Use of anti-tumor necrosis factor biologics in the treatment of rheumatoid arthritis does not change human T-lymphotropic virus type 1 markers: a case series

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Abstract

Anti-tumor necrosis factor (anti-TNF) biologics are effective in the treatment of rheumatoid arthritis (RA); however, it is still not clear whether this treatment promotes the development of malignancies such as lymphoma. Human T-lymphotropic virus type 1 (HTLV-1), which is a causative agent of adult T-cell lymphoma (ATL), is prevalent in Japan. Many HTLV-1-positive patients with RA are assumed to exist; however, there have thus far been no reports on the effect of anti-TNF biologics on HTLV-1-positive patients. We analyzed the response to treatment with anti-TNF biologics and change of HTLV-1 markers in two cases of RA. The two cases showed no response based on the European League Against of Rheumatism response criteria 60–96 weeks after administration of anti-TNF biologics (infliximab and etanercept). No signs of ATL were observed and the rate of HTLV-1 infection in patients with RA to be higher than that of healthy blood donors [4]. HTLV-1 has been reported to be associated not only with ATL, but also with chronic inflammatory diseases, such as HTLV-1-associated myelopathy (HAM), uveitis, arthropathy, Sjogren syndrome (SS), and myositis [5, 6].

Keywords

Anti-TNF biologics, Human T-lymphotropic virus type 1, Lymphoma, Rheumatoid arthritis, Viral infection

History

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Introduction

The effectiveness of biologics, which target inflammatory cytokines, has revolutionized the treatment of rheumatoid arthritis (RA); however, there are many concerns regarding potential adverse effects to be resolved. It is still not clear whether this treatment promotes the development of malignancies such as lymphoma, and epidemiological studies on this matter are ongoing [1]. RA has been considered a risk factor for the development of lymphoma. The most common lymphoma associated with RA is diffuse large B-cell type non-Hodgkin lymphoma [1, 2].

In Japan, human T-lymphotropic virus type 1 (HTLV-1), which is a causative agent of adult T-cell lymphoma (ATL), is prevalent, with the number of HTLV-1 carriers estimated to be 1.08 million individuals [3]. Therefore, the number of patients in Japan with RA who are also infected with HTLV-1 can be estimated at approximately 10,000. Moreover, a cohort study in Nagasaki prefecture, one of the highest areas of HTLV-1 prevalence in Japan, showed the rate of HTLV-1 infection in patients with RA to be higher than that of healthy blood donors [4]. HTLV-1 has been reported to be associated not only with ATL, but also with chronic inflammatory diseases, such as HTLV-1-associated myelopathy (HAM), uveitis, arthropathy, Sjogren syndrome (SS), and myositis [5, 6].

Patients and methods

Patients

Case 1

A 52-year-old woman with polyarthritis, rheumatoid factor and anti-cyclic citrullinated peptide antibody (ACPA) was diagnosed with RA based on the 1987 American College of Rheumatology (ACR) classification criteria for RA 3 years prior to the present study [10]. She had pneumonitis and was treated with bucillamine...
and salazosulfapyridine, but not with methotrexate (MTX). As these medicines proved inefficacious, we recommended biologics. She had dry mouth and tested positive for anti-Ro/SSA antibody. She was diagnosed with SS based on the American-European consensus criteria for SS [11]. She tested positive for HTLV-1 antibody. Her disease activity score in 28 joints (DAS28) based on the European League Against Rheumatism (EULAR) response criteria was 4.05. After obtaining informed consent, she was started on treatment with etanercept (ETN). Her RA seemed to respond at 12 weeks after treatment with ETN. However, after this time point, DAS28, the levels of C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) gradually increased despite treatment with ETN (Figure 1-A). The number of swollen and tender joints and her modified health assessment questionnaire (mHAQ) did not improve significantly (Figure 1-A). As a result, she was judged to have had no response by EULAR response criteria [12].

