宇佐俊郎.					
川尻真也, 川上　純, 岩本直樹, 藤川敬太, 荒牧俊幸, 一瀬邦弘, 蒲池　誠, 玉井慎美, **有馬和彦**, 中村英樹, 喜多雅子, 井田弘明, 折口智樹, 江口勝美.	肺胞出血および急速進行性糸球体腎炎により再燃した顕微鏡的多発血管炎の一例.	日本臨床免疫学会会誌	32 (3)	189-194	2009

Ⅴ．研究成果の刊行物・別冊
（主なもの）

RS3PE 症候群の暫定診断基準

診断項目

1．手足の左右対称性の圧痕を残す浮腫

2．急性発症の多関節炎

3．50 歳以上

4．リウマトイド因子陰性

＜参考＞

a. 血沈・CRP などの炎症所見

b. X 線上関節破壊を伴わない

c. エコー・MRI で皮下浮腫を認める

d. 血清 VEGF 著明高値（>1,000pg/ml）

e. ステロイド薬が有効である

f. 悪性腫瘍の合併例がある

上記診断項目の 4 項目が存在するものを RS3PE 症候群とする。

ただし、他のリウマチ性疾患、感染症、Crow-Fukase 症候群やその他循環器疾患、腎疾患など浮腫をきたす疾患、薬剤によるものを除外する

新臨床内科学

第9版

監修

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医学書院

有病率は，男性 0.5%(0～1.6%)，女性 3.4%(2.4～4.9%)で男女比は 1：7 である．わが国では 40 歳代前半に発症することが多く，発症から診断までに平均 4.3 年かかっている．関節リウマチ(RA) の約 25% に本症の合併がみられる．

■病理・病態生理

家族集積性があり，遺伝的に素因のある患者がある特定の環境に曝露されると発症すると考えられる．身体的外傷(特に体軸，脊椎)，感染症(パルボウイルス，C 型肝炎)，情動障害，内分泌疾患(甲状腺機能低下症)，ストレスなどが誘因となる．病因としてさまざまな説があるが，神経系では，セロトニンの低下，機能的 MRI 解析や SPECT による視床の血流低下，中枢神経レベルにおける疼痛に対する閾値の低下・過敏症がいわれている．精神型では，うつ，心気症や身体表現性障害，慢性疼痛障害が考えられている．視床下部-下垂体-副腎皮質系では，コルチゾールの低反応，成長ホルモン，DHES の低下がみられる．免疫系では，NK 活性の低下，サイトカイン異常がみられる．

■臨床所見

自覚症状で最も多いものは，頸部，腰部を中心とした慢性の全身痛で 3 か月以上持続する．朝に疼痛が強く，移動性で，日によって変動する．激しい運動，非活動，不規則な睡眠，情緒反応，ストレス，ライフイベント，天候により症状が誘発される．微熱，全身疲労感，朝のこわばり感，睡眠障害，頭痛，集中力低下，健忘も訴えとして多い．

身体所見上は，圧痛以外は所見がない．下肢静止不能症候群 restless leg syndrome，僧帽弁逸脱症や間質性肺炎の合併の報告もある．

■検査所見

血液検査では，ほかの疾患が合併していないかぎり，異常を認めない．圧痛の有無に関しては，圧痛点に疼痛計 dolorimeter を使って圧力をかけて検査する．筋電図，筋生検，画像ともに異常ない．

■診断・鑑別診断

米国リウマチ学会が 1990 年に発表した分類基準を参考に診断する．基準は，① 広範囲にわたる疼痛が 3 か月以上持続，② 触診により 18 か所の圧痛点のうち

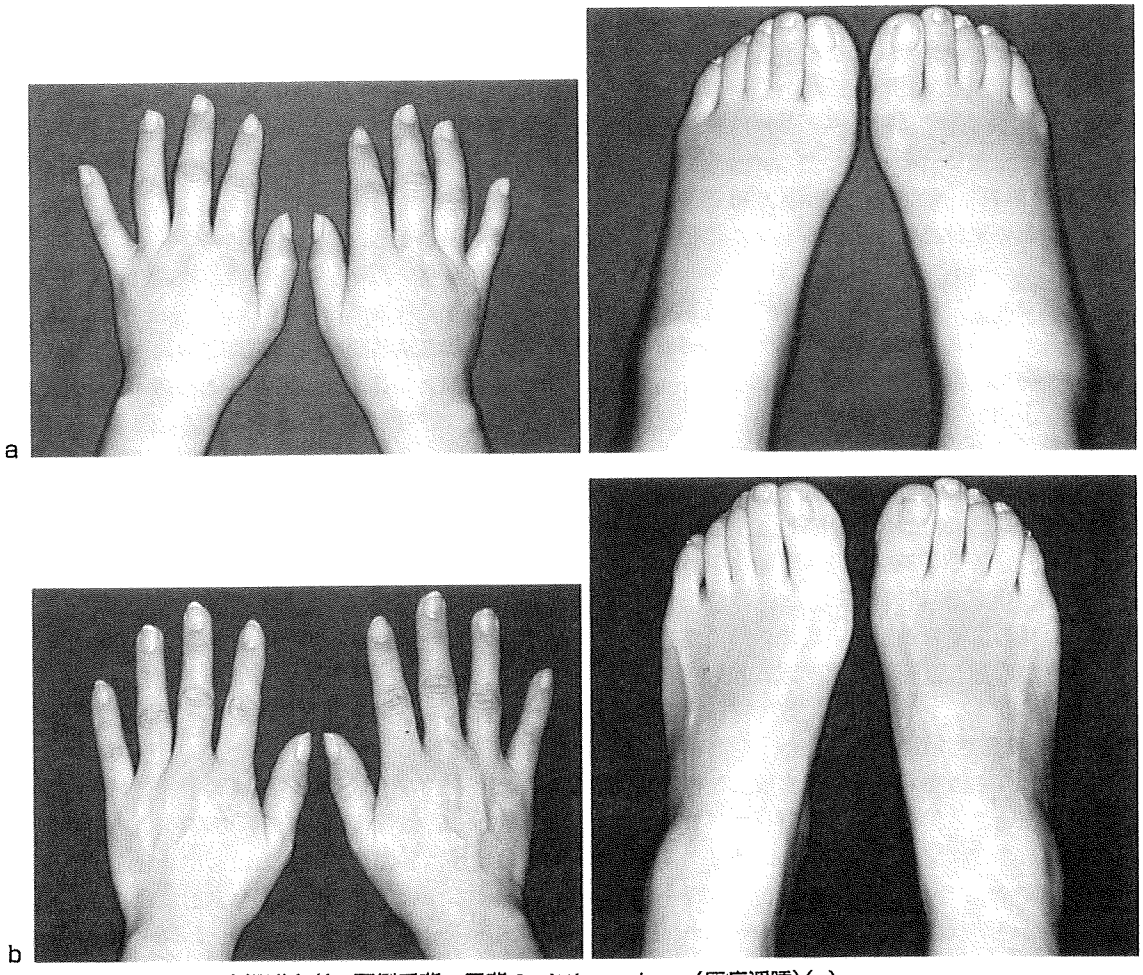

図 11-53　RS3PE 症候群患者の両側手背・足背の pitting edema(圧痕浮腫)(a)
NSAIDs のみで浮腫は軽減した(b)．(久留米大学医療センター・リウマチ膠原病センター：福田孝昭博士のご提供による)

11か所以上に圧痛を認める．圧痛点は，後頭部，下部頸椎，僧帽筋，棘上筋，第2肋骨，外側上顆，殿部，大転子，膝の左右の2か所ずつである．鑑別すべき疾患は，慢性疲労症候群，RA，血清陰性脊椎関節炎，リウマチ性多発筋痛症，SLE，Sjögren症候群などの膠原病，多発性硬化症，炎症性筋疾患，うつ病などである．

■治療

まず，患者の話をよく聞き，安心させることが重要である．特異的治療薬はないが，三環系抗うつ薬が25～43%に有効である．ノイロトロピン®や選択的セロトニン再取り込み阻害薬(SSRI)も使用される．副腎皮質ステロイドは無効である．非薬物療法として認知行動療法や有酸素運動が有効である．治療後2年間で回復する症例は約25%である．

i RS3PE症候群 remitting seronegative symmetrical synovitis with pitting edema

■概念

比較的急性に発症するリウマトイド因子陰性の対称性多発滑膜炎(関節炎)で，手足のpitting edema(圧痕浮腫)を特徴とする予後良好な症候群である．1985年にMcCartyらが概念を提唱したが，関節リウマチやリウマチ性多発筋痛症(PMR)との異同について議論も多く，まだ完全に認められていない疾患である．60歳以上の高齢者に多く，消化器癌，前立腺癌，悪性リンパ腫などの悪性腫瘍の合併が多い．

