Efficacy and Safety of Infliximab for Ankylosing Spondylitis in Japanese Patients: A Retrospective Study of 11 Cases

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Efficacy and Safety of Infliximab for Ankylosing Spondylitis in Japanese Patients: A Retrospective Study of 11 Cases

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Abstract

Purpose: Tumor necrosis factor inhibitors (TNFIs) such as infliximab (IFX) and adalimumab have been shown to be efficacious not only for rheumatoid arthritis but also for Ankylosing Spondylitis (AS). However, only a limited number of reports regarding the effect of TNFIs on AS in Japanese populations have been published.

Materials and methods: We retrospectively evaluated all 11 patients (8 males and 3 females) with AS who were treated with IFX.

Results: After a mean follow-up period of 19 months, the mean BASDAI decreased from 4.7 ± 2.2 to 1.7 ± 1.2 and the serum CRP level decreased from 1.62 ± 1.94 mg/dl to 0.23 ± 0.45 mg/dl. There was no case of serious infection or anaphylaxis.

Conclusions: Our results indicate that IFX is efficacious and safe for AS in Japanese patients.

Keywords: Ankylosing spondylitis・Infliximab・Japanese

Introduction

Ankylosing spondylitis (AS) is a chronic inflammatory disorder characterized by bone formation, syndesmophytes, and ankylosis of the sacroiliac joints and spine. It is widely known that there is a high prevalence of human leukocyte antigen B27 (HLA-B27) among AS patients, although the role of HLA-B27 in the pathogenesis of AS is poorly understood1. The prevalence of AS is higher in Caucasian populations than in Asian populations such as the Japanese2, which may be related to the low proportion (0.5-0.8%) of HLA-B27-positive population among the Asians3. The classic treatment of AS includes nonsteroidal inflammatory drugs (NSAIDs), corticosteroids, and disease-modifying antirheumatic drugs4. NSAIDs have been reported to be effective for pain and stiffness, as well as for ossification of the vertebral column5. Intra-articular and intravenous injections of corticosteroids were shown to effectively relieve the symptoms of AS, although there is no evidence to support the efficacy of oral corticosteroids6,7. The effects of sulfasalazine and methotrexate (MTX) especially on axial lesions have not been proven8,9. Recently, tumor necrosis factor inhibitors (TNFIs) such as infliximab (IFX) and adalimumab...
mab (ADA) have been shown to be efficacious for AS. However, only a limited number of reports regarding the effect of TNFi on AS in the Asian population have been published. Reports on the Japanese population are even more limited. Some of the published case reports were written in Japanese, and only one case report was written in English, which described the efficacy and safety of ADA in 41 AS cases.

This study aimed to evaluate the efficacy and safety of IFX therapy in Japanese patients with AS in our institution.

**Materials and Methods**

This study was approved by our institutional review board. All 11 patients (8 males and 3 females) with AS who were treated with IFX between May 2010 and October 2012 at the Department of Orthopaedic Surgery, Kyushu University Hospital were retrospectively evaluated (Table 1). AS was diagnosed according to the Modified New York Criteria. The IFX dose used in all cases was 5 mg/kg. All patients were treated with a loading IFX regimen, which was administered intravenously at 0, 2, 6 weeks, respectively. Thereafter, they continued to receive the treatment every 6 weeks. Nine patients discontinued their medications prior to the initiation of IFX therapy. Two patients discontinued the treatment after 1.5 and 6 months (cases 7 and 8 in Table 1, respectively) for the following reasons: satisfaction with the result of total hip replacement for the left hip in case 8 and nausea in case 7. Nevertheless, the latter patient experienced improvement of symptoms such as back pain. Excluding the 2 patients, 9 patients were evaluated for changes in disease activity according to the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) and C-reactive protein (CRP) level, and functional disability according to the Bath Ankylosing Spondylitis Functional Index (BASFI). The Mann–Whitney U test was performed to evaluate the statistical differences in BASDAI and CRP level between pretreatment, 6 months after treatment initiation, and final observation at 19 months after treatment initiation. The statistical difference in BASFI between pretreatment and 6 months after treatment initiation was evaluated as well. P < 0.05 was considered statistically significant.

