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RAPID COMMUNICATION

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No change of infliximab levels in stored blood for preoperative autologous blood donation: a preliminary report

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Introduction

Concurrent with the recent wide use of infliximab for rheumatoid arthritis (RA), we are encountering patients in whom total joint arthroplasties must be performed under the administration of this agent.

Because preoperative autologous blood donation (PABD) is the mainstay of countermeasures against blood loss during and after total joint surgery in Japan, the possibility arises in our country that infliximab may remain in the donated blood. If high levels of infliximab are present in the stored blood, transfusion of such blood may cause adverse events, including infection, related to the agent. Nevertheless, the hemokinetics of infliximab in stored blood are not known, although those in serum are well known.

The goal of the current study was, therefore, to clarify the hemokinetics of infliximab in blood stored for PABD. However, because some very interesting data were obtained on the way to that goal, we present them here as a preliminary report.

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Subjects and methods

The subjects were two patients with RA, who gave written informed consent for the study. They had been treated with infliximab 3 mg/kg in combination with methotrexate at 8-week intervals.

Serum sampling

Serum samples were obtained just before, just after, and 24 h, 48 h, 2 weeks, and 4 weeks after the administration of infliximab.

Phlebotomy model

Twenty milliliters of blood was obtained from the patients with the same sterile procedures as those used in PABD just after and 2 and 4 weeks after the administration of infliximab; each sample was immediately and gently mixed with 2.8 ml citrate-phosphate-dextrose-adenine (CPDA-1) (Kawasumi Laboratories, Tokyo, Japan) and then stored, as a model for PABD, in a 50-ml polypropylene conical tube (Becton Dickinson, Franklin Lakes, NJ, USA) at 4°–6°C in a blood transfusion service refrigerator in our hospital.

Plasma sampling from stored blood

Plasma was sampled from the blood stored in the tubes just after mixing with CPDA-1 and 48 h and 1, 2, and 4 weeks following the start of storage.

Measurement of infliximab levels

Levels of infliximab were measured by enzyme-linked immunosorbent assay[1] (actual measurements were performed by Tanabe R&D Service, Osaka, Japan).

Table 1. Infliximab levels in serum and stored blood (μg/ml)

Serum levels relative to time of administration of infliximab		Plasma levels in stored blood by time stored				
		Just after mixing with CPDA-1	48 h	1 week	2 weeks	4 weeks
Case 1						
Just before	<0.1					
Just after	74.7	55.8	n.s.	60.3	62.5	61.2
24 h	n.s.					
48 h	35.1					
2 weeks	8.3	7.4	6.5	6.4	5.6	6.1
4 weeks	1.8	1.3	n.s.	1.2	1.2	1.4
Case 2						
Just before	1.0					
Just after	56.5	44.3	45.8	46.2	50.5	49.0
24 h	46.5					
48 h	40.0					
2 weeks	22.1	17.3	18.9	19.2	18.8	18.8
4 weeks	10.8	9.0	n.s.	10.2	10.1	9.7

CPDA-1, citrate-phosphate-dextrose-adenine; n.s., no sample

Results

Serum levels of infliximab peaked just after infusion, and thereafter decreased. On the other hand, the plasma levels of infliximab in the stored blood remained close to the original serum levels at the time of each corresponding phlebotomy, although they did decrease to some degree with the addition of CPDA-1. Furthermore, no changes in the levels were observed over time in the stored blood; the levels were sustained for the full observed 4 weeks following the start of storage (Table 1).

Discussion

Infliximab demonstrates dose-dependent pharmacokinetics in vivo, and it has an estimated elimination half-life of 8 to 9.5 days at the 3 mg/kg dose.[2] The clinical response reportedly declines rapidly after serum infliximab levels drop below 1 mg/l.[3] The incidence of infection related to this agent has been reported to be 21%, versus 11% in placebo recipients.[4] On the other hand, there have been no specific quantitative reports on the relationship between the serum level of infliximab and the incidence of adverse reaction.

From the standpoint of surgical events, only one study has addressed the risk of infectious complication after orthopedic surgery in RA patients treated with infliximab; that study found that the use of infliximab does not pose an increased risk of complications.[5] However, the surgeries in the study were elective foot or ankle surgery, which are biologically much less invasive than total joint surgery. Furthermore, up to the present time, no fundamental solution has been developed for the infected total joint.

Based on this background, it seems reasonable at this time that any total joint surgery should be undertaken as long as possible, without impacting the RA, after the latest administration of infliximab, and that the next administration should not be performed until after the complete healing of the surgical wound. Still, an additional question remains regarding the timing of PABD for the surgery.

In our actual PABD program, from a patient with 50 kg body weight and hemoglobin over 11.0 g/dl, 400 ml of autologous blood would be drawn at each phlebotomy and stored in a sterile bag (Kawasumi Laboratories) containing 56 ml CPDA-1 at a temperature of 4°–6°C. A total of 800 ml of blood is usually prepared for a total joint surgery. The phlebotomy model in the current study was designed with these procedures in mind.

Our results showed that the levels of infliximab in the stored blood did not change substantially, but remained almost the same as those at the time of the phlebotomy, with only a slight influence from the dilution with CPDA-1.

These data suggest that not only the serum level of infliximab at the time of donation but also the total amount of blood to be stored are important in determining the timing of the phlebotomy.

For example, if a total of 800 ml of blood were donated by patient 2 (55 kg body weight) over a period from 2 to 4 weeks after the latest administration of infliximab, the donated blood would contain a total of 13.2 mg of infliximab, because the average serum level of infliximab during that period is approximately 16.5 μg/ml. Consequently, a transfusion using this blood would cause the serum level of infliximab to rise to 3.1 mg/l if the total volume of circulating plasma was 4.2 l. That level would exceed the 1 mg/l minimum serum level of infliximab at which a clinical response may occur.[3] Moreover, the serum levels of infliximab would continue to rise in accordance with any increase in the amount of donated blood transfused.

Although infliximab demonstrates a shorter half-life than other immunoglobulin agents, its pharmacokinetics might be still altered by several factors other than the dos-

age, namely, the serum level of methotrexate or human antichimeric antibody. Therefore, further detailed studies on these factors are needed.

The findings obtained do not enable us to reach any firm conclusions because of the very small number of subjects. Nevertheless, our results suggest that to prevent side effects, the later after an infusion of infliximab the phlebotomy occurs, the better, because the infliximab levels in the donated blood, mirroring the serum level at the time of phlebotomy, may not change during storage.

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