■臨床所見

発症は突然であり，対称性の滑膜炎による末梢関節痛，両側手背・足背の圧痕を残す浮腫(図11-53)，手指屈筋腱の炎症による疼痛などがみられる．

■検査所見

炎症を反映して赤沈が亢進し，CRPが上昇する．リウマトイド因子，抗核抗体は陰性，一部の症例で白血球増加と補体高値を示す．血清vascular endothelial growth factor(VEGF)の著明な増加が認められ，dynamic MRIでも滑膜組織の著明な血管増生と皮下浮腫が認められる．手背の滑膜組織では，滑膜炎の所見と単核球を中心とした細胞浸潤がみられる．

■診断・鑑別診断

McCartyらが報告した臨床的特徴は，上記症状に加え，治療にて3～36か月のうちに寛解し治療を中止しても再発しないこと，少量の副腎皮質ステロイドに劇的に反応すること，関節変化は軽く，軽度の屈曲拘縮を残すのみであること，HLA-B7との相関を認めることなどである．鑑別診断で重要なものは，PMRとRAである．本症候群では，他疾患にはまれな手指の屈筋腱拘縮がみられることが特徴的である．

■治療

副腎皮質ステロイドに対して反応良好で，通常プレドニゾロン1日量10～15 mgから開始し，漸減する．

〔折口智樹・江口勝美(執筆協力)〕

12 結晶誘発性関節炎(痛風，偽痛風ほか)

crystal induced arthritis(gout, pseudogout)

■概念

体内で異常に形成された結晶が関節炎を引き起こす場合を結晶誘発性関節炎という．尿酸Na結晶による痛風(724頁参照)が最も多く，続いてピロリン酸Ca結晶による偽痛風(仮性痛風)が多い．ヒドロキシアパタイト誘発性関節炎は骨の主成分であるヒドロキシアパタイトなど塩基性リン酸Ca結晶により誘発される関節炎である．

■病態生理

痛風では発作の前から既に形成され関節包などに付着している尿酸Na結晶と，発作時に新たに生成される結晶の両方が炎症を誘発する．尿酸Na結晶ができる原因は尿酸Naの飽和溶解度以上の高尿酸血症であり，これは遺伝的素因に肥満，アルコールなどの環境要因が加わるために起きる．

偽痛風や塩基性リン酸Ca結晶誘発性関節炎では，発作の前から既に形成されている結晶が関節包や軟骨から剝がれ落ち，食細胞により貪食されることが関節炎の原因となる．これらの結晶が沈着する原因は多くの場合不明であるが，副甲状腺機能亢進症が原因となることもまれにある．

いずれの結晶誘発性関節炎にも共通して，結晶を貪食したマクロファージや好中球がサイトカイン(IL-1など)，活性酸素，種々の化学遊走因子，ケミカルメディエータなどを放出して激しい炎症を誘発する．結晶誘発性関節炎による炎症は一般の炎症と基本的には同じであるが，発作性に起きる傾向があり，自然に治癒する傾向があるのが特徴である．

■頻度・性差

痛風は20歳代以降の男性に多い．偽痛風は性差はほとんどなく，高齢者に多い．まれに家族性の若年発症の例もある．

■臨床所見

痛風は第1中足趾節関節の激しい発作性の炎症(podagraという)(図11-54)で発症することが多い．

偽痛風は膝関節に最もしばしば発症し，股関節にも発症する．いずれの場合も全身的に発熱をきたすことがある．

■検査所見

痛風では高尿酸血症，関節液中の尿酸Na結晶の証明などが大切．ピロリン酸Ca結晶が膝，股関節内の

Rheumatol Int
DOI 10.1007/s00296-009-1142-x

CASE REPORT

Monitoring of therapeutic efficacy in a patient with RS_3PE syndrome by serologic variables and radiographic methods

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Received: 22 June 2009 / Accepted: 13 September 2009

Abstract We describe a typical case of a patient with remitting seronegative symmetrical synovitis and pitting edema (RS_3PE) syndrome. He underwent a successful clinical course monitored by serologic variables and radiographic methods. Serum levels of interleukin-6 (IL-6), vascular endothelial growth factor (VEGF), matrix metalloproteinase-3 and serum amyloid A were remarkably elevated. Accumulation of inflammatory cells into the multiple joints was found by gallium-67 scintigraphy. Multiple and symmetrical tenosynovitis with hypervascularity in the presence of subcutaneous edema of the hands and feet were determined by magnetic resonance imaging (MRI) and ultrasonography. These serologic and radiographic abnormalities immediately improved after treatment with a low-dose steroid. Our present case supports a previous observation that synovial tissue is a major inflammatory source of RS_3PE syndrome. IL-6 (and VEGF), probably produced from the synovial tissues, are considered to be essential factors in the development of RS_3PE syndrome.

Keywords Remitting seronegative symmetrical synovitis with pitting edema (RS_3PE) syndrome · VEGF · IL-6 · Ga-67 scintigraphy · MRI · Ultrasonography

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Abbreviations

Anti-CCP Ab	Anti-cyclic citrullinated peptide antibodies
CRP	C-reactive protein
ESR	Erythrocyte sedimentation rate
Ga	Gallium
MMP-3	Matrix metalloproteinase
MRI	Magnetic resonance imaging
IL-6	Interleukin-6
PSL	Prednisolone
RF	Rheumatoid factor
RS_3PE	Remitting seronegative symmetrical synovitis with pitting edema
SAA	Serum amyloid A
TNF	Tumor necrosis factor
USG	Ultrasonography
VEGF	Vascular endothelial growth factor

Introduction

Remitting seronegative symmetrical synovitis with pitting edema (RS_3PE) syndrome is a rare inflammatory disease, first described by McCarty et al. in 1985 [1]. This syndrome is characterized by elderly patient status, acute onset, symmetrical synovitis, pitting edema of the dorsum of the hands and feet, seronegativity for rheumatoid factor (RF), and an excellent prognosis with low-dose corticosteroid therapy [2]. We previously reported that the serum level of vascular endothelial growth factor (VEGF) was markedly elevated in patients with RS_3PE syndrome [3]. As diagnostic imaging tools, magnetic resonance imaging (MRI), ultrasonography (USG), and gallium (Ga)-67

Published online: 07 October 2009

scintigraphy are useful for the detection of inflammatory sites [4–8].

Based on this case report, we suggest that the synovial tissues rich in humoral factors of IL-6, VEGF and matrix metalloproteinase-3 (MMP-3) are principal in the development of RS_3PE syndrome.

Case report

A 59-year-old Japanese woman was admitted to our hospital because of polyarthralgia, edema of the dorsum of the bilateral hands and feet, and high fever on 23 August 2008. A physical examination showed remarkable symmetrical pitting edema of the dorsum of the hands and feet, and tenderness and warmth of joints of the bilateral shoulders, elbows, wrists and knees. Biochemical and serological data are shown in Table 1. The blood count showed anemia. C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) were increased. RF and anti-cyclic citrullinated peptide antibodies (anti-CCP Ab) were negative. The serum levels of interleukin-6 (IL-6), VEGF, MMP-3 and serum amyloid A (SAA) were markedly elevated. Bone erosion was not found by plain radiography. Ga-67 scintigraphy (Fig. 1a) showed symmetrically multiple increased uptakes in the joints of the extremities. Dynamic MRI (Fig. 1b) detected synovitis of the wrists, metacarpophalangeal joints and proximal interphalangeal joints, tenovitis of extensor and flexor tendons, and diffuse subcutaneous edema in the bilateral hands. USG of the hands and feet (Fig. 1c) also detected synovitis, tenosynovitis and subcutaneous edema of the dorsum.

The patient was diagnosed with RS_3PE syndrome fulfilling the following criteria [2]: (1) bilateral pitting edema of the hands, (2) sudden onset of polyarthritis, (3) age >50 years, (4) seronegativity for RF. On 29 August 2009, treatment with oral prednisolone 15 mg daily was initiated. After the initiation of treatment, symptoms including fever, edema of the extremities and arthralgia promptly improved. Serologic variables were remarkably improved beginning 2 weeks after treatment (Table 2). Tenosynovitis and subcutaneous edema in MRI and USG had almost disappeared at 1 month after the initiation of treatment, although a slight elevation of MMP-3 and SAA continued. We succeeded in tapering the dose of prednisolone without any recurrence.

