Preliminary Report of Endovascular Treatment for Critical Limb Ischemia Patients with Connective Tissue Disease: Cases Series and Review of the Literature

Hideaki Obara, MD, PhD, FICA¹ Kentaro Matsubara, MD, PhD¹ Naoki Fujimura, MD, PhD¹
Yasuhito Sekimoto, MD¹ Yuko Kitagawa, MD, PhD¹

¹ Department of Surgery, Keio University School of Medicine, Tokyo, Japan

Address for correspondence Hideaki Obara, MD, PhD, FICA, Department of Surgery, Keio University School of Medicine, 35 Shinanomachi, Shinjuku-ku, Tokyo 160-8582, Japan (e-mail: obara@z3.keio.jp).

Int J Angiol 2015;24:137–142.

Abstract

Only few studies have addressed the surgical revascularization in patients with both connective tissue disease (CTD) and critical limb ischemia (CLI), and the evidence for the endovascular treatment (EVT) is lacking in such patients. The main purpose of this study is to assess our outcome of EVT in patients with CTD and ischemic leg ulcers and review the current situation of the revascularization in such patients. Medical records of 10 consecutive patients with coexistent CTD and CLI-related leg ulcers (in 11 limbs) treated endovascularly at our institution between 2009 and 2013 were reviewed retrospectively. The patients had rheumatoid arthritis ($n = 5$), systemic lupus erythematosus ($n = 1$), progressive systemic sclerosis ($n = 3$), or polyarteritis nodosa ($n = 1$). EVT was technically successful in all the cases. No procedure-related morbidity or mortality occurred. During the mean follow-up period of 26 months, there were no major amputations, and sustained clinical improvement (ulcer healing and reduction in Rutherford category) was observed in eight limbs. The overall 1-year rates of amputation-free survival and freedom from reintervention were 89 and 81%, respectively. In our series of patients with CTD and ischemic leg ulcers, EVT had acceptable outcomes and may be recommended as a safe and reasonably effective initial treatment option for such patients.

Keywords

- ▶ endovascular treatment
- ▶ critical limb ischemia
- ▶ connective tissue disease
- ▶ rheumatoid arthritis
- ▶ scleroderma

Connective tissue disease (CTD) represents a wide spectrum of pathological processes with the common characteristic of tissue inflammation, frequently of an autoimmune origin.¹ Recent studies have shown that the progression of atherosclerosis may be accelerated in patients with CTD such as rheumatoid arthritis (RA) or systemic lupus erythematosus (SLE).^{2–10} Progressive systemic sclerosis (PSS), antiphospholipid syndrome, and systemic vasculitides have also been linked to accelerated atherosclerosis, along with vascular inflammation, altered angiogenesis, and increased cardiovascular morbidity and mortality.¹¹

Leg ulcers also occur frequently in patients with CTD, who usually have long-standing collagen-vascular disease. These lesions are often difficult to treat successfully, since they have a decreased ability to heal from their treatment regimens that include anti-inflammatory agents.^{12–14} Also, at least half the ulcers in patients with CTD have a multifactorial origin, and approximately one-third of patients with CTD and ulcers have peripheral arterial disease (PAD).^{14,15} Without successful revascularization treatment, these ischemic ulcers may result in tissue necrosis requiring amputation.¹⁶

However, critical limb ischemia (CLI) management, including revascularization, in patients with CTD has seldom been

addressed.^{12,17} Also, most of the existing literatures on revascularization in CTD patients mainly describe about the open surgical bypasses and the evidence for the endovascular treatment (EVT) is lacking.^{17–20} The aim of this study is to assess our outcomes of EVT in patients with CTD and ischemic leg ulcers and review the current situation of the revascularization in such patients.

Methods

Approval for this study was obtained from the Institutional Review Board of Keio University School of Medicine, Tokyo, Japan. We conducted a retrospective review of the medical records of all consecutive patients with CTD and ischemic leg ulcers who underwent EVT in our department between July 2009 and March 2013. During this period, no patient with CTD and leg ulcers underwent bypass surgery or primary amputation in our department. The patients had been given a diagnosis of one of the following, in accordance with the American College of Rheumatology criteria²¹: RA, SLE, PSS, or polyarteritis nodosa. All patients had Rutherford category 5 lesions,²² with pain at rest and tissue loss (non-healing leg ulcers, toe gangrene, or both).

