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

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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 infliximab 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 intraindividual variability 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-
Table 1. Background features of both groups

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

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

<table>
<thead>
<tr>
<th></th>
<th>Before</th>
<th>After 14 weeks</th>
<th>After 30 weeks</th>
<th>After 60 weeks</th>
<th>Interaction</th>
<th>Variation between individuals</th>
<th>Intraindividual variability</th>
</tr>
</thead>
<tbody>
<tr>
<td>SDS Infliximab</td>
<td>44.8±10.9</td>
<td>37.1±9.4</td>
<td>&lt;0.001</td>
<td>37.9±10.7</td>
<td>&lt;0.001</td>
<td>0.086</td>
<td>0.006</td>
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<tr>
<td>MTX</td>
<td>44.0±9.9</td>
<td>40.7±11.0</td>
<td>0.022</td>
<td>39.7±10.4</td>
<td>0.002</td>
<td></td>
<td></td>
</tr>
<tr>
<td>DAS28 Infliximab</td>
<td>5.53±1.31</td>
<td>3.99±1.48</td>
<td>&lt;0.001</td>
<td>3.93±1.52</td>
<td>&lt;0.001</td>
<td>0.98</td>
<td>0.199</td>
</tr>
<tr>
<td>ESR4 Infliximab</td>
<td>5.22±0.93</td>
<td>3.64±1.00</td>
<td>&lt;0.001</td>
<td>3.61±1.31</td>
<td>&lt;0.001</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MTX</td>
<td>0.70±0.66</td>
<td>0.40±0.41</td>
<td>0.002</td>
<td>0.39±0.49</td>
<td>0.008</td>
<td>0.94</td>
<td>0.33</td>
</tr>
<tr>
<td>mHAQ Infliximab</td>
<td>0.60±0.56</td>
<td>0.33±0.45</td>
<td>0.004</td>
<td>0.28±0.48</td>
<td>&lt;0.001</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MTX</td>
<td>0.60±0.56</td>
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<td>0.28±0.48</td>
<td>&lt;0.001</td>
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</tbody>
</table>

n=34, mean±SD
* Compared with before treatment
** Compared with before treatment
*** Analysis by repeated-measures ANOVA

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 as TNF-α and interleukin (IL)-6, are reported to be related to the depressive state. 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-Ethics 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.


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


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