Table 1 Biochemical and serological evaluation

Laboratory test	Result	Laboratory test	Result
Urine glucose	Negative	Antinuclear antibodies	1:160 (homogenous pattern)
Urine protein	Negative	Rheumatoid factor	Negative
Urine urobilinogen	Negative	Anti-CCP	<4.5 U/ml
White cell count	7,200/mm^3	Serum MMP-3	1,274.4 ng/ml
Hemoglobin	9.5 g/dl	Serum amyloid A	2,190 μg/ml
Platelets	451,000/mm^3	Serum VEGF	1,560 pg/ml
Sodium	134 mEq/l	Soluble IL-2 receptor	861 U/ml
Potassium	3.6 mEq/l	IgA	343 mg/dl
Chloride	95 mEq/l	IgG	1,310 mg/dl
BUN	7.0 mg/dl	IgM	168 mg/dl
Creatinine	0.4 mg/dl	C3	122 mg/dl
Uric acid	2.4 mg/dl	C4	28.5 mg/dl
Total protein	6.5 g/dl	CH50	40.1 U/ml
Albumin	2.7 g/dl	Ferritin	606 ng/ml
Total cholesterol	134 g/dl	C-reactive protein	9.49 mg/dl
Triglyceride	84 g/dl	ESR	112.4 mm/h
AST	17 IU/l	Free thyroxine	1.56 ng/ml
ALT	27 IU/l	TSH	1.37 μU/ml
LDH	155 IU/l	HLA-B7	Positive
γGTP	13 IU/l		
ALP	266 IU/l		
Creatine kinase	17 IU/l		
Aldolase	6.2 IU/l		

Discussion

We previously reported synovial hypervascularity and subcutaneous edema in dynamic MRI with a remarkable increment of serum VEGF in patients with RS_3PE syndrome [3]. After treatment, MRI abnormalities and high serum VEGF rapidly decreased [3]. We had discussed that both synovial hypervascularity and increment of vascular permeability may be facilitated by VEGF [3]. We have investigated this hypothesis more intensely in the present case by serologic variables and radiographic methods. These abnormalities have been reported previously [3–9]; however, this is the first report of a patient showing recovery from all these parameters at once after treatment. In vitro studies have revealed that IL-6 induces the production of VEGF [10], MMP-3 [11] and SAA [12]. Since IL-6 concentration in synovial fluid of RS_3PE syndrome is much higher than in serum [9], IL-6, probably produced from the synovial tissues, may facilitate the pathologic status of RS_3PE syndrome via VEGF and MMP-3.

Ga-67 scintigraphy allows the detection of the distribution of systemic synovitis, whereas MRI and USG are useful to show the local inflammatory process precisely. As

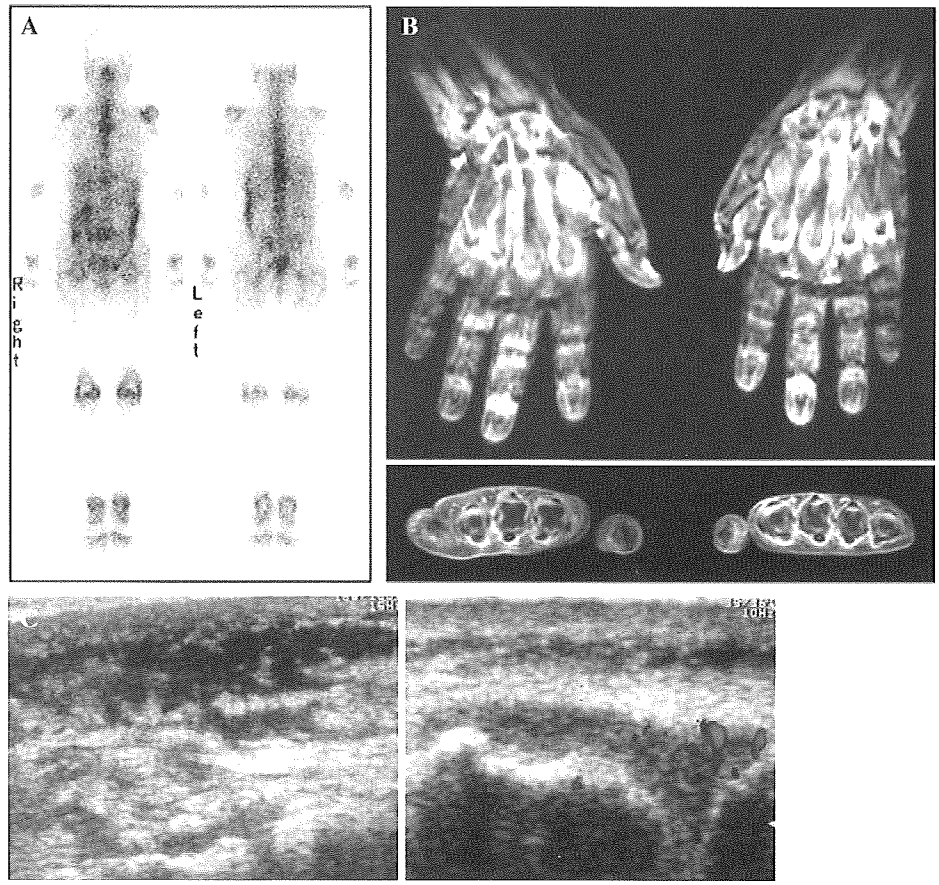

Fig. 1 Ga-67 scintigraphy (**a**) showed symmetrically multiple increased uptakes in the joints of the extremities. Dynamic MRI (**b**) detected synovitis of the wrists, metacarpophalangeal joints and proximal interphalangeal joints, and tenovitis of the extensor and flexor tendons in the bilateral hands. USG of the hands and feet (**c**) also detected synovitis and subcutaneous edema of the dorsum

Table 2 Serologic variables at various points

Laboratory test	August 23	September 4	October 30
Serum VEGF (pg/ml)	2,190	476	510
Serum IL-6 (pg/ml)	125	5.0	2.5
Serum TNF-alpha (pg/ml)	1.4	1.5	1.1
Serum MMP-3 (ng/ml)	1274.4	164	143.8
SAA (μg/ml)	2,190	154	45.5
CRP (mg/dl)	9.49	1.02	0.04
ESR (mm/h)	112.4	71.2	25

Normal concentrations of serum MMP-3 and SAA are 17.3–59.7 ng/ml and <8 μg/ml, respectively

expected, intense accumulation of synovial inflammatory cells with hypervascularity in the presence of subcutaneous edema and tenosynovitis was determined in our case, which may have been driven by IL-6, VEGF, MMP-3 and was clearly improved by traditional low-dose steroid.

The findings in our present case support a previous observation that synovial tissues are a major inflammatory source of RS_3PE syndrome. Both serologic and radiographic methods are quite beneficial in monitoring the disease activity of RS_3PE syndrome.

References

1. McCarty DJ, O'Duffy JD, Pearson L, Hunter JB (1985) Remitting seronegative symmetrical synovitis with pitting edema. RS3PE syndrome. JAMA 25:2763–2767
2. Olivé A, del Blanco J, Pons M, Vaquero M, Tena X (1997) The clinical spectrum of remitting seronegative symmetrical synovitis with pitting edema. The Catalán Group for the Study of RS3PE. J Rheumatol 24:333–336
3. Arima K, Origuchi T, Tamai M, Iwanaga N, Izumi Y, Huang M et al (2005) RS3PE syndrome presenting as vascular endothelial growth factor-associated disorder. Ann Rheum Dis 64:1653–1655
4. Unlu Z, Orguc S, Ovali GY, Tarhan S, Dayan I, Angin A (2005) Magnetic resonance imaging findings in a case of remitting seronegative symmetrical synovitis with pitting edema. Clin Rheumatol 24(6):648–651
5. Cantini F, Salvarani C, Olivieri I, Barozzi L, Macchioni L, Niccoli L et al (1999) Remitting seronegative symmetrical synovitis with pitting oedema (RS3PE) syndrome: a prospective follow-up and magnetic resonance imaging study. Ann Rheum Dis 58:230–236
6. Agarwal V, Dabra AK, Kaur R, Sachdev A, Singh R (2005) Remitting seronegative symmetrical synovitis with pitting edema (RS3PE) syndrome: ultrasonography as a diagnostic tool. Clin Rheumatol 24:476–479
7. Klauser A, Frauscher F, Halpern EJ, Mur E, Springer P, Judmaier W et al (2005) Remitting seronegative symmetrical synovitis with pitting edema of the hands: ultrasound, color Doppler

