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CASE REPORT

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Improved response to infliximab after leukocytapheresis in a patent with rheumatoid arthritis

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Abstract This is the first report on effective leukocytapheresis (LCAP) in an acquired infliximab (IFM) resistant patient with rheumatoid arthritis (RA). A 44-year-old Japanese woman with RA was treated with prednisolone, cyclosporine A, and methotrexate, which failed to stabilize the disease. Infliximab was then administered and the disease activity was controlled on December 2003. However, RA became active again on June 2004 so that LCAP was administered weekly for 5 weeks. After the LCAP treatment, the ACR20% response was obtained again and IFM has regained its efficacy.

Key words Acquired resistance · Infliximab (IFM) · Leukocytapheresis (LCAP) · Rheumatoid arthritis

Introduction

Infliximab (IFM) is a very effective drug for patients with rheumatoid arthritis (RA) refractory to disease-modifying antirheumatic drugs (DMARDs). However, RA often becomes resistant to IFM during the therapeutic course. To overcome the resistance, the dose is increased or the drug is administered at shorter intervals, or switched to etanercept.

Leukocytes play an important role in the inflammatory process of RA. Leukocytapheresis (LCAP) is used as a treatment for abnormal autoimmune states, removing responsible leukocytes from peripheral blood. The effectiveness of the LCAP therapy has been reported in the past decade.[1–3] Therefore, LCAP is sometimes indicated for RA in Japan. Herein, we report a case of effective treatment of LCAP in an acquired IFM-resistant patient with RA whose response to IFM was recovered after LCAP.

Case report

A 44-year old Japanese woman was diagnosed as having dermatomyositis (DM) associated with interstitial pneumonia (IP) at the age of 38 years in October 1998, in terms of myositis in the proximal muscles of upper and lower extremities, skin manifestations, and ground-glass opacity in both lungs on computed tomography (CT). She responded to treatment with prednisolone (PSL) (50 mg/day) and cyclosporine A (CsA) (150 mg/day). Five months after PSL was tapered to 15 mg/day, she developed symmetrical joint swellings including shoulder, elbow, wrist, metatarsophalangeal, and knee and ankle joints with elevated C-reactive protein (CRP, 2.2 mg/dl) and positive rheumatoid factor (RF, 152.2 IU/ml), which fulfilled the 1987 classification criteria for rheumatoid arthritis (RA) proposed by the American College of Rheumatology (ACR). On the diagnosis of RA, she was treated for 9 months with bucillamine (BUC) (200 mg/day) with no effect. Therefore, strong DMARDs were thought to be needed because of the high disease activity of RA under the administration of PSL, CsA, and BUC. Interstitial pneumonia was considered to be stable on clinical, laboratory, and imaging findings. Then, after the withdrawal of BUC on January 2000, methotrexate (MTX) (2.5–8 mg/week) was subsequently added with some improvements in RA. Deterioration of IP after MTX administration was not observed. However, because of the high disease activity, PSL could not be tapered below the dose of 12 mg/day. In December 2003, IFM (3 mg/kg) was added to PSL (12 mg/day), MTX (8 mg/week), and CsA (150 mg/day) at week 0, 2, 6, and every 8th week with an ACR20% response. Rheumatoid factor, CRP, and matrix metalloproteinase (MMP-3) decreased 2 months after the start of IFM: RF 1 from 28.4 to 78.8 IU/ml, CRP from 8.0 to 0.9 mg/dl, and MMP-3 from 628 to 352 U/ml. How-

