Minimum Infliximab Dosage for Keeping Serum Infliximab Levels Greater than 1 µg/mL among Patients with Rheumatoid Arthritis

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Infliximab shows dramatic efficacy for controlling inflammation in rheumatoid arthritis (RA), though the ideal dose of infliximab to keep suppressing inflammation has not yet been identified. Recently, it has been evidenced that the minimum trough serum infliximab levels required for suppressing inflammation are greater than 1 µg/mL. Thirty seven RA patients were enrolled in this study and they were divided into two groups (high-infliximab vs. low-infliximab) in reference to Remi-check Q®. A kit for examining serum infliximab levels above/below 1 µg/mL by LC. Infliximab dosage (p=0.06) and dosage interval (p=0.05) had trends to have differences between groups. A formula calculated by infliximab dosage divided by dosage interval and body weight (mg/weeks/kg) was shown to have significantly higher levels among high-infliximab group (p=0.04). Based on whether serum infliximab levels above/below 1 µg/mL and values led by the equation, infliximab dosage/infliximab interval/body weight (mg/weeks/kg), a receiver operating characteristic curve (ROC) was depicted with area under the ROC curve 0.750 and the cut-off point for the serum infliximab levels greater than 1 µg/mL was identified as infliximab dosage/infliximab interval/body weight ≥0.750 with the sensitivity 0.393 and the specificity 1.000. In conclusion, we identified that the minimum infliximab dosage to maintain serum infliximab levels greater than 1 µg/mL was infliximab dose/dosage interval/body weight (mg/weeks/kg) ≥0.750.

Key words: rheumatoid arthritis; biological therapy; infliximab; minimum dosage

Rheumatoid arthritis (RA) is the most common chronic, inflammatory disease associated with joint destruction and disability.10 Tumor necrosis factor-alpha (TNF-alpha) works critically and primarily in an inflammatory cascade of RA. Infliximab is an anti-TNF-alpha antibody which significantly suppresses inflammation in RA.11

Infliximab has shown drastic efficacy for controlling disease activity in RA, though the ideal dosage of infliximab for suppressing inflammation in well-controlled RA patients has not yet been identified. Takeuchi et al. described that the minimum trough serum infliximab levels required for clinical response were more than 1 µg/mL at 54 weeks of infliximab treatment. Very recently, Remi-check Q® (LSI Medience Corporation, Tokyo, Japan), a kit for examining serum Infliximab levels whether more than 1 µg/mL or not by LC has begun to be used in clinic, covered by insurance in Japan since October 1st, 2017. Referring to package insert information, Remi-check Q® represented high consistency with serum infliximab levels examined by enzyme-linked immunosorbent assay (ELISA) with sensitivity 0.96 and specificity 1.00.3

This cross-sectional study was designed to identify the minimum dosage of infliximab for maintaining serum infliximab levels greater than 1 µg/mL in well-controlled RA patients treated with infliximab for more than 54 weeks.

PATIENTS AND METHODS

Patients and Blood Tests RA patients treated with infliximab for more than 54 weeks were recruited into this study. Of these, patients with serum C-reactive protein (CRP) levels more than 1 mg/dL were excluded as not well-controlled and 37 RA patients were finally included. They were diagnosed with RA according to the 1987 revised American College of Rheumatology classification criteria for RA.4 This study was approved by the Ethical Committees (ID: 20170101) in our institution and informed consent was obtained from the patients. A blood test was used to measure CRP, erythrocyte sedimentation rate (ESR), matrix metalloproteinase-3 (MMP-3), serum amyloid A (SAA), white blood cell counts (WBC), hemoglobin, platelet, aspartate aminotransferase (AST), alanine aminotransferase (ALT) and creatinine. In addition, clinical parameters in RA such as the Clinical Disease Activity Index (CDAI), the Simplified Disease Activity Index (SDAI), the 28-joint Disease Activity Score based on CRP (DAS28-CRP) and the 28-joint Disease Activity Score based on ESR (DAS28-ESR) were also examined. Serum infliximab levels were examined with Remi-check Q® (LSI Medience Corporation, Tokyo, Japan).

