

ORIGINAL ARTICLE

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## The serum concentration of infliximab in cases of autologous blood donation for patients with rheumatoid arthritis

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**Abstract** Our aim was to determine whether the use of infliximab for rheumatoid arthritis (RA) patients is associated with an increased rate of postoperative complications. In this study we evaluated the serum concentration of infliximab to study the influence of autologous blood donation (AB donation) in patients who were administered infliximab and underwent total knee replacement (TKR). We examined five RA patients. Infliximab combined with methotrexate was administered at 3 mg/kg every 8 weeks for all patients. We carried out the TKR operation in the middle of the 8-week interval in which infliximab was administered. The AB donation consisted of 400 ml pooled AB drawn at one point 2 weeks following the final administration of infliximab. Serum infliximab levels were measured using an enzyme-linked immunosorbent assay. Mean serum infliximab levels were  $5.46 \pm 5.62 \mu\text{g/ml}$  2 weeks after the final administration of infliximab,  $2.02 \pm 1.66 \mu\text{g/ml}$  just before the operation, and  $1.48 \pm 1.31 \mu\text{g/ml}$  1 day post operation. Moreover, the mean serum level in an autologous blood bag sampled just before AB donation was  $5.02 \pm 4.79 \mu\text{g/ml}$ . This study indicated the serum level of infliximab in the stored blood remained at almost the same level as the collected autologous blood. However, even after autotransfusion those levels were decreased compared with levels measured just before the operation. Therefore, we conclude that there is little influence of AB donation on the risks of infliximab.

**Key words** Autologous blood donation · Infliximab · Orthopaedic surgery · Rheumatoid arthritis · Total knee replacement

### Introduction

Joint replacement surgeries have substantially improved the overall function and quality of life for patients with rheumatoid arthritis (RA).<sup>1</sup> When orthopedic surgery such as a joint replacement is scheduled, the management of RA is needed. Lately, the option of using preoperative autologous blood donation (AB donation) has become widespread for joint replacement surgeries. Preoperative AB donation is commonly performed to meet potential perioperative transfusion needs, despite the substantial progress that has been made in decreasing the complications of allergenic transfusion.<sup>2</sup>

On the other hand, over 14000 patients have already been treated with infliximab since it was approved in Japan as the tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ) inhibitor, and the number of patients is increasing rapidly. However, there have been no reports of complications in patients who were treated by infliximab and AB donation for joint replacement surgeries. If the levels of infliximab in stored blood are high, AB donation may cause adverse events after the operation. Therefore, in this study we measured the serum concentration of infliximab in the cases of AB donation before and after total knee replacement (TKR), and we examined the influence of infliximab on TKR.

### Patients and infliximab serum assay

We examined five RA patients who were administered infliximab and underwent TKR in our hospital (Table 1). Two patients were male and three patients were female. The median age at operation was 58.0 years (range 55–65 years), and the median duration of disease was 10.0 years (range 5–20 years), while the median duration of treatment with infliximab was 11.4 months (range 5–21 months).

Infliximab combined with methotrexate was administered at 3 mg/kg every 8 weeks for all patients. This prescription was approved in Japan at the time (August 2006). We usually carry out TKR operations in the middle of the

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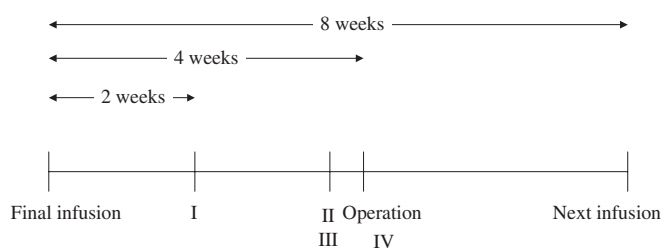
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**Table 1.** Patients studied

Case	Age at operation (years)	Sex	Duration of treatment with infliximab (months)	Duration of disease (years)	Height (cm)	Body weight (kg)
1	57	Male	5	5	162.7	56.3
2	65	Male	5	7	164.2	48.8
3	55	Female	17	13	156.6	50.9
4	58	Female	21	20	149	46.5
5	55	Female	9	5	146.4	46.8



**Fig. 1.** Times of collected samples. *I*, serum level 2 weeks after the final infusion; *II*, serum level in an autologous blood bag just before autologous blood (AB) donation; *III*, serum level just before the operation; *IV*, serum level 1 day after the operation

8-week interval in which infliximab is administered. Japan College of Rheumatology and British Society for Rheumatology guidelines propose that treatment with infliximab should be withheld for 2–4 weeks prior to major surgical procedures.<sup>3</sup>

The AB donation consisted of 400 ml pooled AB drawn at one point 2 weeks following the final administration of infliximab. The whole-blood liquefaction preservation method using a citrate phosphate–dextrose preservative solution was adopted. Recombinant human erythropoietin was not used in all cases. Autologous blood donation was administered immediately after the operation, and this was completed on the same day as the operation.