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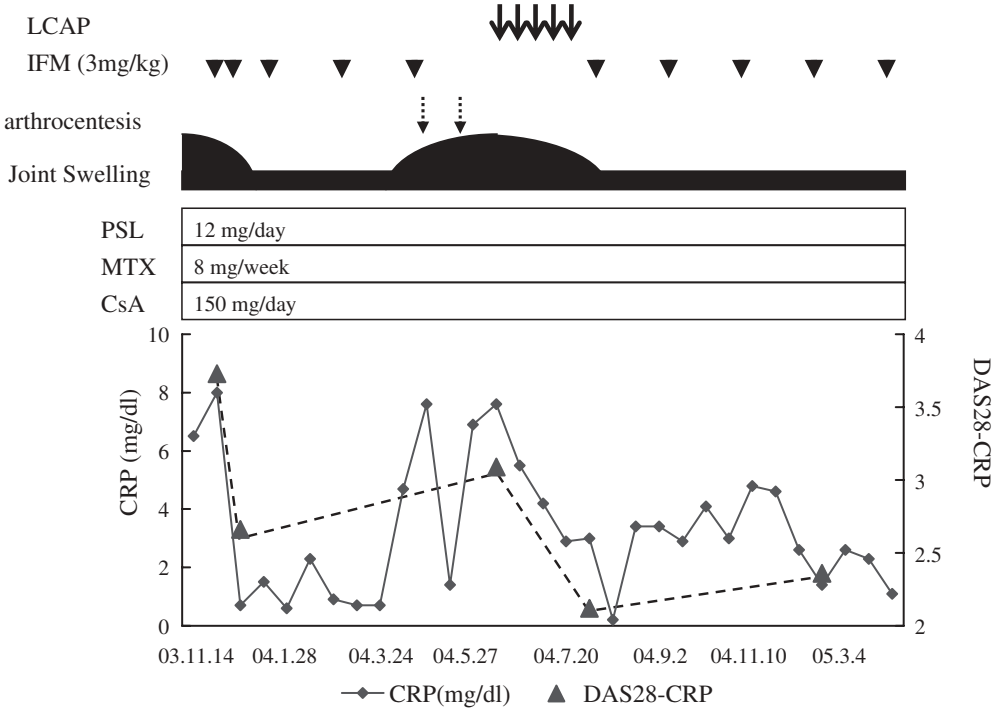

Fig. 1. Clinical course before and after the LCAP therapy. Infliximab showed good efficacy until March 2004 (at 22 weeks), but acquired resistance was observed thereafter. Frequent arthrocentesis with no concurrent intra-articular injection were needed. After the second administration of LCAP, the CRP decreased gradually. The DAS-CRP also decreased after the LCAP therapy. Infliximab was administered for 9 months without changing the dose and interval, observing no exacerbation of RA. *LCAP*, leukocytapheresis; *IFM*, infliximab; *PSL*, prednisolone; *MTX*, methotrexate; *CsA*, cyclosporine A; *CRP*, C-reactive protein; *AS28-CRP*, disease activity score 28-CRP

ever, RA recurred in April 2004 2 weeks from the last infusion of IFM (Fig. 1). In particular, the left knee joint was markedly swollen and tender, requiring repeated arthrocentesis with no intra-articular injection including corticosteroids.

The patient was admitted in June 2004 to receive LCAP for refractory RA. On admission, her height and body weight were 160 cm and 63 kg, respectively. Physical examination revealed bibasal fine crackles, 7 swollen joints, and 5 tender joints. Neither skin eruption nor muscle weakness was observed. Laboratory tests revealed hemoglobin 11.0 g/dl, white blood cell count 13 000/μl^3, platelet count 40.7/μl^3, and CRP 5.4 mg/dl. The levels of aspartate transaminase (AST), alanine transaminase (ALT), lactate dehydrogenase (LDH), and creatine kinase (CK) were normal. The blood urea nitrogen was 25.6 mg/dl and creatinine 1.1 mg/dl. Antinuclear antibodies and anti-double-strand DNA antibodies were negative. Rheumatoid factor and MMP-3 increased to 88.8 IU/ml and 478 U/ml, respectively. The level of KL-6 (235 ng/ml) was within normal limits. The trough concentration of CsA (151 ng/ml) was normal. Chest X-ray and CT showed honeycombing appearance affecting both lower lobes, which remained unchanged. Periarticular bone erosion and narrowing of the articular space was recognized and classified as stage II on Steinbrocker classification. The disease activity score 28-CRP (DAS28-CRP) was 3.09 on June 2, 2004.

