass opacity (GGO) was seen on chest CT (*left*). Three months later, chest CT showed extensive GGO and consolidation in both lungs, compatible with diffuse alveolar damage (DAD) (*right*). **b** Histopathological findings in patient 1. **a** Mild cellular alveolitis in a transbronchial lung biopsy (*left*) performed at the time of the CT scan (*left*). Diffuse alveolar damage was proven in the autopsy (*right*)

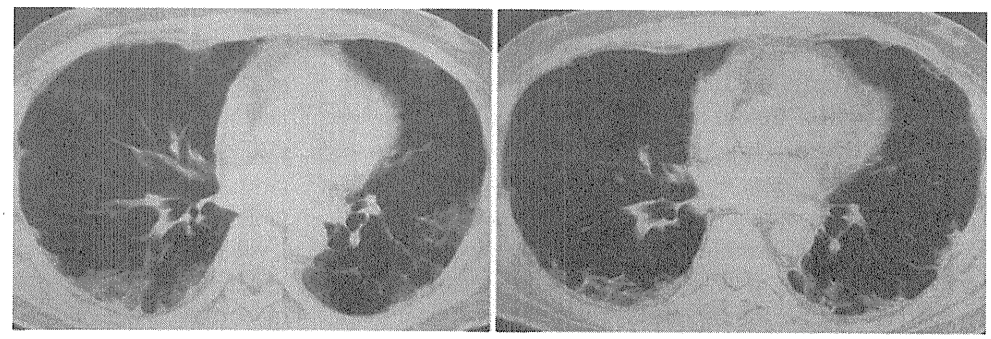

Fig. 2 Changes in chest computed tomography (CT) findings in surviving patient 3. Extensive ground-glass opacity (GGO) and consolidation before starting therapy (*left*). Improved CT findings after six sessions of intravenously administered pulse cyclophosphamide (IVCY) therapy (*right*)

remitted spontaneously, she began to develop a high fever. One month after the appearance of the CT finding, she was admitted to our hospital. Chest CT showed active IP with GGO and consolidation. The IP worsened despite methylprednisolone pulse therapy and tacrolimus. IVCY was also administered twice, but the IP progressed to lethal DAD.

Patient 6

A 16-year-old girl developed eyelid erythema and Gottron's papules, followed by fever, polyarthralgia, muscle pain, and severe muscle weakness; she was diagnosed with definite DM. The blood data on admission showed neutropenia, thrombocytopenia, liver dysfunction, and high levels of serum ferritin and muscle enzymes. OP-like consolidation was found in the left superior segment on chest CT. An extensive search for an underlying malignant lymphoma, including a random skin biopsy, was negative, and few hemophagocytic cells were found in a bone marrow smear. The febrile condition, cytopenia, and liver dysfunction continued, even after the myositis resolved by high-dose steroid therapy combined with methylprednisolone pulse and intravenously administered immunoglobulin. Lipodexamethasone and continuous cyclosporine infusion was started to treat possible macrophage activation syndrome (MAS). Whereas blood cell counts and liver dysfunction improved, the patient experienced seizures three times, and magnetic resonance imaging (MRI) suggested invasion of MAS to the brain. At the same time, diffuse IP with traction bronchiectasis progressed and resulted in lethal respiratory failure despite additional IVCY therapy. The autopsy revealed macrophage invasion in the brain in addition to DAD in the lung.

Serum markers related to IP and the therapy in the six patients

Anti-histidyl-tRNA synthetase (Anti-Jo-1) antibody was negative in all cases. Antinuclear antibodies were positive

Table 1 Clinical features of patients with dermatomyositis (DM) and diffuse alveolar damage (DAD)

Case	Age/ sex	Diagnosis	Anti-Jo-1	KL-6 (U/ml)	Ferritin (ng/ml)	Initial chest CT findings	Treatment	IP therapy[a], days	IVCY (days)[b]	Outcome, (days)[c]
1	60/F	CADM	–	835		Slight GGO	Methylprednisolone pulse, PSL, IVCY, CyA	0	125	131
2	50/M	DM	–	507		GGO and consolidation	Methylprednisolone pulse, PSL, CyA, tacrolimus, IVCY	25	55	57
3	53/M	CADM	–	853	973	GGO and Consolidation	PSL, IVCY, CyA, methylprednisolone pulse	23	23	Surviving
4	71/F	DM	–	823	864	GGO and consolidation	Methylprednisolone pulse, PSL, CyA, IVCY	19	63	54
5	68/F	CADM	–	313	1,623	GGO and consolidation	Methylprednisolone pulse, PSL, IVCY, tacrolimus	36	93	100
6	17/F	DM	–	351	4,172	GGO and consolidation	Methylprednisolone pulse, PSL, IVIG, CyA, IVCY, lipo-dexamethasone	−10	16	44

