EJR European Journal of Rheumatology

DOI: 10.5152/eurjrheumatol.2014.140074

Original Investigation

Combined infliximab and methotrexate treatment improves the depressive state in rheumatoid arthritis patients more effectively than methotrexate alone

Yusuke Miwa[1], Airi Nishimi[1], Shinichiro Nishimi[1], Mayu Saito[1], Takahiro Tokunaga[1], Ryo Yanai[1], Ryo Takahashi[1], Kuninobu Wakabayashi[1], Tsuyoshi Kasama[1], Michio Hosaka[2]

Abstract

Objective: Rheumatoid arthritis (RA) patients have a greater depressive tendency than normal subjects, and infliximab is known to provide quick therapeutic effects and to have high bioavailability for RA. We therefore investigated whether the depressive state of RA patients would be improved by infliximab.

Material and Methods: The Self-Rating Depression Scale (SDS) was used to evaluate 34 RA patients before and 14 or 30 weeks after inflixi mab treatment using the SDS and Disease Activity Score (DAS) 28. The SDS and DAS28 results before and after treatment were compared.

Results: We also included 42 cases treated with methotrexate as the control group. The SDS decreased in both groups, and the intraindi-vidual vari ability was $p<0.001$, indicating that the drugs had significantly different effects on the SDS. The DAS tended to decrease in both groups, but the intraindividual variability was $p=0.199$, indicating no difference between the two drugs.

Conclusion: This study is a preliminary study, but the data suggest that infliximab may reduce RA disease activity and improve the depressive state.

Key words: Rheumatoid arthritis, infliximab, depression

Introduction

Rheumatoid arthritis (RA) patients are known to have a depressive tendency, and the rate of depression reported in RA patients (20%-62%) is higher than that reported in normal subjects (1, 2, 4). The biggest problem facing RA patients is arthritic pain, and pain is closely related to the depressive state (5, 6).

Infliximab is a monoclonal antibody against tumor necrosis factor (TNF)-α, and the availability is high, even in cases in which insufficient effects are observed following treatment with disease-modifying anti-rheumatic drugs (DMARDs) entered on conventional methotrexate (MTX) (7). Additionally, the therapeutic effect of infliximab appears earlier than that of conventional DMARDs for rheumatoid arthritis. In this study, we examined how the level of disease activity and the depressive state of rheumatoid arthritis patients improve following infliximab treatment.

Material and Methods

The subjects were RA outpatients at our hospital. Rheumatoid arthritis was diagnosed according to the diagnostic standards of the American College of Rheumatology, published in 1987 (8). Infliximab was administered according to the TNF inhibition therapy enforcement guidelines for rheumatoid arthritis of the Japan College of Rheumatology, and we administered infliximab in combination with MTX for patients whose disease activity was still high, even when using 6 mg or more of MTX per week (9). During the examination, the dose of MTX administered was not changed.

The RA patient group that was treated with infliximab (group A; 34 cases) was evaluated using the Self-Rating Depression Scale (SDS), developed by Zung, before treatment and at 14 or 30 weeks after treatment. The SDS total value was compared before and after treatment (10, 11). The Zung SDS score ranges from 20 (best) to 80 (worst), and the average is 35.1±8.0 (mean±SD) in the normal Japanese control population (12). A higher SDS score is indicative of a relatively high degree of depressive symptoms. An SDS score of less than 40 points is the normal range; from 40 to 49 points, it is mild depression; and more than 50 points is moderate-severe depression.