Lower limb CLI severity was assessed hemodynamically by determining the ankle-brachial index (ABI) and measuring skin-perfusion pressure (SPP) at the dorsal and plantar regions of the foot, according to a previously described method^{23,24} using a SensiLase PAD-IQ system (Vasamed, Eden Prairie, MN) and in accordance with TransAtlantic Inter-Society Consensus II guidelines.²⁵ When the ABI could not be determined because of intractable pain at rest or a severely calcified artery, an SPP below 40 mm Hg was considered to represent CLI.

EVT was performed with the patient under local anesthesia when angiography showed stenosis of more than 75% of the vessel diameter or occlusive atherosclerosis. The most commonly employed approach was antegrade from the ipsilateral common femoral artery with the use of a 4.5F sheath. To treat infrapopliteal lesions, a 0.014 inch guide wire was advanced into the lesion, and an appropriately sized balloon catheter was introduced. To avoid the flow-limiting dissection, balloon inflation was maintained at nominal pressure (8–14 atm) for at least 120 seconds. Bare-metal stents were used in the superficial femoral artery, but not for infrapopliteal lesions. The target lesion was commonly chosen on the basis of the site of tissue loss. Control angiography was performed to ensure that the affected artery had been successfully revascularized (►Fig. 1).

Antiplatelet therapy with aspirin (100 mg daily), clopidogrel (75 mg daily), or both, or ticlopidine (200 mg daily) was administered on a long-term basis before and after EVT, when tolerated by the patient. All patients were scheduled for a follow-up visit 1, 3, and 6 months after EVT and every 3 months thereafter. The follow-up assessments routinely included measurements of ABI and SPP, as well as a duplex ultrasound examination.

An EVT procedure was considered technically successful if all of the following criteria were met: a straight-line flow of

Fig. 1 Angiograms obtained during percutaneous transluminal angioplasty of the tibial artery in a patient with critical leg ischemia and systemic lupus erythematosus. (A) Long lesion of the posterior tibial artery and (B) recanalization after angioplasty with a 2-mm balloon.

blood to the foot was obtained, no flow-limiting dissection occurred, and residual stenosis comprised less than 30% of the vessel diameter. Freedom from reintervention was defined as not undergoing a subsequent EVT procedure or bypass grafting during the follow-up period. A major amputation was defined as surgical excision of the limb above the ankle. An amputation at or distal to the Lisfranc level was not considered a limb-salvage failure. Sustained clinical improvement was defined as complete healing of all ulcers or the stump from a minor amputation, no major amputation, and an improvement of at least one Rutherford category.

Normally distributed continuous variables are reported as mean $\pm$ standard deviation. Pre- and postprocedural SPP values and Rutherford clinical categories were compared by using a parametric paired *t*-test and nonparametric Wilcoxon test, respectively. A *p*-value of less than 0.05 was considered to represent a significant difference. Kaplan–Meier time-to-event analysis was performed to assess amputation-free survival and freedom from reintervention. All statistical analyses used SPSS version 15.0J (SPSS Inc., Chicago, IL).

Results

The study included 11 limbs of 10 patients (all women; age, 69.6 ± 12.8 years). The patients' baseline characteristics, including their specific CTD, cardiovascular risk factors, and treatment for CTD before EVT, are shown in ►Table 1. One patient with PSS had limited-type CREST syndrome

Table 1 Baseline characteristics of 10 patients (all women) with concomitant connective tissue disease and ischemic leg ulcers who underwent endovascular therapy

Characteristic	Value
Mean $\pm$ SD age (y)	69.6 $\pm$ 12.8
Connective tissue disease	
Rheumatoid arthritis	5 (50)
Systemic lupus erythematosus	1 (10)
Progressive systemic sclerosis	3 (30)
Polyarteritis nodosa	1 (10)
Cardiovascular risk factors	
Hypertension	6 (60)
Hyperlipidemia	6 (60)
Coronary artery disease	1 (10)
Diabetes mellitus	1 (10)
End-stage renal disease (undergoing dialysis)	1 (10)
Treatment for connective tissue disease	
Nonsteroidal anti-inflammatory drug	8 (80)
Steroid agent	7 (70)
Immunosuppressive agent	2 (20)

Note: Values are number (percent) of patients unless otherwise specified.