Anti-Jo-1 anti-histidyl-tRNA synthetase, *KL-6* Krebs von der Lungen-6, *CT* computed tomography, *IP* interstitial pneumonia, *GGO* ground-glass opacity, *IVCY* intravenously administered pulse cyclophosphamide, *CADM* clinically amyopathic dermatomyositis, *PSL* prednisolone, *CyA* cyclosporin A, *IVIG* intravenously administered immunoglobulin

[a] Duration from onset of respiration symptom or identification of GGO on chest CT to start of steroid therapy

[b] Duration from onset of respiration symptom or identification of GGO on chest CT to introduction of IVCY

[c] Duration from start of therapy to outcome

in patient 2 only. We did not evaluate serum anti-CADM-140 antibodies. Serum KL-6 levels on admission were normal in the surviving patient (no. 3) and a patient (no. 6) in the initial disease course without GGO and were elevated in the remaining four patients who had GGO on chest CT. Serum KL-6 level in patient 1 was elevated during the very early course of IP when slight GGO was visible on chest CT, but no abnormalities were observed on a plain chest X-ray (Table 1).

Serum ferritin levels on admission were elevated in four of six patients examined, although the origin of the high ferritin level in patient 6 was attributed to probable MAS. All six patients were treated with a combination therapy, including high-dose steroids and CyA or tacrolimus, which was ineffective for DAD in the five deceased patients. In particular, two patients (nos. 1 and 6) received combination therapy before DAD manifested, but it did not prevent the DAD from developing. Adjunct IVCY was used in all six patients. Of these, only one patient (no. 3) with ADM survived, in whom IVCY was added as an initial therapy.

Discussion

Several reports have demonstrated that CADM is a poor prognostic factor for rapidly progressing IP [3, 7, 8]. A strong association between anti-CADM-140 antibody and lethal IP in patients with CADM has been documented [8], although we did not examine this antibody in this study. A high serum ferritin level in patients with DM is another useful predictor for lethal IP [9] rather than CADM. Those findings were consistent with data in our case series. We compared the ferritin levels between DM patients with DAD and non-DAD. The mean initial ferritin level was 1,908 ± 1,546 ng/ml ($n = 4$) in DAD patients and 184.5 ± 318.4 ng/ml ($n = 7$) in non-DAD patients ($p = 0.05$). Half of our patients with DM and DAD had severe myopathies. The initial ferritin levels in all four patients examined had increased before the onset of respiration symptoms or identification of GGO on chest CT.

According to Tazelaar et al. [10], histology of interstitial lung disease is a better predictor of survival than the radiographic appearance or clinical presentation of patients with polymyositis or DM. However, the rapid progression of IP to DAD in patient 1 could not be predicted by histopathological findings at the early stage of the disease. Patient 1 had an elevated serum KL-6 when slight GGO was visible only on chest CT and not on a plain X-ray, which might have been an early sign of lethal IP. Bandoh et al. [11] reported that elevated serum KL-6 levels are observed particularly in patients with DAD, and proliferating and regenerating type-II pneumocytes secrete KL-6 in pulmonary tissues of patients with DAD. Thus, early elevation of KL-6 may also be a useful prognostic factor in DAD associated with DM. Increased serum KL-6 levels above baseline in DM patients without radiological abnormalities or respiratory symptoms can be a warning sign for developing DAD, and careful radiological

monitoring may be required. Furthermore, increasing levels of serum KL-6 without visible pulmonary abnormalities during steroid therapy for myositis or cutaneous lesions may be an indication for more intensive immunosuppressive therapy.