Blood samples were collected for the measurement of serum infliximab concentrations at several points: serum collected 2 weeks after the final infusion of infliximab (*I*), a sample from an autologous blood bag used at the operation (*II*), serum taken just before the operation (*III*), and serum taken 1 day post operation (*IV*) (Fig. 1). Serum infliximab levels were measured using an enzyme-linked immunosorbent assay as previously described.<sup>4</sup> The lowest level of infliximab that could be reliably detected was 0.1 µg/ml. The measurements were actually performed by Tanabe R&D Service, Osaka, Japan.

## Results

Mean serum infliximab levels were  $5.46 \pm 5.62$  µg/ml 2 weeks after the final infusion of infliximab (*I*),  $2.02 \pm 1.66$  µg/ml just before the operation (*III*), and  $1.48 \pm 1.31$  µg/ml 1 day post operation (*IV*). Moreover, the mean serum level in an autologous blood bag just before AB donation was  $5.02 \pm$

$4.79$  µg/ml (*II*). The serum infliximab levels in each case are shown in Fig. 2. These were: case 1: 2.1 µg/ml (*I*), 2.1 µg/ml (*II*), 1.1 µg/ml (*III*), 1.0 µg/ml (*IV*); case 2: 0.2 µg/ml (*I*), 0.2 µg/ml (*II*), 0.1 µg/ml (*III*), 0.1 µg/ml (*IV*); case 3: 7.2 µg/ml (*I*), 7.1 µg/ml (*II*), 4.5 µg/ml (*III*), 3.6 µg/ml (*IV*); case 4: 3.4 µg/ml (*I*), 3.4 µg/ml (*II*), 1.8 µg/ml (*III*), 1.0 µg/ml (*IV*); case 5: 14.4 µg/ml (*I*), 12.3 µg/ml (*II*), 2.6 µg/ml (*III*), 1.7 µg/ml (*IV*).

These results showed that each level measured 2 weeks after the final infusion was higher than the level just before the operation and that measured 1 day after the operation. Moreover, serum levels in an autologous blood bag sampled just before AB donation were a little bit lower or almost the same level compared with those measured 2 weeks after the final infusion. However, even after AB donation these serum levels never increased, and they went down 1 day after the operation. At a mean follow-up of 14 months, there were no serious wounds or systemic infections in any patient.

