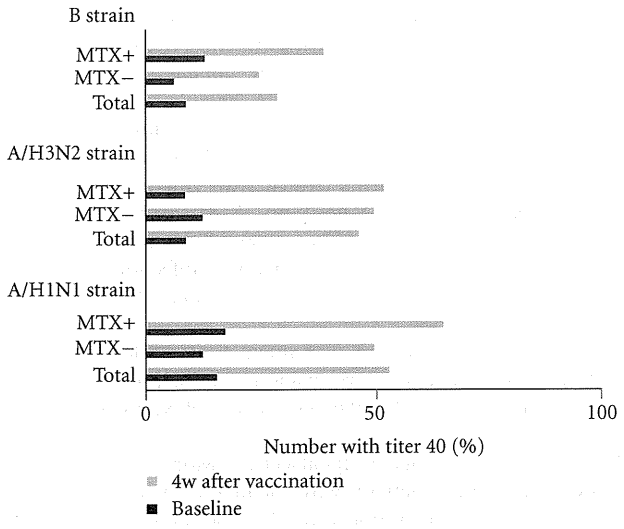

FIGURE 1: Percentage of patients with anti-influenza titers ≥40, as determined by a hemagglutination inhibition assay for each strain after vaccination with a trivalent influenza subunit vaccine, in total RA patients, RA patients treated with MTX, and RA patients treated without MTX. Solid bars represent prevaccination titer ≥40; open bars represent post vaccination titer ≥40.

virus infection as well as suppression of RA disease activity. However, there are various opinions about the efficacy of the influenza vaccination in RA patients. Some reports demonstrate both no differences and significant differences in the response rate between treatment with and without MTX in RA patients [20, 27–29]. This discrepancy may be caused by the different endpoints when measuring the response to the influenza vaccination and different influenza virus roots. Therefore, our data should be limited in reference to the adjuvant effects of Kampo therapy. However, as the baseline titers in this study were less than previous studies, we consider Kampo therapy to be partially beneficial for RA patients in seroprotection and seroconversion. In addition, it has been reported that the response to vaccination was significantly less in patients treated with anti-TNF-a and anti-CD20 antibody (rituximab) drugs than RA patients without biologics [21, 29]. We have checked the titers of the 5 patients treated with biologics, and they were less than those of other RA patient groups (data not shown). Kampo therapy may not influence the response to the influenza vaccination in RA patients treated with biologics. To analyze this problem, further clinical observational studies will be required using a large number of patients.

The RA disease activity by DAS28 did not change after vaccination in our patients. It is generally thought that the vaccination does not influence the disease activity and the titer of the serological markers. A recent report demonstrates that influenza vaccination did not alter the percentage of healthy adults with positive autoantibodies [30].

We have reported several patients with MTX-resistant RA as being successfully treated with Kampo medicine; however, it is still not clear as to how Kampo medicine acts on arthritis in humans [31]. We previously demonstrated that Kampo medicine suppressed polyclonal B cell activation, but not T cell activation, significantly in the CIA mouse model [14, 15]. Recently, it has been clarified that the development of arthritis in the CIA mouse contributed to the differentiation of IL-17 producing cells (Th17), dependent on IL-6 and TGF-β [32, 33]. In our previous study using CIA, Kampo medicine decreased the serum IL-6 levels, but not TNF-α, suggesting that the suppression of Th17 cell activation by Kampo therapy probably improved the development of arthritis. Thus, we suggest that Kampo medicines do not influence the function of antigen presentation in dendrite cells or macrophages. Based on these findings, we suggest that Kampo therapies do not suppress the response to the influenza vaccination in RA patients. Besides, in innate immunity, we have demonstrated that Juzentaihoto enhanced the production of iNOS in macrophages [34] and the upregulation of NK receptor's expression (Killer-cell immunoglobulin-like receptors) in NK cells [35]. Additionally, the direct anti-influenza virus actions of cinnamon cortex and ephedrae herba (the main herbs composing kampo formulae) have been demonstrated, while these actions are not associated with the response to vaccination in RA patients treated with Kampo [36, 37].

In conclusion, we have demonstrated the changes in the titer of each anti-influenza antibody before and after vaccination in RA patients treated with Kampo formula. A low response to the vaccination was not observed compared with previous studies, and in the MTX-treated patients group, the response to vaccination was higher in our study than in previous reports. The present observations may open the way for further clinical trials to establish the efficacy for the influenza vaccination in RA patients treated with Kampo medicines.

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