The optimal treatment for patients with IP-associated DM has not yet been fully established. Steroid therapy has been the first-line therapy for IP in patients with DM [12], particularly for OP or NSIP, whereas DAD usually shows resistance to steroids. Cyclophosphamide has been used for treating rapidly progressive IP in polymyositis (PM)/DM patients [1]. Previous case series have described successful therapy combining IVCY and steroids for progressive IP accompanied by PM/DM [13, 14]. Al-Janadi et al. [15] reported that IVCY therapy during the cellular phase of IP might prevent progression to fibrosis and pulmonary insufficiency. Therefore, the early introduction of IVCY therapy may be necessary for treating DM patients with possible progression to DAD.

Efficacy of CyA for IP complicated in PM/DM has been reported in several recent studies [16–18]. Nawata et al. [18] reported that CyA was effective in all five PM/DM cases of steroid-resistant IP and improved the survival rate. CyA has been effective during the early stages of the disease [14, 19]. Tacrolimus has also been effective for IP associated with PM/DM. Wilkes et al. [20] reported that DM/PM patients with refractory or severe IP were successfully treated with tacrolimus. Recently, Ando et al. [21] reported a case of ADM and CyA-resistant IP that was treated successfully with tacrolimus.

From a histological perspective, however, most of the previous studies have failed to treat DAD in patients with DM. Miyazaki et al. [22] reported a case of DAD in a CADM patient with rapidly progressive IP who was treated successfully with early intervention with corticosteroids, cyclosporine, and pulse cyclophosphamide. Further studies are necessary to investigate the optimal treatment of DM patients, particularly those developing DAD.

In this study, the IP in all five deceased patients did not respond to cyclosporine or tacrolimus. Of these, patient 6 developed DAD during intensive combination therapy with high-dose lipodexamethasone and a continuous cyclosporine infusion for treating MAS associated with DM, which suggests that even early therapy by steroid and cyclosporine does not prevent DAD.

Kameda et al. [23] stated that a combination therapy regimen including prednisolone, CyA, and IVCY improves the survival rate of patients with DM and acute or subacute IP. Furthermore, favorable outcomes have been reported for early intervention with IVCY therapy [24]. In fact, in this case series, the only surviving case (patient 3) was treated with IVCY during the early course of IP, 27 days after the diagnosis. Thus, starting IVCY in the remaining patients might have been too late (Table 1). Therefore, early selection of patients requiring IVCY therapy seems important when treating DM accompanied by IP.

Conclusions

Combination therapies with steroids and cyclosporine or tacrolimus not including cyclophosphamide may be ineffective for treating acute IP in some patients with DM. Cyclophosphamide therapy may be an effective optional therapy when elevated serum levels of ferritin or KL-6 are present along with the appearance of slight abnormalities on chest CT in patients with DM.

Conflict of interest None.

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Mod Rheumatol (2011) 21:92–96
DOI 10.1007/s10165-010-0348-9

CASE REPORT

Benefit and a possible risk of tocilizumab therapy for adult-onset Still's disease accompanied by macrophage-activation syndrome

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Received: 30 March 2010 / Accepted: 29 July 2010 / Published online: 26 August 2010

Abstract We report a 57-year-old female case of intractable adult-onset Still's disease (AOSD). Initial high-dose prednisolone therapy was ineffective, and macrophage-activation syndrome (MAS) manifested after one session of additional tocilizumab therapy. After successful treatment for MAS with lipo-dexamethasone and cyclosporin, tocilizumab therapy aided in the rapid reduction of the therapeutic steroid dose. Tocilizumab may be useful for maintenance therapy for AOSD, although its efficacy is unclear for the highly active phase of the disease.

Keywords Adult-onset Still's disease · Tocilizumab · Macrophage-activation syndrome · Hemophagocytic lymphohistiocytosis

Introduction

Still's disease (SD) is a systemic inflammatory disorder of unknown etiology and has been regarded as the synonym of systemic-onset juvenile idiopathic arthritis (sJIA) [1]. An adult-onset form of the disease (adult-onset Still's disease, AOSD) has been known since the first report by Bywaters [2]. The clinical manifestations of SD and AOSD are similar [3], although fever and skin rash were reported to be more common in AOSD than SD/sJIA in 130 patients [1]. Recent studies have shown that inflammatory cytokines, including interleukin (IL)-6, IL-18, interferon-γ, and tumor necrosis factor, play pathogenic roles in the disease processes of AOSD [4, 5]. Thus, inhibiting these cytokines may be a sensible therapeutic strategy for Still's disease. On the other hand, it is unknown whether the blockade of a single cytokine pathway in the setting of a cytokine storm, if any, causes an unfavorable imbalance in the cytokine system or whether it is sufficient to suppress the inflammatory condition.

