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RAPID COMMUNICATION

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Anti-tumor necrosis factor therapy does not diminish the immune response to influenza vaccine in Japanese patients with rheumatoid arthritis

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Introduction

The recent widespread employing of potent biologic agents targeting tumor necrosis factor (TNF) for the therapy of rheumatoid arthritis (RA) raises the question as to whether patients treated in this way respond normally to the influenza vaccine. To the best of our knowledge, there are only a few articles in the English language literature discussing this issue,[1–3] and no data have been reported from Japan. We therefore studied the humoral immune response to influenza vaccination in Japanese patients with RA who were treated/not treated with anti-TNF biologics in comparison with healthy controls.

Patients and methods

This study was approved by the Ethics Committee of Tokyo Medical and Dental University, and a written informed consent was obtained in advance from the patients. RA was diagnosed according to the American College of Rheumatology 1987 criteria, but the duration and activity of the disease were not considered in this study. All the subjects were subcutaneously injected with 0.5 ml of the authorized influenza vaccine for the 2006/2007 season containing 15 μg each of hemagglutinin of the A/New Caledonia/20/99(H1N1) strain (A-NC), A/Hiroshima/52/2005(H3N2) (A-Hiro), and B/Malaysia/2506/2004 (B-Ma). Antibody titers to each antigen were measured prior to and 4–6 weeks following vaccination by a hemagglutination inhibition test according to the standard World Health Organization procedure, and the results were expressed as the highest dilution of serum that completely inhibited the hemagglutination; 27 RA patients who received anti-TNF biologics during this study (Bio; infliximab 11, etanercept 16), and 36 RA patients who did not receive any biologics (non-Bio), and 52 healthy controls (Cont) were enrolled. The mean age (±SD) of the Bio, non-Bio, and Cont groups was 55.7 (±12.6), 59.7 (±12.0), and 55.9 (±9.82), respectively, not significantly different ($P > 0.05$ by Student's t test). The ratio of females in Bio, non-Bio, and Cont was 77.8%, 86.1%, and 78.8%, respectively, also not significantly different ($P > 0.05$ by Fisher's exact test).

Results and discussion

Defining the response to vaccine as either a ≥ fourfold rise in antibody titer, or a rise from a non-detective baseline level of <10 to a protective level of ≥40, resulted in the proportion of responders to A-NC in Bio being significantly higher than in Cont (Fig. 1a). There was a similar trend in the response to A-Hiro and B-Ma, although not statistically significant (Fig. 1b, c). These data are consistent with an earlier study by Fomin et al.[1] who also observed a higher proportion of vaccine responders from RA patients treated with infliximab than from other RA patients, although the difference was not statistically significant.

In systemic lupus erythematosus, treatment with glucocorticoids is reported to diminish responsiveness to influenza vaccine.[4] In the present study, a total of 31 RA patients

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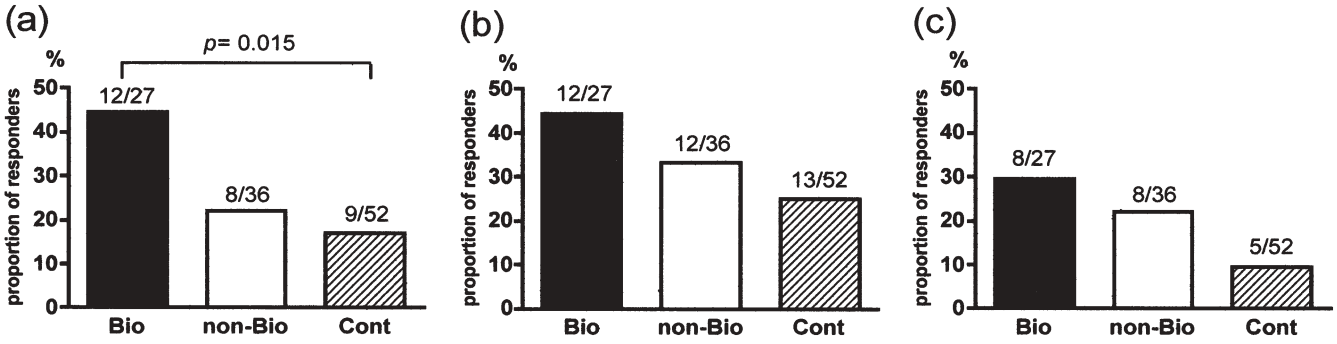

Fig. 1. The proportion of responders to influenza vaccination. Antibody responses against A/New Caledonia/20/99 (**a**), A/Hiroshima/52/2005 (**b**), and B/Malaysia/2506/2004 (**c**) were estimated in rheumatoid arthritis (RA) patients receiving anti-tumor necrosis factor (TNF) biologics (*Bio*), not receiving any biologics (*non-Bio*), and healthy controls (*Cont*). Each *bar* represents the proportion of responders (%) defined as described in text, and *numbers* at the top of each bar indicate responders/subjects in the group. Data were compared by Fisher's exact test and *P* values were shown when they were less than 0.05