We also evaluated rheumatoid arthritis disease activity using the Disease Activity Score 28 (DAS28-ESR4), which is normally used as an appraisal method (13). The DAS28 is calculated using tender joint count, swollen joint count, patient global assessment (using a 100-mm VAS scale), and the erythrocyte sedimentation rate (1-hour value). Scores greater than or equal to 5.1 indicate high disease activity, 3.2 to 5.1 indicates mod-

1 Department of Rheumatology, Showa University Faculty of Medicine, Tokyo, Japan

2 Department of Rheumatology, Clini of Katsuyama, Yamanashi, Japan

Address for Correspondence: Yusuke Miwa, Department of Rheumatology, Showa University Faculty of Medicine, Tokyo, Japan

E-mail: y.miwa@mbf.ocn.ne.jp

Submitted: 29.07.2014
Accepted: 03.09.2014

Table 1. Background features of both groups

	Group A (infliximab)	Group B(MTX)	p value
n	34	42	
age (mean±SD)	55.1±14.3	58.5±14.2	n.s*
sex (female/male)	29/5	37/5	n.s**
Disease duration (year) (mean±SD)	5.42±5.62	4.46±8.89	n.s*
Dosage of steroid (mg) (mean±SD)	5.7±3.0	3.2±3.3	>0.001*
DAS28-ESR4 (mean±SD)	5.53±1.31	5.22±0.93	n.s*
mHAQ (mean±SD)	0.70±0.66	0.60±0.56	n.s*
SDS (mean±SD)	44.8±10.9	44.0±9.9	n.s*

DAS: disease activity score; mHAQ: modified Health Assessment Questionnaire; SDS: self-rating depression scale
* : analysis by Mann-Whitney U-test
** : analysis by Fisher's exact probability test

Table 2. Clinical features and laboratory findings before and after treatment

		Before	After 14 weeks		After 30 weeks		Interaction	Variation between individuals	Intraindividual variability
	Group		Value	p*	Value	P**	p***	p***	p***
SDS	Infliximab	44.8±10.9	37.1±9.4	<0.001	37.9±10.7	<0.001	0.086	0.006	0.001
	MTX	44.0±9.9	40.7±11.0	0.022	39.7±10.4	0.002			
DAS28 (ESR4)	Infliximab	5.53±1.31	3.99±1.48	<0.001	3.93±1.52	<0.001	0.98	0.199	<0.001
	MTX	5.22±0.93	3.64±1.00	<0.001	3.61±1.31	<0.001			
mHAQ	Infliximab	0.70±0.66	0.40±0.41	0.002	0.39±0.49	0.008	0.94	0.33	<0.001
	MTX	0.60±0.56	0.33±0.45	0.004	0.28±0.48	<0.001			

mean±SD
*Compared with before treatment
**Compared with before treatment
*** Analysis by repeated-measures ANOVA

erate disease activity, and less than 3.2 indicates low disease activity. To evaluate patient quality of life (QOL), we used the modified Health Assessment Questionnaire (mHAQ). The control group included rheumatoid arthritis patients (group B; 42 cases) who had recently started treatment with MTX. The control group underwent the same examination as group A. Control group patients were close to the average age of the approximately 500 RA outpatients treated at our hospital, and the average SDS value was also close to the average value at our hospital. The male-female ratio was similar to the national average. Meanwhile, both groups received nonsteroidal anti-inflammatory drugs (NSAIDs) at the usual dose.

This study was performed during regular clinic visits, and no placebo control was used. During the study, the steroid dose was not changed for patients normally treated with steroid. The exclusion criteria included the following: the use of antidepressant medications before treatment, discontinued treatment because of side effects, change of residence, and not completing the full treatment course. Meanwhile, all subjects provided their consent for this study.

Repeated-measures ANOVA was used to analyze the SDS, DAS28, and mHAQ of each case during the 30-week treatment course with both drugs. The Mann-Whitney *U*-test was used to examine differences in age, steroid dosage, disease duration, DAS28, mHAQ, and SDS before treatment. Fisher's exact probability test was used to examine differences in gender. JPM 10 (SAS Institute Inc., Tokyo, Japan), was used for all analyses.