Tocilizumab, a humanized anti-interleukin-6 receptor monoclonal antibody, is an effective cytokine inhibitor for the treatment of rheumatoid arthritis [6]. A recent clinical trial demonstrated the therapeutic efficacy of tocilizumab for treating pediatric patients with sJIA [7–9] or rheumatoid arthritis [10–13]. Several case reports have suggested that tocilizumab therapy was also effective for intractable AOSD [14–16]. These reports on AOSD did not include cases with hemophagocytic syndrome (HPS) or macrophage-activation syndrome (MAS).

Macrophage-activation syndrome is one of the most serious complications of sJIA [17–19], and a similar clinical manifestation, HPS, has been documented in AOSD [20–22]. These hematological disorders, as described in the literature, were caused by accidental viral infections in some cases and directly by the underlying sJIA or AOSD in others [20, 23–25].

Here, we describe tocilizumab therapy in a case of AOSD that involved MAS during the induction therapy.

Case report

A 57-year-old Chinese woman was admitted to our hospital in 2009 because of fever, polyarthralgia, sore throat, and cervical lymphadenopathy. She had been well until approximately 3 weeks earlier, when lymphadenopathy

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developed on the right cervix. One week later, she developed fever and sore throat, and an evanescent skin rash on the upper limbs, lower limbs, and trunk manifested, followed by polyarthralgia. Until 1 week prior to admission, she had received antibiotics, including ceftriaxone sodium hydrate, tosufloxacin tosilate hydrate, and piperacillin sodium, but had shown no response.

Initial blood data on admission were as follows: leukocytes 20790/μL (neutrophils 18000/μL), red blood cells 421 × 10^4/μL, hemoglobin 12.8 g/dL, platelets 28.3 × 10^4/μL, erythrocyte sedimentation rate 99 mm/h, prothrombin time INR 1.50, activated partial thromboplastin time 25.5 s, fibrinogen 598 mg/dL, D-dimer 3 μg/mL, aspartate aminotransferase 40 IU/L, alanine aminotransferase 32 IU/L, blood urea nitrogen 9.5 mg/dL, creatinine 0.53 mg/dL, C-reactive protein (CRP) 26.4 mg/dL, rheumatoid factor 14.9 IU/mL, soluble interleukin-2 receptor (sIL-2R) 1640 IU/L, and ferritin 7924 ng/mL. Anti-DNA antibodies and anti-neutrophil cytoplasmic autoantibodies were negative, and anti-nuclear antibodies were positive at a dilution of 1:80. Urine β2-microglobulin was 1185 mg/dL. Serological tests for Epstein–Barr virus and anti-cytomegalovirus (CMV) IgM antibodies and a skin test for tuberculosis showed negative results.

A computed tomography (CT) scan showed mediastinal lymphadenopathy. A positron emission tomography/CT scan indicated ^{18}F-flourodeoxyglucose uptake in the bilateral knee joints, spleen, mediastinal lymph nodes, and bone marrow. Bone marrow aspiration showed no atypical cells.

A diagnosis of AOSD was made based on the above findings, including spiking fever, polyarthritis, salmon pink skin rash, leukocytosis, sore throat, lymphadenopathy, and elevated serum transaminases. The above findings met the criteria for the classification of adult Still's disease from Yamaguchi et al. [3], and steroid therapy was started at a daily dose of 80 mg (1.3 mg/kg) oral prednisolone (PSL). After a transient improvement with the initial therapy, as shown in Fig. 1, a high fever occurred on day 23, which indicated that the inflammatory condition was resistant to >1 mg/kg/day of PSL (Fig. 1). To avoid cushingoid side effects due to further increases in steroid dose, we added 480 mg of tocilizumab therapy on day 35, and the patient