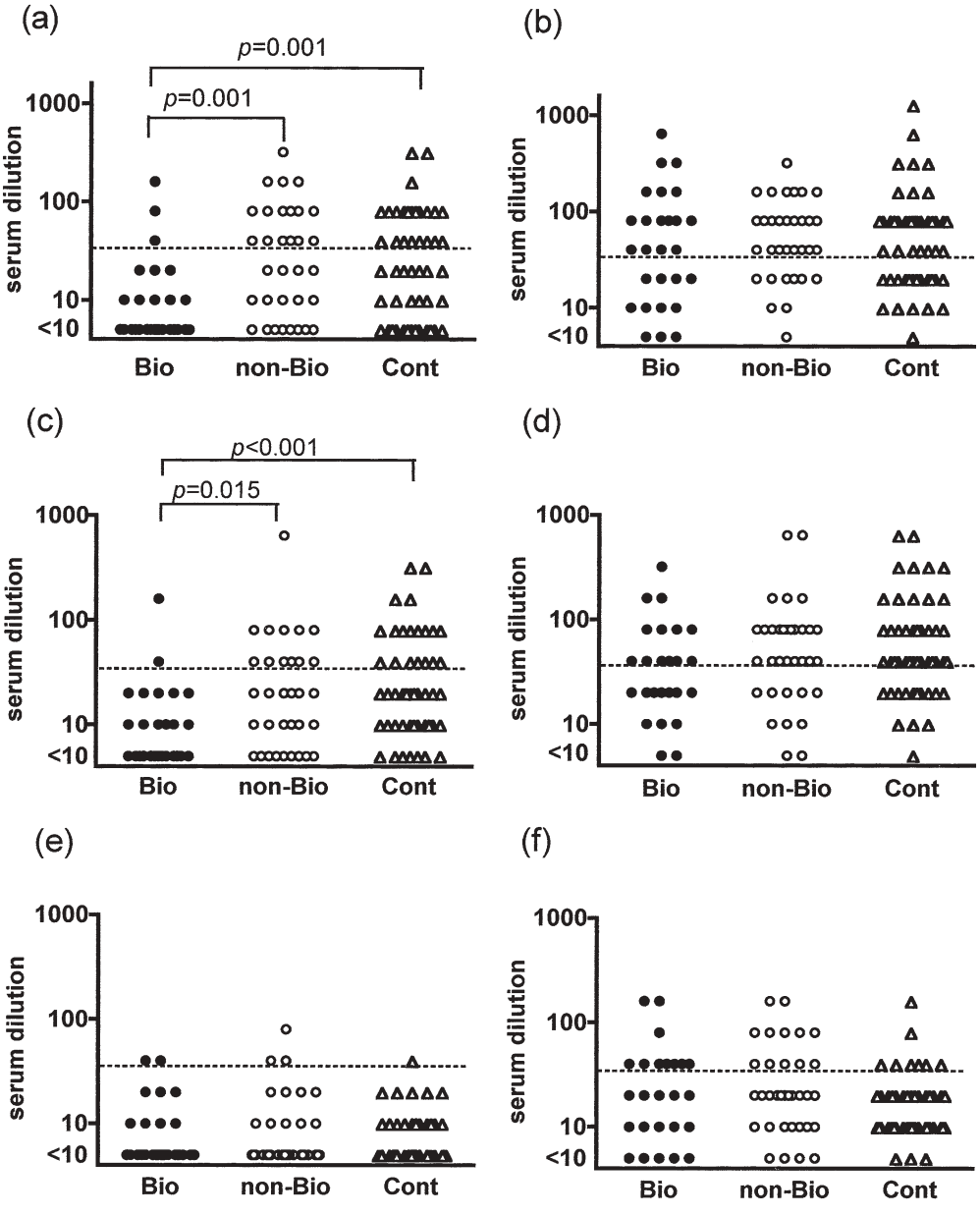

Fig. 2. Change of antibody titers before (**a**, **c**, **e**) and after (**b**, **d**, **f**) vaccination. Antibody titers of individual subject for A/New Caledonia/20/99 (**a**, **b**), A/Hiroshima/52/2005 (**c**, **d**), and B/Malaysia/2506/2004 (**e**, **f**) are shown in RA patients receiving anti-TNF biologics (*Bio*), not receiving any biologics (*non-Bio*), and healthy controls (*Cont*). The *dotted horizontal line* represents the lower limit of protective titer (×40). Data were compared by the Mann–Whitney test and *P* values were shown when they were less than 0.05