Case 2
A 32-year-old woman with polyarthralgia, rheumatoid factor, and ACPA was diagnosed with RA based on the 1987 ACR classification criteria for RA [10] when she was pregnant 4 years prior to the present study. She tested positive for HTLV-1 antibody. After giving birth, treatment with MTX was started; however, she complained of worsening arthralgia. As MTX dosage could not be increased because of the adverse effect, she accepted our recommendation to use biologics. She also had dry eyes and dry mouth. She tested positive for anti-Ro/SSA antibody and was diagnosed with SS based on the American-European consensus criteria for SS [11]. Her DAS28 was 5.17. After obtaining informed consent, she was started on treatment with infliximab (IFX) in addition to MTX. Her DAS28 remained unchanged and high disease activity continued. For this reason, we changed IFX to ETN and the dosage of MTX was escalated; however, DAS28 and mHAQ at 60 weeks after the beginning of biologics remained high. Therefore, she was judged to be non-responsive to anti-TNF agents (Figure 2-A) [12]. The levels of serum CRP gradually decreased; however, the levels of CRP and ESR remained high, in this case. DAS28 after the IFX and ETN treatments was judged not to have changed in this case based on the absence of significant improvement in the number of swollen joints, the number of tender joints, the levels of inflammatory markers and her mHAQ.

Change of HTLV-1 PVLs and clonality of infected cells in peripheral blood
HTLV-1 PVLs and clonality of HTLV-1-infected cells in peripheral blood in these two cases were analyzed. Written informed consent was obtained, and the study protocol was approved by the institutional review board of University of Miyazaki.

The methods for measuring HTLV-1 PVL and clonality of HTLV-1-infected cells are described in detail elsewhere [13, 14]. In brief, peripheral blood mononuclear cells (PBMCs) were obtained from both cases and genomic DNA was isolated. Real-time polymerase chain reaction (PCR) using primers and probe for HTLV-1 pX regions and human RNase P gene were performed to evaluate PVL (HTLV-1 copies per 100 PBMCs).

Inverse-long PCR (IL-PCR) was performed with slight modification to determine the clonality of HTLV-1-infected cells in each case [14]. In brief, the genomic DNA was digested with EcoR I, and then self-ligated by T4 ligase following digestion with Mlu I. The resultant DNA was amplified using the LA Taq Hot start version (Takara Bio, Shiga, Japan) in triplicate. PCR products were analyzed using 0.6% agarose gel, and each band represented the individual HTLV-1-infected clone.

The PVL of Case 1 before ETN therapy was low at 0.2 copies per 100 PBMCs and continued at the same level until 96 weeks after the beginning of treatment (Figure 1-B). Analysis using IL-PCR in this case showed many bands with different sizes, suggesting oligoclonal expansion of HTLV-1-infected cells before ETN therapy, which did not change thereafter (Figure 1-C). The PVL of Case 2 before anti-TNF biologics was also low at 0.3 copies per 100 PBMCs. It increased slightly after the beginning of IFX; however, it had returned to nearly the same level by 60 weeks after the beginning of treatment (Figure 2-B). Analysis using IL-PCR also showed oligoclonal expansion of HTLV-1-infected cells before anti-TNF therapy, which remained unchanged to the end of observation (Figure 2-C). In addition, there were no signs, symptoms, or laboratory abnormalities, suggesting ATL or HAM during treatment with anti-TNF agents.
Figure 2. Case 2. Clinical course (A); time sequential analysis of HTLV-1 proviral loads (B) and detection of clonalities of HTLV-1-infected cells in Case 2 by IL-PCR (C). IL-PCR assays were performed in triplicate. The abbreviations used in this figure were same as those in Figure 1.

Discussion

We experienced two cases of RA associated with SS in HTLV-1 carriers. A high incidence of arthritis and SS in HTLV-1 carriers has been reported in Japan [4, 15]. Sato et al. reported oligo-arthritis in the shoulders, wrists, and knees in HTLV-1 carriers in Japan [16]. The reported patients tended to have high inflammation and extra-joint symptoms such as SS. Both cases in the present study had features similar to the patients reported by Sato et al. At the same time, the present cases were ACPA positive and fulfilled both the definition of ACR (1987) and ACR/EULAR criteria for RA in 2010 [17].