Results

Groups A and B did not significantly differ by age, gender, or disease duration. The steroid dose was greater in Group A, but we felt that a high infliximab dose should be used because of the high disease activity observed in the patients. SDS, mHAQ, and DAS28 did not differ significantly before treatment (Table 1). In Group A, the total SDS was 44.8±10.9 before treatment, and it decreased to 37.1±9.4 and 37.9±10.7 at 14 and 30 weeks after treatment, respectively. In Group B, the total SDS was 44.0±9.9 before treatment, and it decreased to 40.7±11.0 and 39.7±10.4 at 14 and 30 weeks after treatment, respectively (Table 2). The effects of the medications were also compared between groups. The drug and the dosing period did not significantly interact (p=0.086), but the drug variety and the dosing period both individually affected the SDS (p=0.006 and p<0.001, respectively).

When the DAS28 was analyzed, no interaction was demonstrated between the drug variety and the dosing period (p=0.98 by repeated--measures ANOVA). The individual variability was p=0.199, indicating that the drug variety did not individually impact the DAS28. The intraindividual variability was p<0.001, which indicates that the dosing period significantly affected the DAS28. The mHAQ score was analyzed, and no interaction was demonstrated between the drug variety and the dosing period (p=0.94). The individual variability was p=0.33, indicating that the drug variety did not individually impact the mHAQ. The intraindividual variability was p<0.001, which indicates that the dosing period significantly affected the mHAQ (Table 2).

Discussion

Rheumatoid arthritis patients are known to have a depressive tendency. A report demonstrated that the rate of depression is 20%-60% in RA patients, which is higher than in normal subjects. Infliximab is a monoclonal antibody against tumor necrosis factor (TNF)-α. It inhibits the binding of TNFα to the TNF receptor, and it decreases inflammation due to rheumatoid arthritis. Many studies have already shown that infliximab quickly results in treatment effects for rheumatoid arthritis patients. In many cases, treatment can be continued, and it will maintain low disease activity for long periods. Infliximab has also been shown to inhibit the progression of joint destruction (14).

Infliximab is a monoclonal TNF-α antibody, and some studies show that it has various secondary effects, in addition to its inhibitory effects on bone and joint destruction. For example, some reports demonstrate that compared to mass steroid use, infliximab treatment improves bone metabolism markers in rheumatoid arthritis patients, prevents weight gain, reduces blood pressure, and lowers the risk of cardiovascular diseases (15, 16). In addition, some reports have demonstrated that infliximab improves the life expectancy and QOL of RA patients with high disease activity (17). Improving the QOL using effective treatment modalities in the early stage of disease can result in economic benefits (16).

Cytokines, such TNF-α and interleukin (IL)-6, are reported to be related to the depressive state[18][19]. Some reports suggest that TNF-α levels change, relative to mood improvements, following the treatment of depressed patients (20). SSRI use is known to decrease serum IL-6 in depressed patients (21). Some reports also state that the use of infliximab lowers serum TNF-α, IL-6, and dehydroepiandrosterone-sulfate (DHEA-S), which is a hormone related to the depressive state (22, 24-26). In this study, we did not measure TNF-α, IL-6, or DHEA-S, but their levels may provide data that will help clarify the cause of the depressive state and improve the depressive state of rheumatoid arthritis patients using drug therapy.

This study showed that the use of infliximab lowered the disease activity of rheumatoid arthritis. Compared to the MTX-treated group, infliximab significantly improved the depressive state. When comparing the disease activity levels of rheumatoid arthritis patients treated with infliximab and MTX, infliximab was faster acting and significantly improved the disease activity level in the beginning. However, although MTX was slower-acting, both treatment groups had similarly reduced disease activity levels at 30 weeks. This indicates that infliximab treatment not only lowers the disease activity of rheumatoid arthritis by improving the depressive state but also impedes other pathways, such as the direct action on the brain. An SDS score of less than 40 points is in the normal range, 40 to 49 points is mild depression, and more than 50 points is moderate-severe depression. Although an SDS score of 44.8±10.9 is mild depression, an SDS score 37.1±9.4 is in the normal range. Depression state is normalized. It is clinically important.