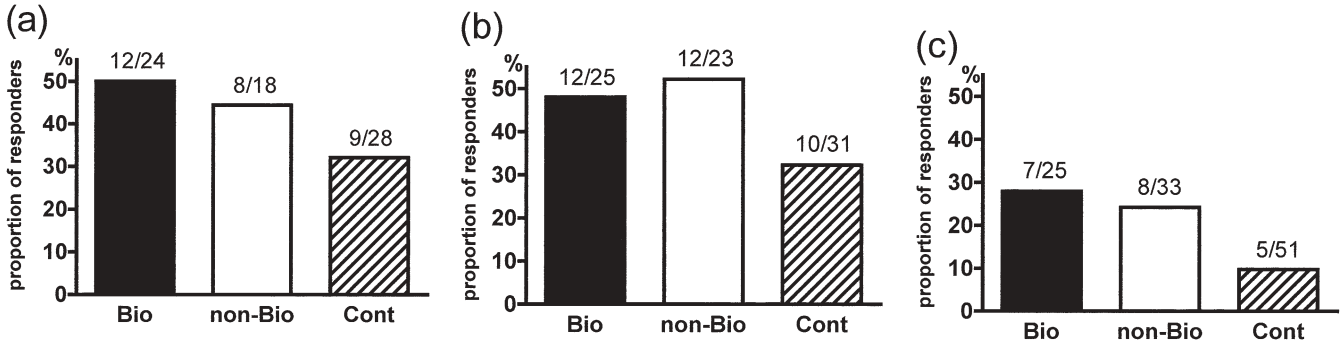

Fig. 3. The proportion of responders who had not had protective levels of antibodies prior to the influenza vaccination. Antibody responses against A/New Caledonia/20/99 (**a**), A/Hiroshima/52/2005 (**b**), and B/Malaysia/2506/2004 (**c**) were estimated in RA patients receiving anti-TNF biologics (*Bio*), not receiving any biologics (*non-Bio*), and healthy controls (*Cont*). Each *bar* represents the proportion of responders (%) defined as described in text, and *numbers* at the top of each bar indicate responders/subjects in the group. Data were compared by Fisher's exact test and not significantly different from each other ($P > 0.05$)

from both the Bio (17 patients) and non-Bio (14 patients) groups were taking prednisolone (1–10 mg/day). Their responsiveness to each influenza antigen was not significantly different from the other 32 patients in both the groups (Bio 10, non-Bio 22) who were not taking prednisolone. Similarly, methotrexate, which was reported to reduce induction of human anti-chimeric antibodies in patients receiving infliximab,[5] was given to 41 patients (Bio 16, non-Bio 25) at weekly dosages of 4–12.5 mg without significantly affecting responsiveness to any of the influenza antigens. Neither did we find any significant effect of other disease-modifying antirheumatic drugs on responsiveness.

As shown in Fig. 2, antibody titers were in general raised following vaccination, but it is noteworthy that pre-vaccination antibody titers to A-NC in Bio patients were significantly lower than in non-Bio and Cont. Following vaccination the Bio group caught up with the other groups. Similarly, pre-vaccination titers – but not post-vaccination titers – in A-Hiro in the Bio group were significantly lower than in the other groups. In the aforementioned article by Formin et al.[1] pre-vaccination titers to the infliximab group were not given.

Lower titers of pre-vaccination antibodies in the Bio group may be related to their high responsiveness to the antigens. Both in RA patients and in healthy controls, subjects who did not have protective titers of antibodies (<40) prior to vaccination showed significantly higher responsiveness to A-NC and A-Hiro than those who did (data not shown). This finding is similar to observations of other investigators.[2,3] To minimize the effect of pre-vaccination titers, therefore, we reanalyzed the responsiveness to the vaccination excluding the subjects who had had protective levels of antibody prior to vaccination. As a result, no significant difference of response ratio to each antigen was observed among the three groups, indicating that anti-TNF agents do not affect immune response to the influenza vaccine (Fig. 3). On the other hand, many subjects in the control group were the staff working for our hospitals and had been exposed to influenza antigens by yearly vaccination, which may have possibly caused the low responsive tendency of this group.

The reason why only the Bio group had lower pre-vaccination titers than the other two groups (Fig. 2) remains elusive. In the present study, prior histories of infection and vaccination were not fully determined, although it is possible that the Bio patients had had less infection or vaccination earlier. Another possibility, which should be addressed, is that antibody titers, once raised in the Bio patients, decline faster than in the non-Bio patients because of disease activity and/or intensive therapy; but this hypothesis needs further investigation.

Conclusion

Bio patients responded well to the influenza vaccine indicating that anti-TNF therapy does not diminish humoral immune response to the vaccination. However, pre-vaccination titers of anti-influenza antibodies in the Bio were lower than in the non-Bio and Cont, suggesting the possibility that the antibodies once raised in the Bio patients decline faster than those in the other groups.

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