Statistical Analysis Values are expressed as the mean±standard deviation (S.D.) unless otherwise stated. For our calculations, we used the statistical software XLSTAT (Addinsoft, Inc., Paris, France). When p-value was less than 0.05 (5%), it was considered statistically significant. Based on the infliximab serum levels examined with Remi-check Q®, patients were categorized into two groups: high infliximab concentration (high-infliximab) with serum infliximab levels greater than 1 µg/mL and low infliximab concentration (low-infliximab) with less than 1 µg/mL. Between the high-infliximab and low-infliximab groups, each parameter was compared with an unpaired t-test and if there was a significant difference in a parameter among groups, the parameter was set as an explanatory variable and a receiver operating characteristic (ROC) curve was depicted for predicting the serum infliximab levels greater than 1 µg/mL. The cut-off point was identified using Youden index with ROC curve. Remission rates in RA disease activity indexes such as CDAI, SDAI, DAS28-CRP and DAS28-ESR were compared between high-infliximab and low-infliximab groups using Fisher’s exact test.

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Table 1. Demographic and Clinical Characteristics of Patients Enrolled in This Study

|                      | High-infliximab | Low-infliximab | p Value |
|----------------------|-----------------|----------------|---------|
| Age, years           | 64.9±14.1       | 69.4±11.2      | 0.38    |
| Sex, M:F             | 2:26            | 3:6            | 0.08    |
| Body weight (BW), kg | 52.9±10.1       | 53.1±6.8       | 0.95    |
| IFX-dosage, mg       | 279±117         | 200±50         | 0.06    |
| Dosage interval, weeks | 7.5±1.5        | 8.7±1.4        | 0.05    |
| Methotrexate, mg/week | 6.3±1.9        | 5.8±1.2        | 0.48    |
| IFX-use duration, years | 10.0±3.9      | 9.1±4.2        | 0.60    |
| IFX-dosage/dosage interval/BW, mg/weeks/kg | 0.78±0.45 | 0.45±0.15 | 0.04 |
| WBC, /µL             | 112000±241000   | 48000±9000     |        |
| Hemoglobin, g/dL     | 12.6±2.8        | 10.9±2.1       |        |
| Platelet, /µL        | 233000±480000   | 240000±43000   | 0.48    |
| AST, U/L             | 39±24           | 38±16          | 0.92    |
| ALT, U/L             | 25±9            | 20±7           | 0.11    |
| Creatinine           | 0.61±0.14       | 0.62±0.15      | 0.92    |
| CRP, mg/dL           | 0.12±0.15       | 0.22±0.20      | 0.10    |
| ESR, mm/h            | 26.2±17.2       | 35.9±25.0      | 0.20    |
| MMP-3, ng/mL         | 56.9±37.6       | 57.8±40.0      | 0.96    |
| SAA, µg/mL           | 6.8±4.5         | 9.4±6.7        | 0.23    |
| CDAI                 | 4.3±5.0         | 1.4±1.2        | 0.09    |
| SDAI                 | 4.5±5.0         | 1.6±1.2        | 0.10    |
| DAS28-CRP            | 1.92±0.79       | 1.54±0.40      | 0.18    |
| CAS28-ESR            | 2.85±0.95       | 2.62±0.59      | 0.50    |

Values are expressed with mean±S.D. Unpaired t-test was used, except for sex with Fisher’s exact test. IFX, infliximab; WBC, white blood cell counts; AST, aspartate aminotransferase; ALT, alanine aminotransferase; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; MMP-3, matrix metalloproteinase 3; CDAI, Clinical Disease Activity Index; SDAI, Simplified Disease Activity Index; DAS28, Disease Activity Index of 28 joints.

RESULTS

In this study, nine patients were categorized into the low-infliximab group with serum infliximab levels at less than 1 µg/mL as examined by Remi-check Q®. Between the high-infliximab and low-infliximab groups, there were no significant differences in CRP, ESR, MMP-3, SAA, WBC, hemoglobin, platelet, AST, ALT, creatinine, and RA disease activity indexes between groups as are shown in Table 1. Remission rates in CDAI (p=0.14: high-infliximab 13/28 vs. low-infliximab 9/9), SDAI (p=0.08: 19/28 vs. 9/9), DAS28-CRP (p=0.08: 19/28 vs. 9/9) and DAS28-ESR (p=0.46: 11/28 vs. 5/9) did not differ between groups.