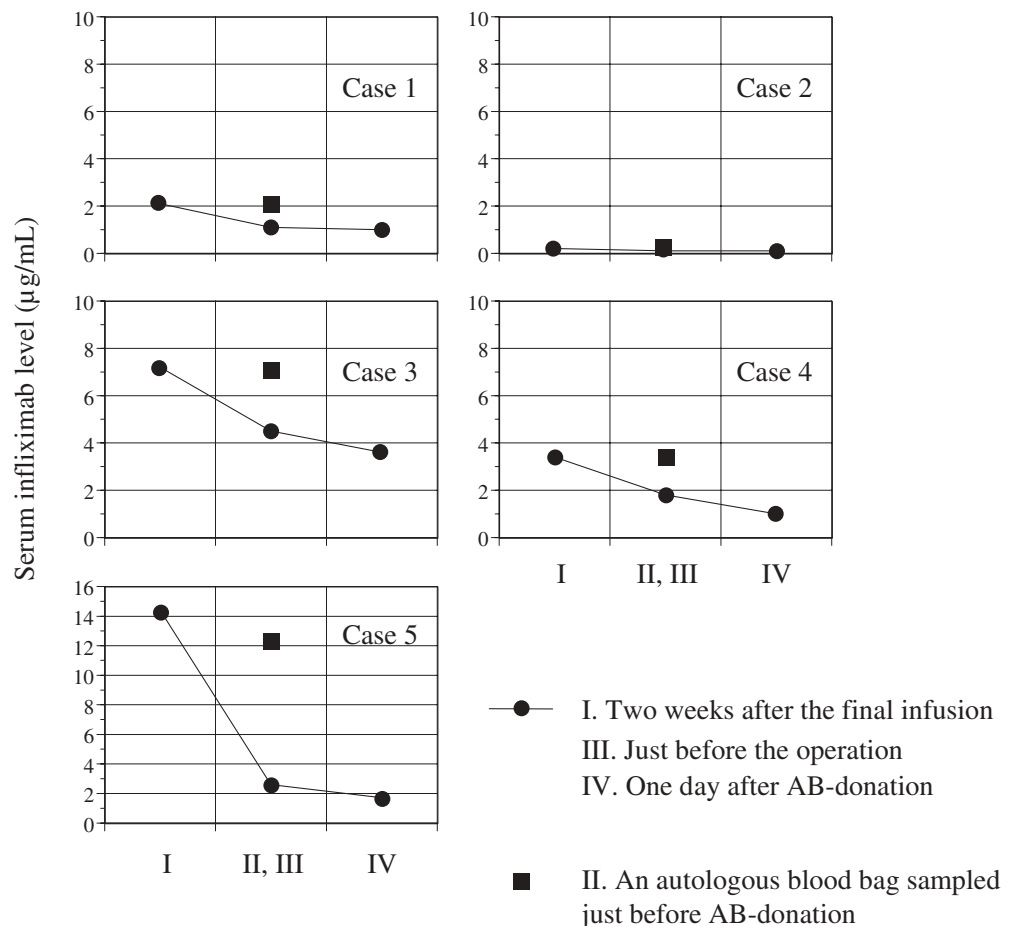
## Discussion

Biologics are assuming a larger role in the management of patients with RA. Infliximab is administered as the TNF-α inhibitor, and it improves patients' symptoms and function.<sup>5</sup> However, this agent has been reported to be associated with risks in healing properly and infectious complications due to the systemic blockade of TNF-α, a ubiquitous mediator required in the normal inflammatory response in tissue healing and infection surveillance.<sup>6</sup> Currently, little information is available regarding the relationship between infliximab treatment and surgery outcomes.

Previous studies have shown that the TNF-α inhibitors infliximab and etanercept do not increase the risk of postoperative surgical complications in patients with Crohn's disease who undergo resection surgery of the bowel.<sup>7</sup> Early complications after abdominal surgery for Crohn's disease are not associated with infliximab use, as in the case of steroid dose and immunosuppressive therapy.<sup>8</sup>

However, the safety of these drugs in patients with RA who undergo orthopedic surgery has not yet been established. Giles et al. reported that TNF-α inhibitor therapy was associated with a risk of serious postoperative orthopedic infection in RA.<sup>9</sup> Besides this, there is no evidence that TNF-α inhibitors, whether or not their use is discontinued, increase either the rate of infection or the complication

**Fig. 2.** Serum levels of collected samples in the following cases: *I*, 2 weeks after the final infusion; *III*, just before the operation; *IV*, 1 day after the AB donation. *II*, an autologous blood bag just before AB donation



rate.<sup>10,11</sup> Bibbo and Goldberg suggested that for patients with RA undergoing elective foot and ankle surgery, the use of TNF- $\alpha$  inhibitors might be safely undertaken in the perioperative period without increasing the risk of healing or infectious complications.<sup>12</sup> Arguments concerning the possible complications in patients with RA who undergo orthopedic surgery still need to be discussed.

There have as yet been no reports concerning the safety of AB donation in patients who are administered infliximab and undergo joint replacement surgeries. Therefore, we decided to measure the serum concentration of infliximab in patients with RA who underwent TKR with AB donation.

Our results showed that serum levels 2 weeks after the final infusion were higher than those just before the operation and those 1 day after the operation. Furthermore, the serum level of infliximab in the stored blood remained close to the level measured 2 weeks after the final infusion. In other words, the serum level of infliximab in the stored blood apparently remained at the same level as the collected autologous blood. Nishimura et al. have reported that no changes in the levels were observed in stored blood, and the levels were sustained through 4 weeks of observation following the start of storage.<sup>13</sup>

The half-life of infliximab in blood was reported to be 199.2h (median value) (REMICADE for i.v. Infusion 100 Interview Form, Tanabe Seiyaku, Osaka, Japan). There-

fore, we were somewhat anxious as to whether the serum level after AB donation might increase. However, we found that all levels actually decreased, even after AB donation, compared with the levels just before the operation. The body weights of these patients ranged from 46 to 56 kg, and the 400 ml volume of transfusion was low compared with their total volume of blood. That is the reason why the level decreased even after AB donation. These results lead us to conclude that there is little influence of AB donation on the risk of increasing serum level of infliximab.

The medicinal action of infliximab *in vitro* was reported to be effective at a level of 4–5  $\mu\text{g/ml}$ .<sup>14,15</sup> In this study, all serum levels measured 1 day after the operation were below 4  $\mu\text{g/ml}$ . Therefore, we consider there is little risk of infliximab levels increasing after the operation, even after AB donation.

In this study, our sample cohort was only five cases, and we investigated only the dose of 3 mg/kg in each patient. However, to our knowledge there is no report concerning the serum concentration of infliximab in cases of autologous blood donation for patients with RA. This is the first report showing that the serum concentration of infliximab in RA patients decreased after AB donation, compared with the levels just before the operation. Therefore, we conclude that there is no evidence that infliximab increases the complication rate of patients with RA who utilize AB donation for TKR. Further study is necessary to determine whether

the use of infliximab prior to joint replacement surgeries for RA is associated with an increased rate of postoperative complications, and it will be desirable to study the relationships between infliximab and AB donation.

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