(calcinosis cutis, Raynaud phenomenon, esophageal motility disorder, sclerodactyly, and telangiectasia). No patient was a smoker at the time of EVT. Before EVT, the mean C-reactive protein level was 2.8 ± 2.8 mg/dL (range, 0.15–8.33 mg/dL). Two of the seven patients undergoing steroid therapy were receiving methotrexate.

The arteries treated with EVT and therapeutic outcomes in each limb are shown in **Table 2**. No patient had an aortoiliac lesion that would have had a hemodynamic effect on limb ischemia. All limbs had an infrainguinal lesion. Below-the-knee lesions were treated with balloon angioplasty alone. Occlusion of the superficial femoral artery (two limbs) was treated with placement of a bare-metal stent. The initial technical success rate of EVT was 100%.

The mean follow-up period was 26.7 ± 13.3 months (range, 6–49 months). Two patients died during follow-up, one due to a renal failure 6 months after EVT and the other due to an unknown cause approximately 3 years after the procedure. No EVT-related morbidity or mortality was observed, and no major amputations were necessary (limb-salvage rate, 100%). In four limbs, ulcer healing occurred without amputation, whereas a minor amputation was necessary in four other limbs. Two patients underwent a toe amputation 1 month after EVT because of previously established gangrene. Another patient required a transmetatarsal amputation 9 months after the procedure, when gangrene

became completely dry. The fourth patient underwent a Lisfranc amputation 10 days after EVT. All amputation stump wounds healed completely. In the remaining three limbs in the series, the ulcers did not heal during follow-up, although amputation was avoided. The cumulative amputation-free survival rates at 12 and 36 months were 89 and 70%, respectively (**Fig. 2**).

Sustained clinical improvement, including pain relief, was achieved in 8 of the 11 limbs in the follow-up period, as indicated by ulcer healing and improvement in the Rutherford category ($n = 3$, category 5; $n = 2$, category 3; $n = 1$, category 2; $n = 3$, category 1; and $n = 2$, category 0; $p = 0.011$ compared with pre-EVT categories).

Four limbs required at least one subsequent intervention because of ulcer recurrence with severe pain at rest or non-healing of the ulcer. In two of these limbs, complete healing was achieved after target-lesion revascularization to treat ulcer recurrence with severe pain at rest. In the other two limbs, neither healing nor pain relief was obtained, even though EVT was performed three times. One of the two patients died during follow-up; the other continued to receive wound care and medical therapy for her leg ulcers, which remained stable, without progression or infection. The cumulative rates of freedom from reintervention at 12 and 36 months were 81 and 59%, respectively (**Fig. 3**).

Before EVT, the mean overall SPPs at the dorsal and plantar regions of the foot were 38.4 ± 28.5 and 31.9 ± 20.5 mm Hg, respectively. After EVT, the SPPs were 55.3 ± 34.2 mm Hg ($p = 0.047$) and 55.6 ± 29.0 mm Hg ($p = 0.016$), respectively.

Discussion

In our series of 10 patients (11 limbs) with CTD, ischemic leg ulcers, and primarily infrapopliteal arterial lesions who underwent EVT, the outcomes of EVT with respect to overall limb salvage and ulcer healing were satisfactory, with an initial technical success rate of 100%. Sustained clinical improvement, including pain relief, was achieved in 8 of the 11 limbs, and no major amputations were necessary during the follow-up.

The causes of the various CTDs are unknown, although an immune-mediated injury is generally regarded as the primary mechanism. Manifestations of CTD vary widely and can involve several organ systems including legs.²⁶ Patients with CTD are predisposed to the development of leg ulcers and gangrene with severe pain at rest that may be related to ischemia, vasculitis, thrombosis, or a combination of these disorders.^{14,15} Because the lesions in patients with CTD are not always ischemic in origin, good wound care may result in ulcer healing, as long as the blood supply to the extremity is adequate. Therefore, revascularization should be offered on the basis of the severity of ischemia, irrespective of skin ulceration, to avoid any unnecessary complications.¹⁹

However, literature discussing revascularization of ischemic limbs in patients with CTD is limited and mainly describes only about surgical reconstruction. In the study by Deguchi et al,¹⁷ bypass surgery in patients with systemic sclerosis and CLI initially produced pain relief and healing