Therefore, RA was considered to be active, but DM associated with IP inactive, respectively. Leukocytapheresis (LCAP), an extracorporeal circulation therapy utilizing a fiber filter, was administered once a week for 5 weeks, without changing the dosage of other drugs (PSL 12 mg/day, CsA 150 mg/day, MTX 8 mg/week), from 7 weeks after the last IFM infusion. A total amount of 3 liters of blood was filtrated with a leukocyte removal column equipped with a fine fiber (CS-100 Cellsorba, Asahi Medical, Tokyo, Japan) at a blood flow rate of 50 ml/min for 60 min. Nafamostat mesilate (Futhan, Torii Pharmaceutical, Tokyo, Japan) was used as an anticoagulant at a rate of 50 mg/h. As the result, the symptoms and the CRP showed gradual improvement after the second administration of LCAP. On July 28, 2004, 1 week after the last administration of LCAP, the ACR20% response was obtained (Table 1) and DAS28-CRP decreased from 3.09 to 2.12. Arthrocentesis was unnecessary during and after the LCAP therapy. The CRP decreased from 5.4 to 2.9 mg/dl. However, the RF and MMP-3 were almost unchanged during the whole period of the LCAP therapy. Thereafter, IFM was restarted and has been successfully administered for 9 months at the same dose and interval as before the LCAP therapy with no exacerbation of RA, although RA was resistant to IFM before the LCAP

Table 1. Efficacy of the LCAP therapy by ACR core set

	Before LCAP (June 2)	After LCAP (July 28)
Swollen joints	7	5
Tender joints	5	1
Patient's global assessment of disease activity (VAS, mm)	20	13
Patient's assessment of pain (VAS, mm)	35	15
Physician's global assessment of disease activity (VAS, mm)	50	30
mHAQ	1.125	1.125
CRP (mg/dl)	5.4	2.9

LCAP, leukocytapheresis; ACR, American College of Rheumatology; VAS, visual analog scale; mHAQ, modified Health Assessment Questionnaire; CRP, C-reactive protein

therapy. The CRP decreased further from 2.9 to 1.1 mg/dl after the LCAP therapy (Fig. 1). The ACR20% response has been maintained and the DAS28-CRP is 2.36 in April 2005. Human antichimeric antibody (HACA) was negative just before the restart of IFM. There were no complications associated with the LCAP therapy and no infusion reactions of IFM at its restart after the long interval of 14 weeks.

Discussion

Infliximab is a well-tolerable anti-tumor necrosis factor-α (TNF-α) blocking agent for the treatment of RA, but primary and acquired resistance to IFM are becoming important problems. The primary resistance is thought to be due to enhanced activities of other cytokines apart from except TNF-α, including lymphotoxin α (TNF-β)[4] and genetic determinants in the HLA complex.[5] The acquired resistance is thought to be caused by long intervals of IFM administration, low dosage of IFM, or the appearance of HACA. Therefore, to overcome the resistance several methods are proposed, including shortening the interval or increase the dose of IFM,[6] switching to etanercept, which blocks both TNF-α and lymphotoxin α,[7] or increasing the dose of MTX.

Favorable effects of the LCAP therapy on RA have been reported in the past decade; the ACR20% response occurs in 64%–79% and ACR50% response in 16%–44.4% of patients with RA resistant to DMARDs, including MTX.[1–3] No major adverse effects have been observed so far. Kempe et al.[3] reported that improvements in symptoms appeared slowly, but persisted until 12 weeks after the LCAP therapy. A slow response was also observed in our case. The mechanism by which LCAP produces therapeutic effects on RA is not clear, but it is speculated that the clinical improvements in RA patients may be partly explained by redistribution of granulocytes and lymphocytes from peripheral blood by filtration.[1] On the other hand, Izumi et al.[8] reported an ACR20% response decrease from 73% at 4 weeks to 45% at 24 weeks after the final LCAP therapy, which suggests that efficacy of the LCAP therapy on RA may be transient. Therefore, the next therapy should be considered even as the LCAP therapy is being effective.