As conventional disease-modifying anti-rheumatic drugs proved ineffective, these two HTLV-positive cases were treated with anti-TNF therapy. According to the RECONFIRM study, 84.5% of Japanese patients with RA showed good or moderate response to treatment with IFX by EULAR response criteria [18]. On the basis of post-marketing surveillance, approximately 80% of Japanese patients with RA showed good or moderate response to treatment with ETN [19]. However, the two HTLV-1-positive cases of RA in the present study showed no response to anti-TNF agents.

It has been reported that patients with advanced RA and long disease histories showed low response rates to anti-TNF treatments; however, the duration of RA in the present study was only 3–4 years, and neither case was advanced (Steinbrocker’s Classification stage II, data not shown). Both of the cases in the present study had SS in addition to RA; however, association of SS was not always a factor in RA resistance to anti-TNF therapy [20, 21].

Thus far, there have been no reports on the effectiveness of anti-TNF agents or other biologics in HTLV-1 carriers with RA. In an animal model experiment, transgenic mice carrying the HTLV-I genome showed strong expression of mRNA of IL-1 and IL-6, but not TNF [22]. There is a possibility that cytokines such as IL-1 and IL-6, but not TNF, are more important to RA activity in HTLV-1-positive patients than in HTLV-1-negative patients.

In fact, one of the two patients in the present study was treated with IL-6 inhibitor (tocilizumab), thereafter, and showed a better response, although the period of observation was not sufficient for a definite conclusion to be reached (data not shown). There have been no studies on the risk of progression to ATL in HTLV-1 carriers receiving biologics for the treatment of RA. Patients with RA are considered to be at high risk of lymphoma, mainly B-cell type [2]. Thus far, anti-TNF therapy has not been reported to be associated with lymphoma [23, 24]. However, re-activation of Epstein–Barr virus has been reported to be associated with MTX-related lymphoproliferative diseases in RA [2]. In addition, progression to ATL in HTLV-1 carriers who received the immunosuppressive agent tacrolimus after liver transplant has been reported [7]. Therefore, it is important to clarify whether treatment of RA with the biologics increases the risk of ATL.

High HTLV-1 PVL has also been reported in patients with various connective tissue diseases [25]. High PVL, greater than 4–5 copies per 100 PBMCs, has been reported to be associated with progression to ATL in carriers [8, 9]. Therefore, HTLV-1 PVL was monitored during treatment with anti-TNF reagents in the present study. HTLV-1 PVL was low at less than 0.5 copies per 100 PBMCs before treatment with anti-TNF agents in both the present cases. In fact, we thought that the two cases in the present study were not in the high-risk group for the development of ATL and could choose anti-TNF agents for their treatment. Fortunately, even after the beginning of treatment, the levels of PVL showed no significant increase.

In addition, the clonal evolution of HTLV-1-infected cells has also been reported to occur before the onset of ATL [9]. We also monitored the clonality of HTLV-1-infected cells, and neither case showed significant change. In addition, there were no signs (lymphadenopathy, eruption), symptoms or laboratory abnormalities (abnormal lymphocytes on blood smear) related to the progression of ATL. Therefore, no data suggesting the progression of HTLV-1-related diseases such as ATL were observed for 60–96 weeks after anti-TNF therapy in the present cases.

This study has a number of limitations. The number of patients was small, and the observation period was short. Generally, expansion into ATL from HTLV-1 exposure requires a period of 50–60 years. Therefore, we have to follow patients over a longer period of time to see the actual incidence of ATL among them. Because RA patients with high PVL were not included in this study, we could not say whether such patients would show the same course. From this point of view, future study should include RA patients with various levels of PVL ranging from low to high.
In conclusion, two HTLV-1-positive patients with RA were treated with anti-TNF agents. They had high RA disease activity and did not exhibit a good response to anti-TNF agents. Virological study on HTLV-1 infection showed no data suggesting that progression of ATL was promoted by these treatments. Further study including a greater number of patients is necessary to clarify whether these results can be generalized or whether HTLV-1 screening is necessary for RA patients before treatment with biologics.

Conflict of interest

None.

References