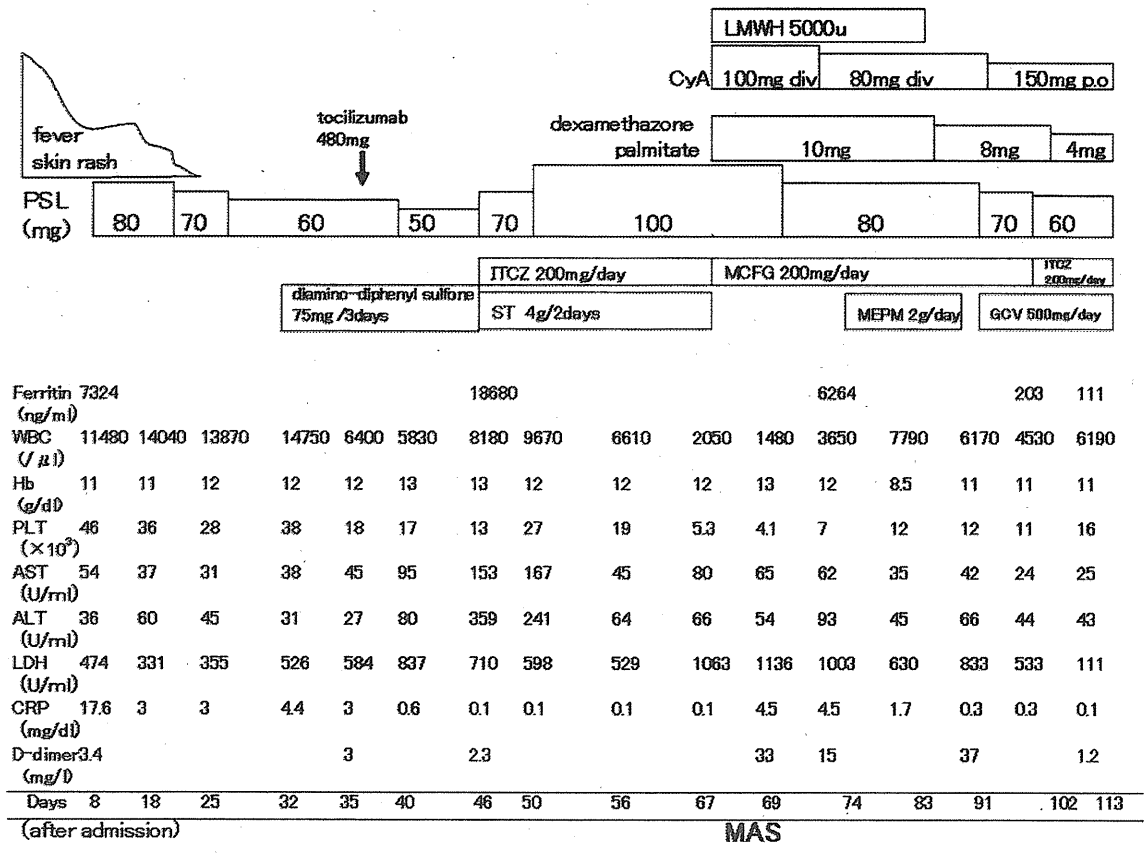

Fig. 1 The disease course during the induction therapy. The intractable disease conditions despite initial steroid therapy, macrophage-activation syndrome (MAS) after one session of tozilizumab therapy, and the successful suppression of MAS by combination therapy with high-dose steroid and cyclosporin A are shown serially. *WBC* white blood cell count; *Hb* hemoglobin; *Plt* platelet count; *ST* sulfamethoxazole/trimethoprim; *ITCZ* itraconazole; *Cy A* cyclosporin A; *LMWH* low molecular weight heparin; *MEPM* meropenem; *GCV* ganciclovir; *MCFG* micafungin

showed rapid resolution of fever and serum CRP level. After the improvement, a disease flare that included thrombocytopenia and elevated levels of serum transaminases and ferritin occurred on day 46, although serum CRP levels were still falling with tocilizumab treatment. This suggested tocilizumab-resistant Still's disease, given the negative results for infectious agents. Bone marrow aspiration revealed no hemophagocytic cells, and the dose of steroid therapy was increased (day 46). Despite the intensified therapy, fever and arthralgia recurred on day 67, and these were accompanied by neutropenia, thrombocytopenia, and re-elevation of serum transaminase and ferritin levels. No infectious etiology was detected, but bone marrow aspiration uncovered significant numbers of macrophages that had phagocytosed blood cells. These observations indicated that the patient had MAS associated with AOSD, and she was treated with intravenous dexamethasone palmitate (10 mg/day), continuous infusion of cyclosporin (100 mg/day), and low-molecular-weight heparin (5000 units/day). These therapies effectively reduced the disease activity of AOSD and MAS (Fig. 1). During the above immunosuppressive therapies, the patient suffered sequentially from *Clostridium* bacteremia and CMV viremia, which were successfully treated with specific drugs.