ultrasound, and magnetic resonance imaging findings. Arthritis Rheum 53:226–233
8. Takeguchi T, Sugawara Y, Kikuchi K, Miki H, Mochizuki T, Ikezoe J et al (2003) Remitting seronegative symmetric synovitis with pitting edema: scintigraphic and magnetic resonance imaging findings. Clin Nucl Med 28:766–768
9. Oide T, Ohara S, Oguchi K, Maruyama M, Yazawa M, Inoue K et al (2004) Remitting seronegative symmetrical synovitis with pitting edema (RS3PE) syndrome in Nagano, Japan: clinical, radiological, and cytokine studies of 13 patients. Clin Exp Rheumatol 22:91–98
10. Nakahara H, Song J, Sugimoto M, Hagihara K, Kishimoto T, Yoshizaki K et al (2003) Anti-interleukin-6 receptor antibody therapy reduces vascular endothelial growth factor production in rheumatoid arthritis. Arthritis Rheum 48:1521–1529
11. Fuchs S, Skwara A, Bloch M, Dankbar B (2004) Differential induction and regulation of matrix metalloproteinases in osteoarthritic tissue and fluid synovial fibroblasts. Osteoarthr Cartil 12:409–418
12. Castell JV, Gómez-Lechón MJ, David M, Hirano T, Kishimoto T, Heinrich PC (1988) Recombinant human interleukin-6 (IL-6/BSF-2/HSF) regulates the synthesis of acute phase proteins in human hepatocytes. FEBS Lett 232:347–350

Mod Rheumatol (2010) 20:40–45
DOI 10.1007/s10165-009-0235-4

ORIGINAL ARTICLE

Switching to the anti-interleukin-6 receptor antibody tocilizumab in rheumatoid arthritis patients refractory to antitumor necrosis factor biologics

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Received: 11 March 2009 / Accepted: 2 September 2009 / Published online: 3 October 2009

Abstract We evaluated the short-term effects of the anti-interleukin-6 (IL-6) receptor antibody tocilizumab (TCZ) in six patients with rheumatoid arthritis (RA) who had been refractory to tumor necrosis factor (TNF) antagonist therapy. All subjects were considered to be secondary nonresponders to TNF antagonists as decided by each physician. The Disease Activity Score of 28 Joints (DAS28) appeared to improve slowly by TCZ compared with TNF antagonist therapy, but significantly decreased at 24 weeks. One patient achieved DAS28 remission [DAS28–erythrocyte sedimentation rate (ESR) <2.60, and 5 of 6 patients showed good or moderate clinical response. The change in the clinical Disease Activity Index was similar to that of the DAS28–ESR. The serum level of matrix metalloproteinase-3 (MMP-3), a marker for synovial overgrowth, also significantly decreased after the treatment (518 ± 567 at baseline, 141 ± 90 ng/ml at 24 weeks, $p < 0.05$). One patient discontinued TCZ because of tuberculous peritonitis. Although physicians need to watch for infectious adverse events, these data indicate that TCZ is effective for treating RA patients refractory to TNF antagonists.

Keywords Tocilizumab · TNF antagonist · Rheumatoid arthritis · DAS28 · Tuberculosis

Abbreviations

ACR	American College of Rheumatology
CRP	C-reactive protein
CDAI	Clinical Disease Activity Index
DAS28	Disease Activity Score of 28 Joints
DMARDs	Disease-modifying antirheumatic drugs
ESR	Erythrocyte sedimentation rate
IL-6	Interleukin-6
mHAQ	Modified Health Assessment Questionnaire
MMP-3	Matrix metalloproteinase
PSL	Prednisolone
RA	Rheumatoid arthritis
SAA	Serum amyloid A
TCZ	Tocilizumab
TJC	Tender joint count
TNF	Tumor necrosis factor
SJC	Swollen joint count
VAS	Visual analogue scale

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Introduction

Tumor necrosis factor (TNF) antagonist treatment is remarkably effective in rheumatoid arthritis (RA), but 20–40% of RA patients show insufficient responses. Although switching from one TNF antagonist to another is effective in some of these cases, there are limited options for the remaining refractory cases. Tocilizumab (TCZ) is a humanized anti-interleukin-6 (IL-6) receptor monoclonal antibody that blocks IL-6 from binding to its receptor [1].

Japanese clinical studies such as the Study of Active Controlled Monotherapy for Rheumatoid Arthritis, an IL-6 Inhibitor (SAMURAI) trial [2] or the Study of Active Controlled Tocilizumab Monotherapy for Rheumatoid Arthritis Patients with Inadequate Response to Methotrexate (SATORI) trial [3] elucidated the efficacy and safety of TCZ monotherapy in RA patients refractory to disease-modifying antirheumatic drugs (DMARDs) and naïve to TNF antagonists. In the SAMURAI trial, the proportions of patients achieving American College of Rheumatology (ACR)20, ACR50, and ACR70 responses were 78%, 64%, and 44% in the TCZ group and 34%, 13%, and 6% in the control DMARD group, respectively. These data established the significant superiority of TCZ monotherapy to conventional DMARD therapy.

As the target of TCZ is different from TNF antagonists, TCZ is suggested to be effective in RA patients resistant to TNF antagonists. Based on this point of view, the Rheumatoid Arthritis Study in Anti-TNF Failures (RADIATE) trial was carried out to determine the effect of TCZ plus methotrexate in patients with an inadequate response to TNF-antagonist therapy [4]. At 52 weeks after the initial infusion, the proportions of patients achieving ACR20, ACR50, and ACR70 responses were 50.0%, 28.8%, and 12.4% in the 8 mg/kg TCZ group, respectively. The proportions of patients achieving low disease activity and Disease Activity Score of 28 Joints (DAS28) remission were 51.2% and 30.1%, respectively. These data imply that TCZ is effective even for RA patients who show inadequate responses to TNF antagonists. The RADIATE trial has revealed important evidence, whereas the dosage as well as kinds of nonbiologic DMARDs on the "real world" of RA in Japan is quite different from in Western countries. Thus, we tried to clarify the usefulness of TCZ for treating RA patients who did not respond well to TNF antagonists, and showed short-term (24 weeks) efficacy and safety in six RA patients.

Materials and methods

Patients

Six RA patients, who met the 1987 criteria of the ACR for RA [5] and showed insufficient response to one or two TNF antagonists (infliximab, etanercept, adalimumab) were consecutively enrolled in the study. All 6 patients were considered to be secondary nonresponders to previous TNF antagonists, as decided by each physician. All 6 patients began receiving TCZ from May 2008 to July 2008. They gave their informed consent to the protocol, which was approved by the Institutional Review Board of Nagasaki University. They received 8 mg/kg of TCZ intravenously every 4 weeks for 24 weeks. There was no change in the DMARDs they were receiving during this period. To maintain patient safety, especially against infection, we did not directly change TNF antagonists to TCZ at the time schedule anticipated for which TNF antagonists had been administrated just before TCZ, and the washout period was considered for 4 out of the 6 cases, which are described in "Results". Clinical response to the therapy was evaluated by the DAS28 (high disease activity >5.1, moderate disease activity ≦5.1 and >3.2, low disease activity ≦3.2, remission <2.6), ACR response and Clinical Disease Activity Index (CDAI; high disease activity >22, moderate disease activity ≦22 and >10, low disease activity ≦10, remission ≦2.8) [6]. The erythrocyte sedimentation rate (ESR), C-reactive protein (CRP) (Eiken Chemical Co. Ltd., Tokyo, Japan), matrix metalloproteinase-3 (MMP-3) (Daiichi Pure Chemicals, Fukuoka, Japan), tender joint count (TJC), swollen joint count (SJC), patient visual analogue score (VAS), and modified Health Assessment Questionnaire (mHAQ) values were also evaluated.

Statistical analyses

Changes from baseline were compared using Wilcoxon's signed rank test. The overall significance level for statistical analysis was 5% (two-sided). P values <0.05 were considered statistically significant.

Results

Patients

Demographic and clinical characteristics of the 6 RA patients are shown in Table 1. The patients had high disease activity [mean ± standard deviation (SD) of DAS28–ESR: 6.54 ± 1.17 and that of CDAI: 29.7 ± 13.8, respectively] and were classified as having advanced-stage disease. Three patients had previously received one TNF antagonist and the other three patients had received two. All patients had taken oral prednisolone (PSL) (mean dose 6.3 ± 2.3 mg per day). During the study period, PSL was reduced in three patients. One patient discontinued TCZ at 22 weeks after the administration of TCZ because of tuberculous peritonitis (case 6).