Table 2 Outcomes of EVT in 11 limbs of 10 patients (all women) with concomitant CTD and ischemic leg ulcers

Age (y)	CTD	Target artery	EVT procedures (n)	Ulcer recurrence	Ulcer outcome	Survival outcome (mo of follow-up)
65	PN	PTA	1	No	Healed	Alive (49)
64	CREST	PTA	3	No	Not healed	Died, renal failure (6)
43	RA	PTA	2	Yes	Healed after transmetatarsal amputation	Alive (44)
85	MRA	–	–	–	–	Died (31)
Left leg	–	ATA	1	No	Healed after toe amputation	–
Right leg	–	ATA + peroneal	1	No	Not healed	–
76	PSS	SFA + peroneal	1	No	Healed after toe amputation	Alive (33)
59	SLE	PTA	2	Yes	Healed	Alive (30)
86	RA	SFA + popliteal	1	No	Healed	Alive (29)
75	PSS	Popliteal + peroneal	3	No	Not healed	Alive (21)
69	RA	Popliteal	1	No	Healed	Alive (14)
74	RA	ATA	1	No	Healed after Lisfranc amputation	Alive (6)

Abbreviations: ATA, anterior tibial artery; CREST, CREST syndrome (calcinosis cutis, Raynaud phenomenon, esophageal motility disorder, sclerodactyly, and telangiectasia); CTD, connective tissue disease; EVT, endovascular therapy; MRA, malignant rheumatoid arthritis; PN, polyarteritis nodosa; PSS, progressive systemic sclerosis; PTA, posterior tibial artery; RA, rheumatoid arthritis; SFA, superficial femoral artery; SLE, systemic lupus erythematosus.

Fig. 2 Cumulative amputation-free survival in 10 patients with connective tissue disease and ischemic leg ulcers who underwent endovascular therapy. **Fig. 3** Cumulative freedom from reintervention in 11 limbs affected by critical ischemia in patients with connective tissue disease who underwent endovascular therapy.

of CLI-related ulcers, but graft patency was poor, with five of six patients having graft occlusion within approximately 18 months. Harries et al¹⁸ also observed that in patients with CTD and ischemic leg ulcers, only five of nine surgical bypasses were patent at 3 months. Similarly, Henke et al¹⁹ reported that surgical revascularization in their series ($n = 41$) were satisfactory (overall 5-year limb-salvage rate, 70%), even with poor long-term graft patency. From these reports, we can probably conclude that even though long-term patency of bypass graft cannot be expected, good limb salvage rate is achievable, and patients with CTD should be treated in accordance with standard criteria as in regular CLI patients for managing limb ischemia.

On the other hand, in patients in whom long-term patency of surgical bypasses is likely to be poor and revascularization is targeted primarily for limb salvage, EVT may be an acceptable initial treatment option because it is less invasive than surgery and results in less morbidity and mortality, just like EVT for high-morbid CLI patients. In that view, patients with CTD and ischemic leg ulcers may benefit from EVT as an initial treatment option, if there is evidence that the results for EVT in patients with CTD and ischemic leg ulcers have comparable results with EVT for regular CLI patients.

In our series, angioplasty provided a better overall 1-year amputation-free survival rate than that specified in the 2009 document on objective–performance goals for EVT of CLI²⁷ (89 vs. 77%). In the study by Iida et al²⁸ of 884 patients with CLI who underwent EVT for pure isolated infrapopliteal lesions, the 3-year rate of freedom from any reintervention was 52%, which is similar to our rate of 59%. From these data, we recommend that patients with CLI and CTD receive the same initial treatment (i.e., EVT) as patients with CLI and atherosclerosis, even though their demographic characteristics and risk factors may be somewhat different from those of patients with atherosclerosis alone.