In the present report, the effectiveness of the LCAP therapy with the ACR20% response and decrease in DAS28-CRP was observed in a patient with RA, who showed an acquired resistance to IFM under the negative result for HACA. The reason for the acquired resistance in our case may be low dosage of IFM (3 mg/kg). On the other hand, a long interval of IFM administration was unlikely because the CRP increased again only 3 weeks after the last IFM administration before the LCAP therapy. Leukocytapheresis was adopted in our case because increasing the dose of MTX to more than 8 mg/week or IFM more than 3 mg/kg was not approved by the Japanese Ministry of Health, Labor and Welfare and etanercept was not available in Japan in 2004. Interestingly, IFM seems to have regained its effect on RA without increasing the dose due to the LCAP effect, although the mechanism remains unknown. It may be hypothesized in our case that LCAP affects redistribution of granulocytes and lymphocytes from peripheral blood, decreasing both the number of TNF-α producing cells and the amount of TNF-α in the synovium, and IFM at the same dose regains efficacy as does the synergic effect with LCAP. It is hoped that LCAP becomes one of the methods used for overcoming acquired IFM resistance in RA.

References

1. Ueki Y, Yamasaki Y, Kanamoto T, Kawazu T, Yano M, Matsumoto K, et al. Evaluation of filtration leukocytapheresis for use in the treatment of patients with rheumatoid arthritis. Rheumatology 2000;39:165–71.
2. Hidaka T, Suzuki K, Matsuki Y, Takamizawa-Matsumoto M, Kataharada K, Ishizuka T, et al. Filtration leukocytapheresis therapy in rheumatoid arthritis: a randomized, double-blind, placebo-controlled trial. Arthritis Rheum 1999;42:431–7.
3. Kempe K, Tsuda H, Yang K, Yamaji K, Kanai Y, Hashimoto H. Filtration leukocytapheresis therapy in the treatment of rheumatoid arthritis patients resistant to or failed with methotrexate. Ther Apher Dial 2004;8:197–205.
4. Buch MH, Conaghan PG, Quin MA, Bingham SJ, Veale D, Emery P. True infliximab resistance in rheumatoid arthritis: a role for lymphotoxin α? Ann Rheum Dis 2004;63:1344–6.
5. Martinez A, Salido M, Bonilla G, Pascual-Salcedo D, Fernandez-Arquero M, Miguel S, et al. Association of the major histocompatibility complex with response to infliximab therapy in rheumatoid arthritis patients. Arthritis Rheum 2004;50:1077–82.
6. St Clair EW, Wagner CL, Fasanmade AA, Wang B, Schaible T, Kavanaugh A, et al. The relationship of serum infliximab concentrations to clinical improvement in rheumatoid arthritis: results from ATTRACT, a multicenter, randomized, double-blind, placebo-controlled trial. Arthritis Rheum 2002;46:1451–9.
7. Van Vollenhoven R, Harju A, Brannemark S, Klareskog L. Treatment with infliximab (Remicade) when etanercept (Enbrel) has failed or vice versa: data from the STURE registry showing that switching tumor necrosis factor alpha blockers can make sense. Ann Rheum Dis 2003;62:1195–8.
8. Izumi Y, Tominaga M, Iwanaga N, Huang M, Tanaka F, Aratake K, et al. Twenty-four-week follow-up examination of a leukocytapheresis therapy in rheumatoid arthritis. Mod Rheumatol 2006; 16:20–3.