Periods of TNF antagonists washout before TCZ

The washout period was considered to be 2 weeks for the two cases with etanercept (case 1 and 2). In cases 4 and 5, no intentional washout period was planned because etanercept had been stopped 2 months and 1 year before the introduction of TCZ in case 4 and case 5, respectively.

Table 1 Demographic and clinical characteristics of 6 rheumatoid arthritis (RA) patients

	Age (years)	Sex	Disease duration (years)	Stage/class	DAS28	CDAI	mHAQ	Concomitant DMARDs	Previous TNF antagonist therapy
Case 1	45	Female	3	IV/2	6.47	29.8	1.63	MTX 8 mg/week	ETN
Case 2	67	Male	4	IV/3	6.32	22.5	1.63	SASP 1,000 mg/day	ETN
Case 3	65	Female	1	II/2	7.96	47.6	3.38	MTX 8 mg/week	ETN (first), IFX (second)
Case 4	37	Female	8	IV/2	4.95	12.5	0.38	MTX 8 mg/week	IFX (first), ETN (second)
Case 5	55	Female	8	IV/2	7.82	44.5	2.50	MTX 10 mg/week	IFX (first), ETN (second)
Case 6	67	Female	8	IV/3	6.28	21.5	1.25	No	ADA

DAS28 Disease Activity Score of 28 Joints, *CDAI* Clinical Disease Activity Index, *mHAQ* Modified Health Assessment Questionnaire, *DMARDs* disease-modifying rheumatoid drugs, *TNF* tumor necrosis factor, *MTX* methotrexate, *SASP* salazosulfapyridine, *IFX* infliximab, *ETN* etanercept, *ADA* adalimumab

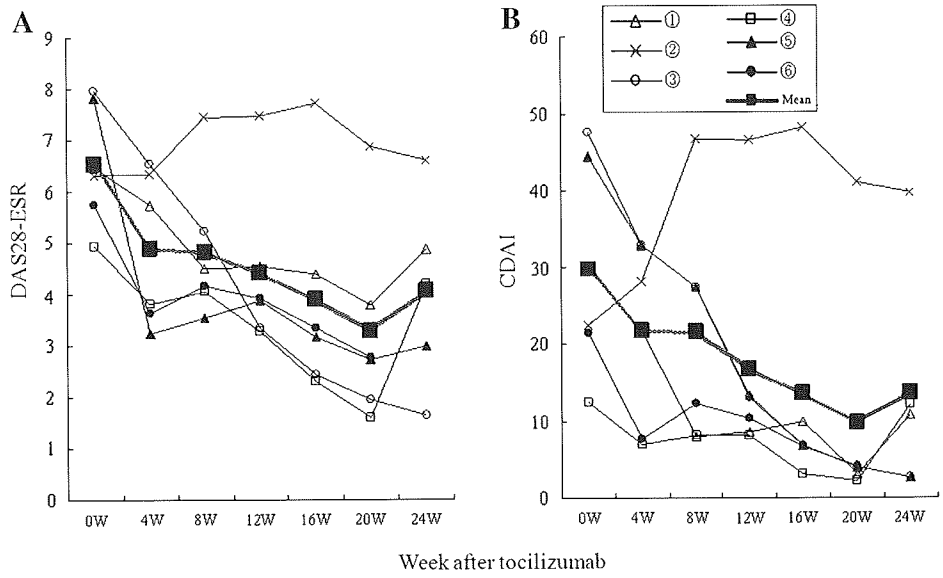

Fig. 1 Disease Activity Score of 28 Joints—erythrocyte sedimentation rate (DAS28–ESR) (**a**) and Clinical Disease Activity Index (CDAI) (**b**) during 24 weeks after tocilizumab administration. Changes in each patient as well as the mean change of the six patients are shown in the figure

The washout period was 4 weeks for infliximab (case 3) and 3 weeks for adalimumab (case 6). Intravenous dexamethasone palmitate was administrated in cases 2 and 3, and oral PSL was increased in case 5 before TCZ developed clinical efficacy in order to control disease activity.

Efficacy

The decrement of DAS28 by TCZ was relatively slow, but significant improvement was achieved at 24 weeks (mean ± SD of DAS28–ESR at 24 weeks: 3.85 ± 1.77, $p < 0.05$, Fig. 1a). As for the European League Against Rheumatism (EULAR) response at 24 weeks, a good response was observed in 3 patients (cases 3, 5, 6) and a moderate response in two (cases 1, 4). One patient (case 2) showed no response. One patient (case 3) achieved DAS remission. The ACR20, ACR50, and ACR70 responses were confirmed in four patients, three patients, and one patient, respectively. In Fig. 2, changes in TJC (Fig. 2a), SJC (Fig. 2b), and patient VAS (Fig. 2c) during the study period are demonstrated. The numbers of both TJC and SJC were gradually decreased in all patients except the one nonresponder (case 2). The mHAQ values were also improved from baseline by −0.35 greater than −0.22, which means clinically significant improvement. Disease activity was also monitored by CDAI, and the change of CDAI was similar to DAS28–ESR (Fig. 1b). At 24 weeks, two patients (cases 3, 5) achieved CDAI remission, one (case 6) achieved low CDAI disease activity, and two had moderate CADI disease activity.

Laboratory findings

Changes in laboratory findings during the study are shown in Table 2. The ESR and serum levels of CRP were markedly decreased to almost the normal range (Table 2; Fig. 2d, e). Hemoglobin and albumin levels were restored, and platelet level decreased significantly at 24 weeks. The total cholesterol level increased at 24 weeks ($p < 0.05$), but no patient needed cholesterol-lowering agents. The MMP-3

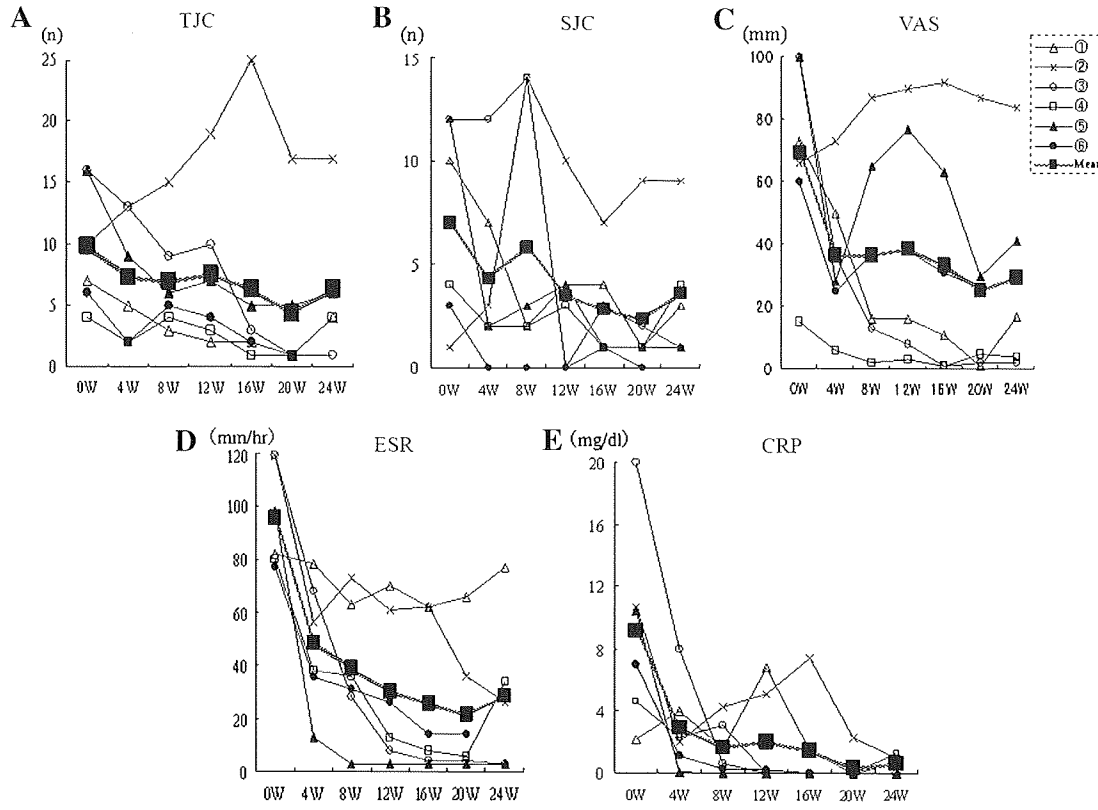

Fig. 2 Change in tender joint count (TLC) (**a**), swollen joint count (SJC) (**b**), patient visual analogue scale (VAS) (**c**), erythrocyte sedimentation rate (ESR) (**d**), and C-reactive protein (CRP) (**e**) during the 24-week period after tocilizumab administration. Changes in each patient as well as the mean change of the six patients are shown

serum concentration markedly decreased (59.5% reduction, significant, $p < 0.05$).