**Results**

The mean age of the patients was 36.5 years (range, 19–57 years). The mean disease duration

<table>
<thead>
<tr>
<th>Case</th>
<th>Age</th>
<th>Gender</th>
<th>Duration</th>
<th>Duration of IFX treatment</th>
<th>Comorbidities and prior operations</th>
<th>Adverse events</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>31</td>
<td>male</td>
<td>13 years</td>
<td>29 months</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>2</td>
<td>36</td>
<td>male</td>
<td>8 months</td>
<td>28 months</td>
<td>-</td>
<td>Infusion reaction</td>
</tr>
<tr>
<td>3</td>
<td>51</td>
<td>female</td>
<td>30 years</td>
<td>27 months</td>
<td>Left THA</td>
<td>-</td>
</tr>
<tr>
<td>4</td>
<td>19</td>
<td>male</td>
<td>5 years</td>
<td>25 months</td>
<td>Uveitis</td>
<td>-</td>
</tr>
<tr>
<td>5</td>
<td>27</td>
<td>male</td>
<td>12 years</td>
<td>23 months</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>6</td>
<td>27</td>
<td>male</td>
<td>2 years</td>
<td>23 months</td>
<td>Rash</td>
<td>Rash</td>
</tr>
<tr>
<td>7</td>
<td>57</td>
<td>female</td>
<td>4 years</td>
<td>1.5 months</td>
<td>-</td>
<td>Nausea</td>
</tr>
<tr>
<td>8</td>
<td>47</td>
<td>male</td>
<td>30 years</td>
<td>6 months</td>
<td>Bilateral THA</td>
<td>-</td>
</tr>
<tr>
<td>9</td>
<td>57</td>
<td>female</td>
<td>23 years</td>
<td>25 months</td>
<td>Atopic dermatitis</td>
<td>Upper respiratory infection</td>
</tr>
<tr>
<td>10</td>
<td>29</td>
<td>male</td>
<td>9 years</td>
<td>8 months</td>
<td>Obsolete pulmonary tuberculosis</td>
<td>-</td>
</tr>
<tr>
<td>11</td>
<td>20</td>
<td>male</td>
<td>9 years</td>
<td>7 months</td>
<td>Ventricular septal defect</td>
<td>-</td>
</tr>
</tbody>
</table>

THA, total hip arthroplasty
Table 2  CRP level, BASDAI, and BASFI before and after infliximab administration

<table>
<thead>
<tr>
<th>Case</th>
<th>CRP before IFX</th>
<th>Latest CRP</th>
<th>BASDAI before IFX</th>
<th>Latest BASDAI</th>
<th>BASFI before IFX</th>
<th>BASFI 6 months after IFX</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0.02</td>
<td>0.29</td>
<td>4.8</td>
<td>1.4</td>
<td>1.8</td>
<td>1.3</td>
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<tr>
<td>2</td>
<td>1.74</td>
<td>0.07</td>
<td>6.8</td>
<td>1.8</td>
<td>4.5</td>
<td>4.1</td>
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<tr>
<td>3</td>
<td>0.05</td>
<td>0.04</td>
<td>7.3</td>
<td>4.0</td>
<td>7.2</td>
<td>8.1</td>
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<tr>
<td>4</td>
<td>0.46</td>
<td>0.01</td>
<td>0.4</td>
<td>0</td>
<td>6.5</td>
<td>0.3</td>
</tr>
<tr>
<td>5</td>
<td>6.23</td>
<td>0.08</td>
<td>4.1</td>
<td>1.0</td>
<td>3.9</td>
<td>0.2</td>
</tr>
<tr>
<td>6</td>
<td>1.46</td>
<td>0.09</td>
<td>4.6</td>
<td>2.8</td>
<td>4.6</td>
<td>1.8</td>
</tr>
<tr>
<td>7</td>
<td>0.03</td>
<td>0.01</td>
<td>6.0</td>
<td>1.0</td>
<td>9.8</td>
<td>3.0</td>
</tr>
<tr>
<td>8</td>
<td>0.63</td>
<td>0.28</td>
<td>5.6</td>
<td>3.4</td>
<td>6.2</td>
<td>4.4</td>
</tr>
<tr>
<td>9</td>
<td>0.42</td>
<td>1.42</td>
<td>3.3</td>
<td>2.3</td>
<td>6.0</td>
<td>1.3</td>
</tr>
<tr>
<td>10</td>
<td>1.63</td>
<td>0.01</td>
<td>3.5</td>
<td>0.8</td>
<td>6.7</td>
<td>5.3</td>
</tr>
<tr>
<td>11</td>
<td>2.59</td>
<td>0.03</td>
<td>7.3</td>
<td>1.4</td>
<td>3.3</td>
<td>1.8</td>
</tr>
</tbody>
</table>

CRP=C-reactive protein, BASDAI=Bath Ankylosing Spondylitis Disease Activity Index, and BASFI=Bath Ankylosing Spondylitis Functional Index

Fig. 1 Changes in Bath Ankylosing Spondylitis Disease Activity Index before and 6 months after infliximab administration (N = 9) and at the final observation.