One thing to note is that, in the study of Harries et al,¹⁸ outcomes of vascular intervention in patients with CTD and ischemic leg ulcers were poor compared with the results in our patients. Harries et al reported that only 4 of 12 limbs treated with vascular intervention (9 surgical bypasses and 3 endovascular procedures) had been salvaged at 1 year after the procedure. They concluded that patients with CTD and ischemic leg ulcers appeared to be at high risk of limb loss after vascular intervention compared with the general population of patients with vascular disease. Therefore, it is possible that the CTD process and the severity of cutaneous vasculitis have a marked influence on limb salvage and that aggressive treatment of CTD itself may be as important as vascular intervention.^{9,26}

Also, it has been reported that patients with RA have mortality rates higher than those of the general population, with most deaths due to complications of arteriosclerosis.^{10,29,30} Patients with RA were also found to have increased intima-media thicknesses, a factor strongly associated with adverse cardiovascular events.²⁹ A meta-analysis by Tyrrell et al⁷ showed that patients with rheumatic disease have a higher occurrence of atherosclerosis as determined by ultrasonographically measured intima-media thickness. Therefore, when treating such patients, clinicians should address their

increased risk of atherosclerosis and cardiovascular disease by making efforts to mitigate cardiovascular risk factors and control disease symptoms, including inflammation.¹⁰

Our study had several limitations, including its retrospective, uncontrolled, nonrandomized nature and small sample size. Also, we could not identify the specific etiologic factors that produced the arterial lesions in the patients in our series. Because EVT precludes obtaining an arterial specimen for histological examination, it was impossible to demonstrate whether a given arterial lesion was caused by vasculitis. However, in some patients, angiography and ultrasound examination showed that, except for the lesion, the infringuinal arteries were almost normal, without any atherosclerosis. Also, patient demographics were different from that of Iida et al (69 men, 71 with diabetes mellitus, and 64% with end-stage renal failure)²⁸; all our patients were women with CTD, and the prevalence of diabetes, coronary artery disease, and end-stage renal disease was only 10% for each of these disorders. These findings suggest that the lesion may have been due to local vasculitis.

Conclusions

In a series of patients with CTD and ischemic leg ulcers causing severe pain at rest, EVT had acceptable outcomes with respect to ulcer healing, pain relief, and freedom from amputation and reintervention. Endovascular revascularization may be a safe and reasonably effective initial treatment option for such patients.

Funding

The authors received no financial support for the research, authorship, and/or publication of this article.

Acknowledgment

The authors thank Renée J. Robillard, MA, ELS, for the editorial assistance.

References

- 1 Birdas TJ, Landis JT, Haybron D, Evers D, Papasavas PK, Caushaj PF. Outcomes of coronary artery bypass grafting in patients with connective tissue diseases. *Ann Thorac Surg* 2005;79(5):1610–1614
- 2 del Rincón ID, Williams K, Stern MP, Freeman GL, Escalante A. High incidence of cardiovascular events in a rheumatoid arthritis cohort not explained by traditional cardiac risk factors. *Arthritis Rheum* 2001;44(12):2737–2745
- 3 Paseri V, Yeh ET. A tale of two diseases: atherosclerosis and rheumatoid arthritis. *Circulation* 1999;100(21):2124–2126
- 4 Thiagarajan P. Atherosclerosis, autoimmunity, and systemic lupus erythematosus. *Circulation* 2001;104(16):1876–1877
- 5 Urowitz M, Gladman D, Bruce I. Atherosclerosis and systemic lupus erythematosus. *Curr Rheumatol Rep* 2000;2(1):19–23
- 6 Frostegård J. Atherosclerosis in patients with autoimmune disorders. *Arterioscler Thromb Vasc Biol* 2005;25(9):1776–1785
- 7 Tyrrell PN, Beyene J, Feldman BM, McCrindle BW, Silverman ED, Bradley TJ. Rheumatic disease and carotid intima-media