Adverse events

One patient (case 6) underwent an emergency operation for ileus due to peritonitis at 22 weeks after the initial TCZ infusion. She had bloody ascites and multiple nodules on her peritonea. Culture and PCR of acid-fast bacillus were all negative in the sputum, ascites, and gastric juice. The tuberculin skin test, QuantiFERON TB-2G (QFT-TB), was also negative. In addition, CRP was completely negative, and this patient did not run a fever until the operation. Pathologic examination of the peritonea confirmed epithelioid cell granuloma with caseous necrosis, indicating peritonitis by *Mycobacterium tuberculosis* infection. She had no history of exposure to *M. tuberculosis*. Before administration of TCZ, QFT-TB and culture and PCR of acid-fast bacillus in the sputum and gastric juice were all negative. Each time she was administered TCZ, her chest X-ray findings were normal, and they were also normal when peritonitis was diagnosed. She discontinued TCZ therapy and is being treated with antituberculosis drugs.

One patient (case 3) developed hypercholesterolemia and liver dysfunction, both of which were mild. One patient (case 2) developed leucopenia, $1.3 \times 10^3/mm^3$.

Discussion

IL-6 is one of the crucial proinflammatory cytokines involved in rheumatoid synovial inflammation [7, 8]. As its signaling pathway is different from TNF, IL-6 blockade therapy is a suggested alternative for RA patients with an unsatisfactory response to TNF antagonists. Moreover, Karlsson et al. [9] reported that the therapeutic response to a second or third TNF antagonist is limited compared with the first TNF antagonist. These data prompted us to administer TCZ to RA patients who showed insufficient response to TNF antagonists. In this study, we excluded patients who discontinued TNF antagonists for adverse events and only selected patients who showed an insufficient response toward TNF antagonists. All six cases were considered secondary nonresponders to TNF antagonists by their attending physician. TCZ demonstrated remarkable clinical effects for 5 out of the 6 patients in this study,

Table 2 Changes of laboratory findings in 6 rheumatoid arthritis (RA) patients after 6-month treatment with tocilizumab

	Baseline	After 24 weeks	*P* value
Hemoglobin (g/dl[a])	9.6 (7.3–10.9)	12.9 (14.6–8.8)	<0.05
Platelets ($\times 10^4$/mm^3)	33.2 (22.9–36.1)	18.0 (15.1–26.2)	<0.05
White blood cell ($\times 10^3$/mm^3)	6.6 (4.5–10.2)	4.8 (1.3–7.5)	NS
CRP (mg/dl[a])	8.7 (2.0–20)	0.7 (0–1.4)	<0.05
ESR (mm/h[a])	90 (119–77)	26 (3–77)	<0.05
Albumin (g/dl[a])	3.2 (2.7–3.5)	4.2 (3.7–4.7)	<0.05
AST (U/l[a])	25 (11–28)	26 (14–49)	NS
ALT (U/l[a])	15 (7–22)	26 (11–38)	NS
Total cholesterol (g/dl[a])	160 (119–208)	199 (162–258)	<0.05
Triglyceride (g/dl[a])	59 (51–108)	67 (46–120)	NS
MMP-3 (U/l[a])	299 (137–1647)	121 (58–310)	<0.05

CRP C-reactive protein, *ESR* erythrocyte sedimentation rate, *AST* aspartate aminotransferase, *ALT* alanine aminotransferase, *MMP-3* matrix metalloproteinase-3, *NS* not significant

[a] Median (range)

which is comparable to its efficacy observed in the RADIATE trial [4]. It should be noted that the 5 out of 6 cases achieved a moderate to good EULAR response. In addition to CRP and ESR, the synovial inflammatory marker MMP-3 was significantly decreased, supporting evidence that TCZ truly acts as biologic DMARDs in RA. The decrement of CDAI at 24 weeks may also support this notion.

As the simultaneous blockade of TNF and IL-6 may induce severe immune dysfunction, a washout period was intentionally planned for 4 out of the 6 cases. The disease activity of RA can be exacerbated before the effect of TCZ develops. Systemic administration of low-dose glucocorticoids is effective in relieving short-term signs and symptoms in patients with RA. As mentioned in our case series, the temporary use of glucocorticoids at the early therapeutic course of TCZ may be a clinically good choice.

Peritonitis due to *M. tuberculosis* occurred in one patient who had switched from adalimumab to TCZ. Before the switch, all of the examinations for acid-fast bacilli were negative. This patient refused chemical prophylaxis for tuberculosis because she had a repeated history of allergic reactions to a variety of drugs, including DMARDs. Both TNF and IL-6 play crucial roles in the cell-mediated immune response to *M. tuberculosis*, which was elucidated by infecting the bacteria to TNF-alpha or IL-6 knockout mice, whereas the antituberculous effect is achieved by different mechanisms through TNF-alpha or IL-6 [10–12]. A previous report showed that the incidence of infections in the RA population was nearly twice as high as in matched non-RA controls [13]. Furthermore, older age, longer RA duration, prior infections, higher comorbidity, and use of corticosteroid were reported to increase the risk of serious infections [14]. This patient was 67 years old at the initiation of TCZ, with 8 years of RA duration, and was concurrently administrated with 6 mg per day of prednisolone, suggesting that this case would be at high risk for infectious adverse events. TCZ, as well as adalimumab in this case, might accelerate to induce immune compromise to *M. tuberculosis*. Also, physicians need to be aware that TCZ may mask the increment of inflammatory reactions in such cases, as this patient did not show an elevation of CRP and fever until the emergency operation was performed. Further research on the safe use of TCZ, especially when switching from other biologics, is needed.

Conflict of interest statement None.

References

1. Mihara M, Kasutani K, Okazaki M, Nakamura A, Kawai S, Sugimoto M, et al. Tocilizumab inhibits signal transduction mediated by both mIL-6R and sIL-6R, but not by the receptors of other members of IL-6 cytokine family. Int Immunopharmacol. 2005;5:1731–40.
2. Nishimoto N, Hashimoto J, Miyasaka N, Yamamoto K, Kawai S, Takeuchi T, et al. Study of active controlled monotherapy used for rheumatoid arthritis, an IL-6 inhibitor (SAMURAI): evidence of clinical and radiographic benefit from an X-ray reader-blinded randomised controlled trial of tocilizumab. Ann Rheum Dis. 2007;66:1162–7.
3. Nishimoto N, Miyasaka N, Yamamoto K, Kawai S, Takeuchi T, Azuma J, et al. Study of active controlled tocilizumab monotherapy for rheumatoid arthritis patients with an inadequate response to methotrexate (SATORI): significant reduction in disease activity and serum vascular endothelial growth factor by IL-6 receptor inhibition therapy. Mod Rheumatol. 2009;19:12–9.
4. Emery P, Keystone E, Tony HP, Cantagrel A, van Vollenhoven R, Sanchez A, et al. IL-6 receptor inhibition with tocilizumab improves treatment outcomes in patients with rheumatoid arthritis refractory to anti-tumour necrosis factor biologicals: results from

a 24-week multicentre randomised placebo-controlled trial. Ann Rheum Dis. 2008;67:1516–23.
5. Arnett FC, Edworthy SM, Bloch DA, McShane DJ, Fries JF, Cooper NS, et al. The American Rheumatism Association 1987 revised criteria for the classification of rheumatoid arthritis. Arthritis Rheum. 1988;31:315–24.
6. Mierau M, Schoels M, Gonda G, Fuchs J, Aletaha D, Smolen JS. Assessing remission in clinical practice. Rheumatology (Oxford). 2007;46:975–9.
7. Houssiau FA, Devogelaer JP, Van Damme J, de Deuxchaisnes CN, Van Snick J. Interleukin-6 in synovial fluid and serum of patients with rheumatoid arthritis and other inflammatory arthritides. Arthritis Rheum. 1988;31:784–8.
8. Madhok R, Crilly A, Watson J, Capell HA. Serum interleukin 6 levels in rheumatoid arthritis: correlations with clinical and laboratory indices of disease activity. Ann Rheum Dis. 1993;52:232–4.
9. Karlsson JA, Kristensen LE, Kapetanovic MC, Gülfe A, Saxne T, Geborek P. Treatment response to a second or third TNF-inhibitor in RA: results from the South Swedish Arthritis Treatment Group Register. Rheumatology (Oxford). 2008;47:507–13.
10. Flynn JL, Goldstein MM, Chan J, Triebold KJ, Pfeffer K, Lowenstein CJ, et al. Tumor necrosis factor-alpha is required in the protective immune response against *Mycobacterium tuberculosis* in mice. Immunity. 1995;2:561–72.
11. Bean AG, Roach DR, Briscoe H, France MP, Korner H, Sedgwick JD, et al. Structural deficiencies in granuloma formation in TNF gene-targeted mice underlie the heightened susceptibility to aerosol *Mycobacterium tuberculosis* infection, which is not compensated for by lymphotoxin. J Immunol. 1999;162:3504–11.
12. Ladel CH, Blum C, Dreher A, Reifenberg K, Kopf M, Kaufmann SH. Lethal tuberculosis in interleukin-6-deficient mutant mice. Infect Immun. 1997;65:4843–9.
13. Doran MF, Crowson CS, Pond GR, O'Fallon WM, Gabriel SE. Frequency of infection in patients with rheumatoid arthritis compared with controls: a population-based study. Arthritis Rheum. 2002;46:2287–93.
14. Lacaille D, Guh DP, Abrahamowicz M, Anis AH, Esdaile JM. Use of nonbiologic disease-modifying antirheumatic drugs and risk of infection in patients with rheumatoid arthritis. Arthritis Rheum. 2008;59(8):1074–81.