After the inflammatory findings had resolved completely, tocilizumab therapy was resumed in order to avoid prolonged high-dose steroid therapy, and the steroid dose was tapered rapidly, as shown in Fig. 2. Thereafter, the patient has been successfully maintained on tocilizumab every 2 weeks in combination with a maintenance dose of oral prednisolone and 75 mg/day of oral cyclosporin A.

Discussion

Still's disease (SD) responds to steroid monotherapy and shows a benign course in most cases. On the other hand, steroid-resistant and steroid-dependent forms of the disease remain challenging problems in some subsets of SD patients. Combination therapy with steroids and cyclosporin A is effective for SD [26], as observed in this patient. However, reducing the steroid dose frequently results in disease flares in patients with highly active SD, and cushingoid side effects are a serious concern in these patients, although immunosuppressants such as methotrexate may have a steroid-sparing effect [27]. In our patient, a rapid reduction in the therapeutic dose of steroids and prolonged remission on low-dose steroids were accomplished by combination therapy with tocilizumab.

Tocilizumab therapy is effective for juvenile idiopathic arthritis, including SD/sJIA, and for AOSD, as described in the "Introduction." Tumor necrosis factor blockade is also effective for treating JIA [28–31], and a case of intractable ASOD treated with infliximab has been reported [32]. There have been a number of controversial observations in the literature regarding etanercept therapy for sJIA or ASOD; MAS was induced or worsened after etanercept therapy for AOSD [33, 34], but intractable MAS in a sJIA patient was successfully treated with etanercept therapy [35]. The time profile of laboratory data in our patient (Fig. 1) suggested that MAS occurred as a consequence of highly active AOSD and that 1 mg/kg/day of PSL combined with one session of tocilizumab therapy was partially effective but insufficient for preventing MAS.

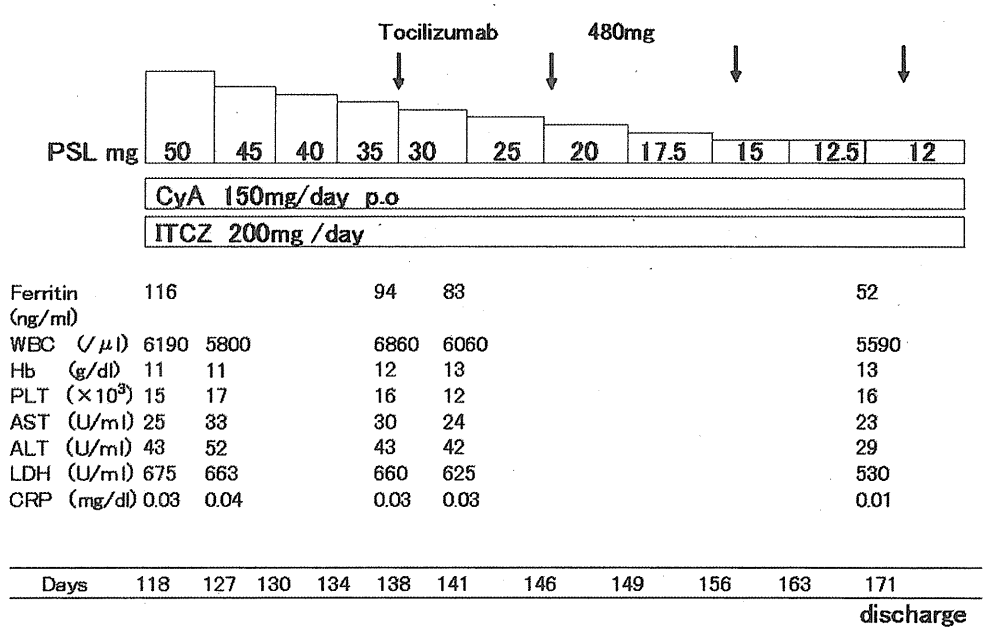

Fig. 2 Successful reduction of the therapeutic dose of steroids in combination with tocilizumab therapy

