Suppression of infliximab antibody levels by azathioprine in patients with rheumatoid arthritis

T. AOMORI1*, A. TSUCHIYA1, S. SUZUKI1, A. JIBIKI1, N. OTSUKA1, E. ISHIOKA2, Y. KANEKO2, T. TAKEUCHI2, T. NAKAMURA1

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*Corresponding author: Tohru Aomori, Division of Pharmaceutical Care Sciences, Center for Social Pharmacy and Pharmaceutical Care Sciences, Faculty of Pharmacy, Keio University, 1-5-30 Shibakoen, Minato-ku, Tokyo 105-8521, Japan
aomori-th@pha.keio.ac.jp

In rheumatoid arthritis (RA) treatment, the concomitant use of methotrexate has been shown to reduce the incidence of antibodies to infliximab (ATI), on the other hand, it is unclear whether azathioprine can reduce ATI production. We enrolled a total of 10 Japanese adult patients with RA who were treated with infliximab concomitantly with methotrexate or azathioprine. Serum concentrations of infliximab and ATI of these patients were measured. The mean serum infliximab concentrations was 1.6±1.3 μg/ml in patients with methotrexate and 1.0±0.5 μg/ml in patients with azathioprine. Serum ATI concentrations were below the limit of quantitation in 4 of 5 patients in each group. The results from the present study suggest that azathioprine suppresses ATI production.

1. Introduction

Rheumatoid arthritis (RA) is a chronic inflammatory disease characterized by synovial proliferation and is classified as an autoimmune disease. Drug therapies for RA include disease-modifying anti-rheumatic drugs (DMARDs) using methotrexate as an anchor drug, with the supportive use of non-steroidal anti-inflammatory drugs and low-dose steroids. In Japan, azathioprine has been included under national health insurance coverage for treatment of rheumatic diseases since 2011. Although the first-line treatment for RA is methotrexate, azathioprine is increasingly used as a second-line treatment for patients who are intolerant to methotrexate, such as those with impaired liver/kidney function. If sufficient treatment response is not observed within 3-6 months, the addition of other DMARDs or switching to biological drugs such as infliximab, should be considered as standard practice (Schuna 2011). Infliximab is a chimeric antibody composed of murine variable and human constant regions (Scallon 1995). Immune response to murine proteins produced from the variable regions will lead to the expression of ATI. In RA treatment, as the concomitant use of methotrexate has been shown to reduce the incidence of ATI (Maini et al. 1998; Pascual-Salcedo et al. 2011). Only few studies have shown a reduced incidence of ATI in patients with Crohn’s disease treated with concomitant immunosuppressants, including azathioprine (Vermeire et al. 2007). No association in RA patients has been demonstrated between the concomitant use of DMARDs other than methotrexate and reduced incidence of ATI. Thus, we investigated whether azathioprine co-administered with infliximab can reduce ATI production in RA patients.

2. Investigations, results and discussion

Table 1 summarizes the demographics, serum concentrations of infliximab and ATI in 10 patients included in this study. Patient No. 8 was also treated with prednisolone, in addition to infliximab and azathioprine. The mean serum infliximab concentrations was 1.6±1.3 μg/ml in patients with methotrexate and 1.0±0.5 μg/ml in patients with azathioprine. Serum ATI concentrations were below the limit of quantitation in 4 of 5 patients in each group. The results from the present study suggest that azathioprine suppresses ATI production.

Table 1: Pharmacotherapy of each patients and concentration of infliximab and antibodies to infliximab

<table>
<thead>
<tr>
<th>Patient</th>
<th>Dose of IFX</th>
<th>Administration interval (week)</th>
<th>Administration period (month)</th>
<th>Concomitant drug</th>
<th>Concentration</th>
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<tbody>
<tr>
<td></td>
<td>(mg/body)</td>
<td>(mg/kg)</td>
<td></td>
<td></td>
<td>IFX (pg/ml)</td>
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<tr>
<td>IFX+MTX</td>
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<td></td>
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<tr>
<td>No. 1</td>
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<td>9</td>
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<tr>
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<td>9</td>
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<tr>
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<td>8</td>
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<tr>
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<td>7</td>
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<td>8</td>
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<td>8</td>
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<td>AZA</td>
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<td>6</td>
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<td>AZA</td>
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</table>