However, this study included only a few cases and was intended to be only a pilot study. A larger number of cases and further examinations are required to prove this hypothesis. Additionally, the control group (Group B) was not a placebo group, and Group A patients had insufficient effects due to their use of 6 mg or more of MTX for more than 3 months. We believe that the lack of a reaction to MTX treatment during this time was due to psychological factors, and the high SDS value for the infliximab group value compared with the control group must be considered for such occasions.

This study suggests that infliximab may improve the clinical condition of RA soon after the start of treatment and that it can improve the depressive state.

Ethics Committee Approval: Ethics committee approval was received for this study from the Bio-Ethical Committee Showa University Faculty of Medicine.

Informed Consent: Written informed consent was obtained from patients who participated in this study.

Peer-review: Externally peer-reviewed.

Author contributions: Concept - Y.M., H.M.; Design - Y.M., K.W.; Supervision - R.Y., R.T.; Resource - Y.M., H.M.; Materials - Y.M., R.Y.; Data Collection&/or Processing - A.N., S.N.; Analysis&/or Interpretation - S.M., T.T.; Literature Search - A.N., S.N.; Writing - Y.M.; Critical Reviews - T.K.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: Yusuke Miwa and Tsuyoshi Kasama received a research grant from Pfizer Co., Ltd., Chugai Pharmaceutical Co., Ltd., Astellas Pharma Inc., Mitsubishi Tanabe Pharma Corporation, Abbott Japan Co., Ltd., Eizai Co., Ltd.