Macrophage-activation syndrome is a disorder characterized by hemophagocytosis, inappropriate systemic proliferation of benign histiocytes throughout the reticuloendothelial system, deregulation of T lymphocytes and macrophages, and subsequent overproduction of cytokines such as IL-1, IL-6, and IFN-γ [4, 5, 17, 19]. Among the rheumatic diseases, sJIA and AOSD are often associated with MAS, and one retrospective study [21] indicated a high frequency (12%) of MAS in AOSD patients. MAS of noninfectious etiology has been observed as a complication in several cases of sJIA during tocilizumab therapy [12], which was administered at various times in the course of sJIA, and the relationship between tocilizumab therapy and MAS has not been determined.

Based on the observations made in the case described here, complete suppression of AOSD activity by high-dose steroid therapy or combination therapy with cyclosporin A, followed by the rapid reduction of the therapeutic steroid dose through the application of additional tocilizumab therapy may be a reasonable strategy for treating AOSD. The efficacy of tocilizumab therapy for the active phase of AOSD is unclear, and we should be cautious of the possible induction of treatment-related MAS.

Conflict of interest None.

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Ann. N.Y. Acad. Sci. ISSN 0077-8923

ANNALS OF THE NEW YORK ACADEMY OF SCIENCES
Issue: *PET/CT Applications in Non-neoplastic Conditions*

FDG PET for rheumatoid arthritis: basic considerations and whole-body PET/CT

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[^{18}F]Fluorodeoxyglucose (FDG) is a tracer for glucose metabolism. Its distribution is not specific to cancer cells but is also observed in inflammatory tissue, including macrophages, capillaries, and fibroblasts. Rheumatoid arthritis (RA) is a systemic, chronic inflammation of the joints resulting in synovitis. The disease is characterized by fibrovascular proliferation leading to the formation of a pannus and causing high FDG uptake. Several clinical studies of RA have demonstrated that FDG uptake in affected joints reflects the disease activity of RA, with strong correlations between uptake and various clinical parameters having been noted. Furthermore, the use of FDG PET for the sensitive detection and monitoring of the response to RA therapy has been reported. FDG PET/computed tomography (CT) enables the detailed evaluation of disease in large joints throughout the whole body, which is a unique advantage of PET/CT. FDG PET/CT can also be used to detect high-risk disease complications, such as atlanto-axial joint involvement, at an early stage. The possible contribution of FDG PET to the management of patients with RA remains to be studied in detail.

Keywords: FDG; PET; PET/CT; inflammation; rheumatoid arthritis

FDG uptake by tumors and inflamed tissues: basic considerations

[^{18}F]2-Deoxy-2-fluoro-D-glucose (FDG) is a useful radiopharmaceutical for detecting tumors, accumulating in malignant tissue as a result of the enhanced rate of glucose use in neoplastic cells. Because of the increased metabolic demand for glucose, the activity of hexokinase (a key enzyme in glycolysis) in tumor tissue is increased. Also, the elevated expression of glucose transporter in malignant cells further enhances FDG uptake in cancer tissue.[1] The application of FDG PET to clinical oncology, especially for differential diagnosis, staging, therapy evaluation, and the detection of recurrences of various types of cancer, has been extensively studied over the last 20 years. Some of these major applications are covered by medical insurance reimbursement in several countries.[2,3] However, elevations in glucose metabolism are not specific to cancer cells, but are also seen in inflammatory tissue.

In 1989, two patients with abdominal abscesses who exhibited high FDG uptakes were reported.[4] This was followed by a report of FDG uptake in a brain abscess.[5] In a previous series examining the differential diagnosis of lung tumors, we confirmed that a false-positive case was actually a tuberculoma;[6] this result prompted us to undertake basic research to elucidate the mechanism responsible for this finding.