IFX: infliximab, MTX: methotrexate, AZA: azathioprine, PSL: prednisolone, ATI: antibody to infliximab, N.D.: not detected

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According to the EULAR DAS28 scores after 3 months of treatment with infliximab were parameters in 10 patients included in this study. In all patients, the concentration of 6-thioguanine nucleosides, an active metabolite of azathioprine, was measured to evaluate its impact on serum infliximab concentrations. For the remaining three patients (Nos. 1, 2 and 9), the concentration was lower than the cut-off for remission. Of the patients with detectable ATI in both groups, the serum infliximab concentrations were less than 1.0 μg/mL (0.68 μg/mL in patient No. 5 who was co-administered with methotrexate and 0.20 μg/mL in patient No. 10 who was co-administered with azathioprine).

The results from the present study suggest that azathioprine also suppresses ATI production, as has been demonstrated with methotrexate. In a previous study involving 174 patients with Crohn’s disease, there was no significant difference in the incidence of ATI between patients treated with combined methotrexate and infliximab and those treated with combined azathioprine and infliximab (Vermeire et al. 2007), which supports our results in patients with RA. We noted two patterns of serum trough concentration of infliximab among patients who were co-administered with methotrexate and infliximab. Two of five patients had higher values (2.5 and 3.8 μg/mL) while the remaining three patients had lower values of 0.51, 0.48 and 0.68 μg/mL, which are below the efficacy cut-off of 1.0 μg/mL (Takeuchi et al. 2009). Similarly, three of five patients in the clinical sample set also had values above 1.0 μg/mL while the other two had values less than the cut-off. Of the patients with lower infliximab concentrations, two patients (Nos. 5 and 10) who were co-administered with methotrexate and infliximab had positive results for ATI, whereas the other two had negative results.

In conclusion, the results of this study indicate that azathioprine can effectively suppress the production of infliximab-neutralizing antibody in patients with active rheumatoid arthritis. Further studies in larger populations, including patients not responding to treatment, are needed to more clearly demonstrate the suppressive effect of azathioprine on neutralizing antibody production.

3. Experimental

3.1. Patients

This study was approved by the Institutional Review Board of Keio University Hospital. All patients provided written informed consent before participating in this study. We enrolled a total of 10 Japanese adult patients with RA who were treated with infliximab concomitantly with methotrexate or azathioprine. Patients were stratified according to the product manual. Of the 10 patients included in this study, 5 were co-administered with infliximab and methotrexate, and 5 were co-administered with infliximab and azathioprine. The results from the present study suggest that azathioprine also suppresses ATI production, as has been demonstrated with methotrexate. In a previous study involving 174 patients with Crohn’s disease, there was no significant difference in the incidence of ATI between patients treated with combined methotrexate and infliximab and those treated with combined azathioprine and infliximab (Vermeire et al. 2007), which supports our results in patients with RA. We noted two patterns of serum trough concentration of infliximab among patients who were co-administered with methotrexate and infliximab. Two of five patients had higher values (2.5 and 3.8 μg/mL) while the remaining three patients had lower values of 0.51, 0.48 and 0.68 μg/mL, which are below the efficacy cut-off of 1.0 μg/mL (Takeuchi et al. 2009). Similarly, three of five patients in the clinical sample set also had values above 1.0 μg/mL while the other two had values less than the cut-off. Of the patients with lower infliximab concentrations, two patients (Nos. 5 and 10) who were co-administered with methotrexate and infliximab had positive results for ATI, whereas the other two had negative results.

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3. Clinical sample

Before administration of infliximab, 2 mL of blood was obtained from patients. Blood specimens were centrifuged at 3,000 rpm for 5 min. Plasma was aliquoted to polyethylene tubes and stored at −20 °C until assay.

3.3. Quantification of serum concentration of infliximab and ATI

Serum concentrations of infliximab and ATI were measured using SHIKARI® Q-INFLIXI and SHIKARI® Q-ATI (Matrits Biotechnology Co. Ltd., Tokyo, Japan) according to the product manual. Acknowledgments: This work was supported by JSPS KAKENHI (Grant Number 15K18913) and The Uehara Memorial Foundation.

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References