Mod Rheumatol (2009) 19:652–656
DOI 10.1007/s10165-009-0216-7

ORIGINAL ARTICLE

Prediction of DAS28-CRP remission in patients with rheumatoid arthritis treated with tacrolimus at 6 months by baseline variables

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Received: 23 March 2009 / Accepted: 14 July 2009 / Published online: 29 September 2009

Abstract We attempted to determine what baseline variables are responsible for the efficacy of tacrolimus at 6 months in Japanese patients with rheumatoid arthritis (RA). One hundred and six RA patients treated with tacrolimus for 6 months were entered in this study. The outcome was set as the achievement of Disease Activity Score 28 C-reactive protein (DAS28-CRP) remission at 6 months. We examined the association of gender, DAS28-CRP at baseline, concomitant use of methotrexate (MTX), and concomitant use of prednisolone with the achievement of DAS28-CRP remission at 6 months by logistic regression analysis. Twenty-three of 106 patients (21.7%) achieved DAS28-CRP remission at 6 months. There was concomitant use of MTX by 20 patients (18.9%), prednisolone by 93 (87.7%), and prednisolone >5 mg/day by 43 (40.6%) at baseline. Logistic regression analysis showed that male gender (first) and moderate disease activity at baseline (second) are independent predictors toward achieving DAS28-CRP remission at 6 months. Maximum tacrolimus dosage administrated for patients over a 6-month period appeared not to be predictive for the DAS28-CRP remission at 6 months. In conclusion, we revealed for the first time that good outcome in RA patients treated with tacrolimus can be predictive by some baseline variables. That is clinically valuable for daily practice in the choice of disease-modifying antirheumatic drugs (DMARDs), especially tacrolimus.

Keywords DAS · Gender · MTX · Rheumatoid arthritis · Tacrolimus

Abbreviations

ACR	American College of Rheumatology
DAS	Disease Activity Score
DMARDs	Disease-modifying antirheumatic drugs
MTX	Methotrexate
RA	Rheumatoid arthritis

Introduction

Tacrolimus targets tacrolimus-binding protein and inhibits calcineurin-dependent expression of cytokine genes such as

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interleukin-2 [1]. Tacrolimus is defined as a new type of nonbiologic disease-modify antirheumatic drug (DMARD) in patients with rheumatoid arthritis (RA) [2]. Its efficacy and safety toward RA have been reported from several countries, including Japan [3–7]. However, compared with standard DMARDs such as methotrexate, there is little evidence published in the literature regarding tacrolimus. Therefore, the American College of Rheumatology (ACR) 2008 recommendations for the use of nonbiologic and biologic DMARDs in rheumatoid arthritis do not refer to tacrolimus in patients with RA [8]. This situation requires clinical evaluation of tacrolimus in patients with RA. We therefore examined prospectively the efficacy of 6 months of tacrolimus treatment in patients with RA and shown that male gender and moderate disease activity at baseline are predictive for good therapeutic response at 6 months.

Patients and methods

Patients

Patients were recruited from Unit of Translational Medicine, Department of Immunology and Rheumatology, Graduate School of Biomedical Sciences, Nagasaki University; Sasebo Chuo Hospital; Gotokai Hospital; The Japanese Red Cross Nagasaki Atomic Bomb Hospital; Nagasaki Citizens Hospital; and Nagasaki Kita Hospital. Written informed consent, approved by the above hospitals, was obtained from each patient. Figure 1 summarizes the study design. At first, 127 patients with RA classified by the 1987 criteria of the ACR [9], whose Disease Activity Score 28 C-reactive protein (DAS28-CRP) at baseline was high or moderate (DAS28-CRP at baseline higher than 2.67 according to the literature) [10] were entered into the study. Seventeen patients discontinued due to adverse events, one discontinued for other reasons, and three were excluded due to lack of data. Twelve patients, who discontinued due to lack of response to tacrolimus, were, however, included in the analysis. Therefore, 106 patients were evaluated.

Statistical analysis

Distribution of baseline variables was examined by Mann–Whitney's U test and chi-square test. Logistic regression analysis was performed to investigate a relationship between baseline variables and clinical efficacy at 6 months. Good clinical efficacy was set as the achievement of DAS28 remission at 6 months calculated by DAS28-CRP. As previously described in the literature, DAS28-CRP < 2.67 was considered as low disease activity [10]. Baseline variables were gender, DAS28-CRP at baseline [high disease activity (≥ 4.09) vs. moderate disease activity ($2.67 \leq$ DAS28-CRP < 4.09)], concomitant methotrexate (MTX) use, and concomitant prednisolone use. Concomitant prednisolone use >5 mg/day was also examined for logistic regression analysis. P value <0.05 is considered significant.

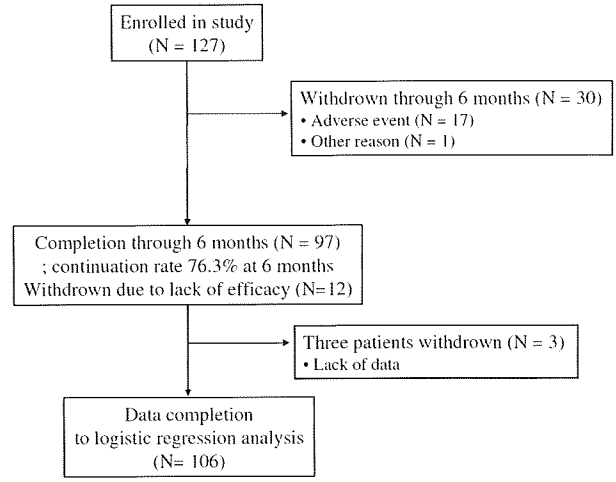

Fig. 1 Patient enrollment. Study design for logistic regression analysis of 106 patients with rheumatoid arthritis treated with tacrolimus for 6 months

Results

Baseline variables of 106 patients with RA treated with tacrolimus for 6 months and gross outcome at 6 months

Table 1 summarized the data. Most patients had established disease with a mean disease duration of 10.2 years at baseline. MTX was already being administered to 20 patients. None of the patients received biologic DMARDs (infliximab, etanercept, adalimumab, tocilizumab) during the 6 months. All 106 patients expressed high ($N = 75$) or moderate ($N = 31$) disease activity at baseline (Table 1), and 23 out of 106 achieved DAS28-CRP remission at 6 months (21.7%). Eighty-four patients (87.7%) received prednisolone, and 38 (40.6%) received prednisolone >5 mg/day at baseline.