While FDG is a useful tumor-imaging agent, its intratumoral distribution has not been thoroughly described at a cellular level. To demonstrate the cellular localization of FDG and 2-deoxy-D-[^{3}H]glucose ([^{3}H]DG) uptake by tumors *in vivo*, C[^{3}H]/He mice with subcutaneously transplanted FM3A tumors were studied one hour after the intravenous injection of FDG or [^{3}H]DG using micro- and macro-autoradiography. The FDG and

doi: 10.1111/j.1749-6632.2011.06031.x
Ann. N.Y. Acad. Sci. 1228 (2011) 29–38

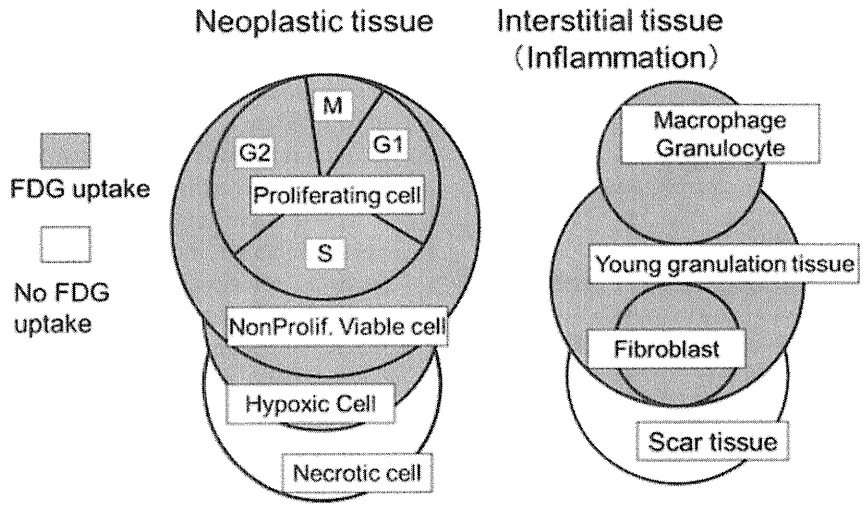

Figure 1. Model explaining FDG accumulation in various cellular elements in a tumor.[8]

[^{3}H]DG uptakes showed the same distribution pattern in the tumor using both autoradiographic methods. The newly formed granulation tissue around the tumor and macrophages, which had massively infiltrated the marginal areas surrounding the necrotic areas of the tumor, showed a higher uptake of FDG than the viable tumor cells. A maximum of 29% of the glucose use was derived from the nontumor tissues in these tumors. The strong accumulation of FDG in these tumors was thought to represent the high metabolic activity of the viable tumor cells. These results indicate that not only the tumor cells, but also the non-neoplastic cellular elements that appear in association with the growth or necrosis of tumor cells should be considered for the precise analysis of FDG uptake in tumors, especially after antineoplastic treatment.[7,a]

We proposed a model for FDG uptake (Fig. 1). The components of tumor tissue can be classified as neoplastic and non-neoplastic tissues. The former is divided into viable cells, which are labeled with FDG, and necrotic cells, which are not. Proliferating fibroblasts are included in the latter group. FDG uptake is concentrated in both macrophages and young granulation tissue, but not in scar tissue. Since *in vivo* tumors are composed of both neoplastic and non-neoplastic cell elements, the contribution of both neoplastic and non-neoplastic cells to FDG uptake in tumors should be considered. Of note, the non-neoplastic tissues are also components of inflammation.[8]

Next, FDG uptake and its distribution in experimentally induced inflammatory tissue were investigated. A rat model of inflammation induced by turpentine oil was used. A time course study of the FDG tissue distribution showed that the uptake of FDG in inflammatory tissue increased gradually until 60 min and then decreased. A longitudinal study of the FDG tissue distribution showed that the uptake increased progressively, peaking four days after inoculation, and then decreased (Fig. 2). This result suggested that FDG uptake may reach a maximum during the subacute phase of inflammation. On the fourth day postinoculation, a section of inflammatory tissue showed changes characteristic of chronic inflammation. Macro- and microautoradiography showed a high density of silver grains in the abscess wall, consisting of an inflammatory cell layer and granulation tissue. Grain counting on microautoradiography images of the abscess wall showed that the highest grain density was found in the marginal zone of young fibroblasts, the endothelial cells of vessels, and the phagocytes of

[a]Autoradiography is an experimental technique used to elucidate the tissue or cellular distribution of a radioisotope using small animals. After the injection of a radiolabeled compound, tissue samples were prepared for frozen thin sections. Radioactive thin sections were directly exposed to films or imaging plates to see the radioactivity distribution and correlated to the histology.