- thickness: a systematic review and meta-analysis. *Arterioscler Thromb Vasc Biol* 2010;30(5):1014–1026
- 8 Wolak T, Todosoui E, Szendro G, et al. Duplex study of the carotid and femoral arteries of patients with systemic lupus erythematosus: a controlled study. *J Rheumatol* 2004;31(5):909–914
 - 9 Hollan I, Prayson R, Saatvedt K, et al. Inflammatory cell infiltrates in vessels with different susceptibility to atherosclerosis in rheumatic and non-rheumatic patients: a controlled study of biopsy specimens obtained at coronary artery surgery. *Circ J* 2008;72(12):1986–1992
 - 10 Ku IA, Imboden JB, Hsue PY, Ganz P. Rheumatoid arthritis: model of systemic inflammation driving atherosclerosis. *Circ J* 2009;73(6):977–985
 - 11 Szekanecz Z, Koch AE. Vascular involvement in rheumatic diseases: 'vascular rheumatology'. *Arthritis Res Ther* 2008;10(5):224
 - 12 Hafner J, Schneider E, Burg G, Cassina PC. Management of leg ulcers in patients with rheumatoid arthritis or systemic sclerosis: the importance of concomitant arterial and venous disease. *J Vasc Surg* 2000;32(2):322–329
 - 13 Oien RF, Håkansson A, Hansen BU. Leg ulcers in patients with rheumatoid arthritis—a prospective study of aetiology, wound healing and pain reduction after pinch grafting. *Rheumatology (Oxford)* 2001;40(7):816–820
 - 14 Pun YL, Barracough DR, Muirden KD. Leg ulcers in rheumatoid arthritis. *Med J Aust* 1990;153(10):585–587
 - 15 Baker SR, Stacey MC, Singh G, Hoskin SE, Thompson PJ. Aetiology of chronic leg ulcers. *Eur J Vasc Surg* 1992;6(3):245–251
 - 16 Wollersheim H, van Zwielen PA. Treatment of Raynaud's phenomenon. *Eur Heart J* 1993;14(2):147–149
 - 17 Deguchi J, Shigematsu K, Ota S, Kimura H, Fukayama M, Miyata T. Surgical result of critical limb ischemia due to tibial arterial occlusion in patients with systemic scleroderma. *J Vasc Surg* 2009;49(4):918–923
 - 18 Harries RL, Ahmed M, Whitaker C, Majeed MU, Williams DT. The influence of connective tissue disease in the management of lower limb ischemia. *Ann Vasc Surg* 2014;28(5):1139–1142
 - 19 Henke PK, Sukheepod P, Proctor MC, Upchurch GR Jr, Stanley JC. Clinical relevance of peripheral vascular occlusive disease in patients with rheumatoid arthritis and systemic lupus erythematosus. *J Vasc Surg* 2003;38(1):111–115
 - 20 Kimura H, Miyata T, Sato O, Furuya T, Iyori K, Shigematsu H. Infrainguinal arterial reconstruction for limb salvage in patients with end-stage renal disease. *Eur J Vasc Endovasc Surg* 2003;25(1):29–34
 - 21 Singh JA, Solomon DH, Dougados M, et al; Classification and Response Criteria Subcommittee of the Committee on Quality Measures, American College of Rheumatology. Development of classification and response criteria for rheumatic diseases. *Arthritis Rheum* 2006;55(3):348–352
 - 22 Rutherford RB, Baker JD, Ernst C, et al. Recommended standards for reports dealing with lower extremity ischemia: revised version. *J Vasc Surg* 1997;26(3):517–538
 - 23 Castronuovo JJ Jr, Adera HM, Smiell JM, Price RM. Skin perfusion pressure measurement is valuable in the diagnosis of critical limb ischemia. *J Vasc Surg* 1997;26(4):629–637
 - 24 Kawarada O, Yokoi Y, Higashimori A, et al. Assessment of macro- and microcirculation in contemporary critical limb ischemia. *Catheter Cardiovasc Interv* 2011;78(7):1051–1058
 - 25 Norgren L, Hiatt WR, Dormandy JA, Nehler MR, Harris KA, Fowkes FG; TASC II Working Group. Inter-society consensus for the management of peripheral arterial disease (TASC II). *J Vasc Surg* 2007;45(Suppl S):S5–S67
 - 26 JCS Joint Working Group; Japanese Circulation Society. Guideline for management of vasculitis syndrome (JCS 2008). *Circ J* 2011;75(2):474–503
 - 27 Conte MS, Geraghty PJ, Bradbury AW, et al. Suggested objective performance goals and clinical trial design for evaluating catheter-based treatment of critical limb ischemia. *J Vasc Surg* 2009;50(6):1462–73.e1, 3
 - 28 Iida O, Soga Y, Yamauchi Y, et al. Clinical efficacy of endovascular therapy for patients with critical limb ischemia attributable to pure isolated infrapopliteal lesions. *J Vasc Surg* 2013;57(4):974–981.e1
 - 29 del Rincón I, Escalante A. Atherosclerotic cardiovascular disease in rheumatoid arthritis. *Curr Rheumatol Rep* 2003;5(4):278–286
 - 30 Goodson N. Coronary artery disease and rheumatoid arthritis. *Curr Opin Rheumatol* 2002;14(2):115–120