Fig. 2 Changes in serum C-reactive protein level before and 6 months after infliximab administration (N = 9) and at the final observation.

Fig. 3 Changes in Bath Ankylosing Spondylitis Functional Index before and 6 months after infliximab administration (N = 9).
from AS diagnosis to initiation of IFX therapy was 12.3 years (range, 8 months to 30 years). The mean follow-up period was 19 months (12–29 months). Medications used prior to IFX administration were sulfasalazine in 3 patients, MTX in 7, and corticosteroid (prednisolone) in 5. Eight patients were also taking NSAIDs. Two patients had participated in a clinical trial of ADA. They had withheld the use of ADA for more than 6 and 18 months, respectively, when they started the IFX therapy. The BASDAI, CRP level, and BASFI in all the cases are shown in Table 2. The BASDAI decreased from 4.7 ± 2.2 (range, 0.4–7.3) to 1.8 ± 1.5 (range, 0–4.3) in 6 months but had improved to 1.7 ± 1.2 (range, 0–2.8) at the final observation (Fig. 1). At least 20% improvement in BASDAI was achieved in all the 9 patients. The mean serum CRP level decreased from 1.62 ± 1.94 mg/dL (range, 0.02–6.23 mg/dL) to 0.38 ± 0.90 mg/dL (range, 0.01–2.75 mg/dL) in 6 months after the initiation of IFX therapy. At the last follow-up, the mean CRP level was 0.23 ± 0.45 mg/dL (range, 0.01–1.42; Fig. 2). Furthermore, at least 50% and 70% improvements in BASDAI were achieved in 66.7% and 33.3% of the patients, respectively. BASFI improved from 4.9 ± 1.8 to 2.7 ± 2.6 at 6 months after the initiation of IFX therapy (Fig. 3). Persistence of AS despite IFX treatment was observed in 11 patients (mean, 19 months; range, 1.5–29 months). Adverse events included 1 case each of infusion reaction, upper respiratory infection, rash, and nausea (Table 1). All the patients who experienced adverse events recovered. In 1 patient, the treatment interval was changed from 8 weeks to 6 weeks because of a decrease in treatment efficiency (case 2 in Table 1).

**Discussion**

In the ASSERT trial\(^{20}\), which is the first reported clinical trial of IFX for AS, patients with a mean disease duration of 8.8 years received 5-mg/kg IFX every 6 weeks and were followed up for 24 weeks. BASDAI improved by −2.9 in 24 weeks. In the present study, BASDAI improved by −2.8 in 24 weeks and −3.1 in 48 weeks. The patients in the present study had a mean disease duration of 12.3 years, but showed clinical results compatible with those from the ASSERT trial.

Infection, infusion reaction, malignant tumors, and reactivation of viral hepatitis are the major adverse events reported in patients treated with IFX therapy\(^{21}\). Our patients had no serious infection or anaphylaxis, and we believe that IFX administration is a safe treatment strategy for AS. Excluding the 2 patients who discontinued treatment, 9 patients continued the IFX therapy for a mean duration of 1 year 10 months. According to the consecutive reports of Braun et al\(^{22–24}\), although persistency slightly decreased over time, IFX was well tolerated for up to 3 years in more than 60% of the patients. Long-term observation in terms of adverse events and efficacy will also be needed for our cases.

The limitation of the present study is the small number of patients. Nevertheless, we believe that our study is valuable because it is the first report of more than 10 cases of AS in Japanese patients treated with IFX therapy.

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References


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日本人の強直性脊椎炎におけるインフリキシマブの有効性と安全性：
II症例の後向き研究

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【背景】インフリキシマブ(IFX)やアダリムマブといったTNF阻害剤は関節リウマチだけでなく、強直性脊椎炎(AS)でも有効であることが示されている。しかしながら、本邦におけるTNF阻害剤のASに対する有効性に関する報告はほとんどないのが現状である。

【材料と方法】我々は11例のAS症例にIFXを投与し、その有効性と安全性について検討を行った。

【結果】平均観察期間は19カ月であった。疾患活動性の評価指標であるBASDAIは投与開始前の4.7±2.2から最終観察時には1.7±1.2まで低下した。また、CRPは投与開始前の1.62±1.94 mg/dLから最終観察時には0.23±0.45 mg/dLまで低下した。アナフィラキシーや重篤感染症を合併した症例は認めなかった。

【結論】日本人においてもIFXはASに対して有効かつ安全であると考えられた。