There were significant differences in scores calculated the following equation: serum infliximab levels divided by the infliximab dosage intervals and body weight (mg/weeks/kg). Infliximab dosage and dosage intervals also had trends to differ between high-infliximab and low-infliximab groups. Based on the equation (infliximab dosage/infliximab interval/body weight), an ROC curve was depicted with area under the ROC curve (AUC)=0.750 as seen in Figure and the cut-off point for the serum infliximab levels greater than 1 µg/mL was clarified as infliximab dosage/infliximab interval/body weight ≥1.0 with the sensitivity 0.393 and the specificity 1.000. The 2×2 contingency table was depicted without any false positive cases, as shown in Table 2.

DISCUSSION

Infliximab is the first biological agent approved in Japan for treating RA and it has been widely used with clinical ef-
Now biologic-naive RA patients have many options for selecting a biologic agent with similar efficacy, though only infliximab requires concomitant use of methotrexate for decreasing risks of anti-infliximab antibodies formation in RA. Owing to the advent of new biological agents, opportunities to start infliximab therapy for biologic-naive RA patients have been limited. In contrast, infliximab is widely used for maintaining disease remission among RA patients previously treated with infliximab, because infliximab is the first approved biologic in Japan and switching of biologics increases potential risks of immunogenicity. For that reason, this cross-sectional study was designed to focus on RA patients continuing infliximab in chronic phase.

The most important finding in our study was the identification of a minimum infliximab dosage required for clinical response for suppressing inflammation among RA patients. There is a consensus that infliximab is truly beneficial in suppressing inflammation and recently, the RISING study, a prospective, multicenter, double-blind study conducted at 88 institutions in Japan clarified that the minimum serum infliximab level required for clinical response was 1μg/mL. However, it had not yet examined what infliximab dosage is required to maintain serum infliximab levels greater than 1μg/mL. In this study, we identified the minimum infliximab dosage to maintain serum infliximab levels greater than 1μg/mL was as follows: infliximab dose/dosage interval/body weight ≥0.750.

The approved dosage of infliximab in RA ranges from 3mg/kg every 8 weeks to 6–10mg/kg every 4 weeks. With the approved dosage, the minimum infliximab dose (mg)/dosage interval (weeks)/body weight (kg) is 0.375. In contrast, our study newly evidenced that the infliximab dose (mg)/dosage interval (weeks)/body weight (kg)≥0.750 is necessary for maintaining serum infliximab levels greater than 1μg/mL. If the inflammation is not suppressed even though the infliximab dose (mg)/dosage interval (weeks)/body weight (kg) exceeds more than 0.750, it may be recommended to switch from infliximab to other biological agents or Janus kinase (JAK) inhibitors such as Tofacinib.

In our study, though remission rates in RA disease activity index scores did not differ between high-infliximab and low-infliximab groups, the low-infliximab group had a trend showing an increase in remission rates in SDAI and DAS28-CRP. This is potentially because of selection bias of RA patients in the low-infliximab group in this study. It was obvious that RA patients in low-infliximab group were well-controlled and thus, they were treated with a relatively small amount of infliximab dosage.

We did have several limitations however. The most noteworthy limitation is that we did not examine serum infliximab levels using Remi-checkQ® during the active inflammatory phase. Longitudinal studies should be conducted to scrutinize optimal infliximab dosage for suppressing RA inflammation in early phase. Second, we did not directly examine serum infliximab levels, instead, we used Remi-checkQ® (LSI Medience Corporation, Tokyo, Japan), a kit for measuring infliximab serum levels by LC to evaluate whether serum infliximab levels are greater than 1μg/mL. To scrutinize the serum infliximab levels more precisely, it may be necessary to be determined by enzyme linked immunosorbent assay (ELISA).

Third, this study was conducted in one institution. To more clearly emphasize differences between high-infliximab and low-infliximab groups, a multi-center study may be required with a larger sample size.

CONCLUSION

In this study, we identified that the minimum infliximab dosage for maintaining serum infliximab levels greater than 1µg/mL was infliximab dose/dosage interval/body weight (mg/weeks/kg)≥0.750 among well-controlled RA patients treated with infliximab for more than 54 weeks of infliximab treatment.

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Conflict of Interest

The authors declare no conflict of interest.

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