Male gender and moderate disease activity at baseline are independent predictors for DAS28-CRP remission at 6 months

Table 2 shows the data of logistic regression analysis. Male gender (first) and moderate disease activity at baseline (second) were independent predictors. Similar results were obtained if the dosage of prednisolone at baseline was limited to >5 mg/day. Other variables of the concomitant

Table 1 The characteristics of rheumatoid arthritis (RA) patients

Baseline characteristics	All patients	Baseline DAS28-CRP		
		High group (DAS ≥ 4.09)	Moderate group (2.67 ≤ DAS < 4.09)	*p* value
No. of patients	*N* = 106	*N* = 75 (70.8%)	*N* = 31 (29.2%)	–
Age (years) mean ± SD	62.1 ± 12.6	64.2 ± 10.8	58.4 ± 16.2	0.20
Gender (male/female)	22/84	17/58	5/26	0.45*
Duration of disease	10.2 ± 8.6	10.9 ± 9.2	7.7 ± 5.7	0.15
DAS28-CRP, mean ± SD	4.76 ± 1.04	5.24 ± 0.80	3.57 ± 0.34	<0.01
Concomitant MTX use at baseline (yes/no)	20/86	12/63	8/23	0.24*
Maximum dosage of tacrolimus over a 6-month period (mg/day)	1.91 ± 0.76	1.93 ± 0.72	1.89 ± 0.85	0.49

Baseline characteristics, including age, gender, duration of disease at baseline, concomitant methotrexate (MTX) use at baseline, and maximum dosage of tacrolimus over a 6-month period were no different between high and moderate Disease Activity Score 28–C reactive protein (DAS28-CRP) patients. The distribution is characterized by Mann–Whitney's *U* test or *chi-square test

SD standard deviation

Table 2 Logistic regression analysis to estimate response to tacrolimus

Baseline variables	Comparison	Odds ratio	95% confidence interval	*p* value
Variables: gender, concomitant use of MTX, concomitant use of nonbiologic DMARDs other than MTX, concomitant use of prednisolone, DAS28-CRP				
Gender	Male/female	*4.75*	1.53–14.78	*0.007*
MTX	Yes/no	2.20	0.69–7.08	0.19
DMARDs other than MTX	Yes/no	2.09	0.25–17.92	0.50
Prednisolone	Yes/no	1.71	0.35–8.42	0.51
Disease activity	Moderate/high	*2.88*	1.07–7.77	*0.04*
Variables: gender, concomitant use of MTX, concomitant use of nonbiologic DMARDs other than MTX, concomitant use of prednisolone >5 mg/day, DAS28-CRP				
Gender	Male/female	*4.43*	1.46–13.44	*0.009*
MTX	Yes/no	2.25	0.71–7.16	0.17
DMARDs other than MTX	Yes/no	2.30	0.27–19.59	0.45
Prednisolone	Yes/no	0.77	0.30–1.96	0.58
Disease activity	Moderate/high	*2.88*	1.07–7.77	*0.04*

Male gender and moderate disease activity at baseline are predictive for low disease activity

MTX methotrexate, *DMARDs* disease-modifying antirheumatic drugs, *DAS28-CRP* Disease Activity Score 28–C-reactive protein

use of MTX and that of prednisolone did not reach statistical significance. We also compared variables at baseline by gender, and accordingly, there was no significant difference in age at baseline, duration of disease, and DAS28-CRP at baseline (Table 3). In addition, maximum dosage of daily tacrolimus did not differ between male and female patients. Baseline demographic data was also compared between high and moderate disease activity, and no significant difference was determined in age at baseline (64.2 ± 10.8 years vs. 58.4 ± 16.2 years), duration of disease (10.9 ± 9.2 years vs. 7.7 ± 5.7 years), concomitant use of MTX at baseline (12 of 75 vs. 8 of 31), and maximum dosage of daily tacrolimus over the 6-month period (1.93 ± 0.72 mg/day vs. 1.89 ± 0.85 mg/day).

Discussion

Postmarketing surveillance (PMS) of biologic DMARDs has revealed that some baseline demographic data associate with better outcome, including male gender, concomitant use of MTX and lower disease activity at baseline for etanercept and younger age, and negative test for rheumatoid factor and lower disease activity at baseline for

Table 3 Baseline characteristics between female and male patients

Gender	Female	Male	*p* value
No. of patients	$N = 84$	$N = 22$	–
Age (years) mean ± SD	61.9 ± 12.7	62.7 ± 12.6	0.82
Duration of disease	10.1 ± 8.9	8.5 ± 7.33	0.30
DAS28-CRP, mean ± SD	4.75 ± 1.07	4.78 ± 0.94	0.68
Concomitant MTX use at baseline (yes/no)	16/68	4/18	0.93*
Maximum dosage of tacrolimus over a 6-month period (mg/day)	1.93 ± 0.75	1.84 ± 0.81	0.57

Baseline characteristics, including age, duration of disease at baseline, Disease Activity Score 28–C reactive protein (DAS28-CRP) at baseline, concomitant methotrexate (MTX) use at baseline, and maximum dosage of tacrolimus over a 6-month period were no different between female and male patients. The distribution is characterized by Mann–Whitney's *U* test or *chi-square test

SD standard deviation

infliximab [11, 12]. We have shown for the first time if the patients of having some characteristics at baseline suggest good therapeutic response in tacrolimus-treated patients with RA. Previous studies reported an efficacy of tacrolimus in RA patients receiving concomitant MTX, though precise statistical analysis was not performed [6, 7]. Our study is based on PMS, and therapeutic options during the treatment are dependent on each physician's decision. Thus, we cannot refer to the concomitant use of DMARDs during the 6-month period, and MTX use at baseline did not determine the achievement of DAS28-CRP remission at 6 months. However, the percentage of achievement of DAS28-CRP remission at 6 months tended to be higher in MTX user at baseline compared with the MTX nonuser [7/20 MTX users (35.0%) vs. 16/86 MTX nonusers (18.6%), $p = 0.11$ by chi-square test]. Therefore, we suggest that in patients with active RA, despite being treated with MTX, add-on therapy of tacrolimus may provide clinical benefit.

Male gender and moderate disease activity at baseline are determined to be predictors of better clinical response by tacrolimus-treated patients with RA. This is a first observation in tacrolimus users and is already published in the case of MTX, etanercept, and infliximab, as described above [11–13], indicating that these demographic data may be common indicators for good therapeutic response of DMARDs in patients with RA.

Maximum dosage of daily tacrolimus during the 6 months was not different if RA patients were divided by either the achievement of DAS28-CRP remission at 6 months (1.93 ± 0.71 mg/day in remission vs. 1.90 ± 0.78 mg/day in nonremission, $p = 0.81$) or gender. A recent report demonstrates that no significant correlation was observed between the blood concentration level of tacrolimus and DAS28 improvement at 4 weeks [14]; however, further studies are necessary with regard to the dose-dependent effect of tacrolimus. Recent studies have shown a good safety profile of tacrolimus in Japanese patients with RA [4, 5]. This is an open-labeled PMS study, which therefore could have limitations. However, our results indicate that efficacy of tacrolimus can be predicted by baseline demographic data. Our data show clinical benefit for tacrolimus use in clinical practice.

Acknowledgments We thank Miss Kuniko Matsushita for excellent practical assistance. This study was supported by a grant from The Ministry of Health, Labour and Welfare, Japan

Conflict of interest statement None.

References

1. Kelly PA, Burckart GJ, Venkataramanan R. Tacrolimus: a new immunosuppressive agent. Am J Health Syst Pharm. 1995; 52:1569–71.
2. Fleischmann R, Iqbal I, Stern RL. Tacrolimus in rheumatoid arthritis. Expert Opin Pharmacother. 2006;7:91–8.
3. Kawai S, Yamamoto K. Safety of tacrolimus, an immunosuppressive agent, in the treatment of rheumatoid arthritis in elderly patients. Rheumatology. 2006;45:441–4.
4. Kawai S, Tanaka K, Ohno I, Utsunomiya K, Seino Y. Safety of long-term therapy for rheumatoid arthritis: an open-label, uncontrolled study in non-elderly patients. Mod Rheumatol. 2008;18:345–53.
5. Akimoto K, Kusunoki Y, Nishio S, Takagi K, Kawai S. Safety profile of tacrolimus in patients with rheumatoid arthritis. Clin Rheumatol. 2008;27:1393–7.
6. Morita Y, Sasae Y, Sakuta T, Satoh M, Sasaki T, Kashihara N. Efficacy of low-dose tacrolimus added to methotrexate in patients with rheumatoid arthritis in Japan: a retrospective study. Mod Rheumatol. 2008;18:379–84.
7. Kremer JM, Habros JS, Kolba KS, Kaine JL, Ann Borton M, Mengle-Gaw LJ, et al. Tacrolimus in rheumatoid arthritis patients receiving concomitant methotrexate. A six-month, open-label study. Arthritis Rheum. 2003;48:2763–8.
8. Saag KG, Teng GG, Patkar NM, Anuntiyo J, Finney C, Curtis JR, et al. American College of Rheumatology 2008 recommendations for the use of nonbiologic and biologic disease-modifying anti-rheumatic drugs in rheumatoid arthritis. Arthritis Rheum (Arthritis Care & Research). 2008;59:762–84.
9. Inoue E, Yamanaka H, Hara M, Tomatsu T, Kamatani N. Comparison of disease activity score (DAS)28-erythrocyte