References

1. Iosifescu DV, Babkier B, Fava M. Impact of medical comorbid disease on antidepressant treatment of major depressive disorder. Curr Psych Rep 2004; 6: 193-201. [CrossRef]
2. el-Miedany YM, el-Rasheed AH. Is anxiety a more common disorder than depression in rheumatoid arthritis? Joint Bone Spine 2002; 69: 300-6. [CrossRef]
3. Dickens C, Jackson J, Tomenson B, Hay E, Creed F. Association of depression and rheumatoid arthritis. Psychosomatics 2013; 44: 209-15. [CrossRef]
4. Yukioka M, Komatsubara Y, Maeda A, et al. Depression tendency in patients with rheumatoid arthritis. Ryumachi 2002; 42: 584-90.
5. Rheumatology white reports * current state of rheumatoid patients. Institution of Japanese rheumatology, Tokyo; 2005. P. 73
6. Miwa Y, Yajima N, Shiozawa F, Yoda Y, Hanaoka R, Hanyuda M, et al. Relationship between psychological factors and arthralgia in patients with rheumatoid arthritis. Mod Rheum 2002; 12: 32-6. [CrossRef]
7. St Clair EW, van der Heijde DM, Smolen JS, Maini RN, Bathon JM, Emery P, et al. Combination of Infliximab and methotrexate therapy for early rheumatoid arthritis: a randomized, controlled trial. Arthritis Rheum 2004; 50: 3432-43. [CrossRef]
8. Arnett FC, Edworthy SM, Bloch DA, et al: The American Rheumatism Association 1987 revised criteria for the classification of rheumatoid arthritis. Arthritis Rheum 1987; 31: 315-24. [CrossRef]
9. Enforcement guideline of TNF inhibition treatment to RA: Japan college of Rheumatology, 2006.
10. Zung WWK, Richards CB, Gables C, et al. Self-rating depression scale in an outpatient clinic. Arch Gen Psychiat 1969; 126: 116-21.
11. Kazuhiko Fukuda and Shigeo Kobayashi: Japanese version SDS (Self-rating Depression Scale) guidance for the use of self evaluation depressiveness scale. Sankyobo; 1983. P.3-15.
12. Fukuda K, Kobayashi S. Guidance for using the Japanese self-rating depression scale. Kyoto: Sankyobo; 1983. p. 3-15.
13. Prevoo ML, van 't Hof MA, Kuper HH, van Leeuwen MA, van de Putte LB, van Riel PL. Modified disease activity scores that include twenty-eight-joint counts: development and validation in a prospective longitudinal study of patients with rheumatoid arthritis. Arthritis Rheum 1995; 38: 44-8. [CrossRef]
14. Lipsky PE1, van der Heijde DM, St Clair EW, Furst DE, Breedveld FC, Kalden JR, et al. Infliximab and methotrexate in the treatment of rheumatoid arthritis. Anti-Tumor Necrosis Factor Trial in Rheumatoid Arthritis with Concomitant Therapy Study Group. N Engl J Med 2000; 343: 1594-602.
15. Seriolo B1, Paolino S, Sulli A, Ferretti V, Cutolo M. Bone metabolism changes during anti-TNF-alpha therapy in patients with active rheumatoid arthritis. Ann N Y Acad Sci 2006; 1069: 420-7. [CrossRef]
16. Goekoop-Ruiterman YP1, de Vries-Bouwstra JK, Allaart CF, van Zeben D, Kerstens PJ, Hazes JM, et al. Clinical and radiographic outcomes of four different treatment strategies in patients with early rheumatoid arthritis. Arthritis Rheum 2005; 52: 3381-90. [CrossRef]
17. Westhovens R, Yocum D, Han J, Berman A, Strusberg I, Geusens P, et al. The safety of infliximab, combined with background treatments, among patients with rheumatoid arthritis and various co morbidities: a large, randomized, placebo-controlled trial. Arthritis Rheum 2006; 54: 1075-86. [CrossRef]
18. Zautra AJ1, Yocum DC, Villanueva I, Smith B, Davis MC, Attrep J, et al. Immune activation and depression in women with rheumatoid arthritis. J Rheumatol 2004; 31: 457-63.
19. Brenda WJHP, Stephen BK, Kristine Y et al. Inflammatory Markers and Depressed Mood in Older Persons: Results from the Health, Aging and Body Composition Study. Biol Psychiatry 2003; 54: 566-72. [CrossRef]
20. Kagaya A, Kugaya A, Takebayashi M, Fukue-Saeki M, Saeki T, Yamawaki S, et al. Plasma concentration of interleukin-1 beta, interleukin-6, soluble interleukin-2 receptor and tumor necrosis factor alpha of depressed patients in Japan. Neuropsychobiology 2001; 43: 59-62. [CrossRef]
21. Basterzi AD, Aydemir C, Kisa C, Aksaray S, Tuzer V, Yazici K, et al. IL-6 level with SSRI treatment in patients with major depression. Hum Psychopharmacol 2005; 20: 473-6. [CrossRef]
22. del Porto F, Aloe L, Lagana B, riaca V, Nofroni I, D'Amelio R. Nerve growth factor and brain-derivrd neurotropic factor levels in patients with rheumatoid arthritis treated with TNF-alpha blockers. Ann N Acad Sci 2006; 1069: 438-43. [CrossRef]
23. Kopp A, Alstergren P, Ernestam S, Nordahl S, Morin P, Bratt J. Reduction of temporomandibular joint pain after treatment with a combination of methotrexate and Infliximab is associated with changes in synovial fluid and plasma cytokines in rheumatoid arthritis. Cells Tissues Organs 2006; 180: 22-30. [CrossRef]
24. Dain L, Braun-Moscovici Y, Baum E, Nahir AM, Hoffer E. Modification of neutrophil function by plasma of rheumatoid arthritis patients with Infliximab. Clin Exp Rheumatol 2006; 24: 38-44.
25. Fabian TJ, Dew MA, Pollock BG, Reynolds CF 3rd, Mulsant BH, Butters MA, et al. Endogenous Concentrations of DHEA and DHEA-S Decrease with Remission of Depression in Older Adults. Biol Psychiatry 2001; 50: 767-74. [CrossRef]
26. Yukioka M1, Komatsubara Y, Yukioka K, Toyosaki-Maeda T, Yonenobu K, Ochi T. Adrenocorticotropic hormone and dehydroepiandrosterone sulfate levels of rheumatoid arthritis patients treated with glucocorticoids. Mod Rheumatol 2006; 16: 30-5. [CrossRef]