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EDITORIAL

The new era of autoimmune disease research

Takao Koike*

See related research by Lee *et al.*, http://arthritis-research.com/content/13/2/R63

Abstract

Recent genome-wide association studies have advanced our understanding of genetic factors that underlie systemic lupus erythematosus (SLE), a multifactorial autoimmune disease characterized by various clinical manifestations. SLE also has an environmental component, which can trigger or exacerbate the disease. Despite extensive efforts aimed at elucidating the cellular and biological abnormalities that arise in the immune system of patients with SLE, its pathology remains unclear. Lee and colleagues recently carried out gene expression profiling of patients with SLE followed by bioinformatics analysis and discovered the existence of abnormal regulatory networks and potential key molecules. The authors found that ATP synthesis and DNA repair pathways may be involved in the pathogenesis, providing a potential explanation for photosensitivity experienced by patients with SLE.

Microarray and bioinformatics analyses

Microarray analysis and gene expression profiling allow patterns of gene expression in diseases and developmental processes to be assessed. Advances in biological databases have enabled the large-scale expression profiling data to be processed and the foundation for biological interpretation to be laid. Despite this, a major limitation involves the interpretation of massive amounts of microarray data. In microarray analysis, which is often used to identify differentially expressed genes, genes that are expressed at higher or lower levels than controls are of interest. In the previous issue of *Arthritis Research & Therapy*, Lee and colleagues [1] conducted gene expression and bioinformatics analyses between healthy individuals and patients with systemic lupus erythematosus (SLE) and provided insights into biological and functional abnormalities in SLE as well as abnormal regulatory networks. Such analyses – that is, gene ontology analysis, which is used to classify genes into functionally related gene groups, and network pathway analysis, which identifies relationships among these genes – provide an additional layer of insight that cannot be achieved by focusing on individual molecules [1].

Interferon signature

Lee and colleagues [2] previously demonstrated, by DNA microarray and bioinformatics analyses, that genes related to the immune response were differentially expressed in patients with SLE compared with healthy controls. Other studies have also reported increased expression of IFN-inducible genes (that is, the 'IFN signature') in peripheral blood cells from patients with SLE [2-4]. Many groups are currently looking into pathological roles of plasmacytoid dendritic cells (pDCs) and IFN-inducible genes in SLE since pDCs are major producers of IFN-α [4-7]. Given that SLE is a systemic disease that influences multiple organs, Lee and colleagues [1] emphasized the importance of assessing biological and cellular abnormalities associated with SLE other than those related to the immune response. To this end, the authors revealed not only that apoptosis-related genes are upregulated but also that genes related to sensory perception and response to radiation/light were downregulated.

Abnormalities in DNA repair and ATP synthesis

Downregulated genes associated with sensory perception and response to radiation/light included ATPase/ATPase domain-containing genes, two excision repair cross-complementing genes (*ERCC2* and *ERCC5*), and six mitochondrial DNA (mtDNA) encoded genes: ATP synthase 6 (*ATP6*), cytochrome c oxidases 1 (*COX1*) and 3 (*COX3*), cytochrome b (*CYTB*), and NADH dehydrogenase subunits 1 (*ND1*) and 2 (*ND2*). *ERCC2/XPD* and *ERCC5/XPG* are both involved in excision repair of UV-induced DNA damage. Patients with Xeroderma pigmentosum, Cockayne syndrome, or trichothiodystrophy harbor mutations in *ERCC* genes, and such patients exhibit photosensitivity. The process of UV-induced DNA damage repair is known to require ATP, and the main function of mitochondria is to generate ATP

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through oxidative phosphorylation. Accordingly, down-regulation of ATP-dependent *ERCC* genes and mtDNA-encoded genes implies that impaired DNA repair and ATP synthesis, or increased apoptosis, may contribute to the various manifestations of SLE. Consistent with this, a study by Fernandez and Perl [8] showed that mitochondrial hyperpolarization and ATP depletion predispose lupus T cells to necrosis. Via network pathway analysis, Lee and colleagues [1] demonstrated that cytokines IL-6, transforming growth factor-beta (TGF-β); and TNF play central roles as ATP synthesis-related molecules. Patients with SLE had significantly higher levels of TNF and IL-6, which are proinflammatory, whereas levels of the anti-inflammatory cytokine TGF-β were lower [9]. Furthermore, Pflegerl and colleagues [10] reported that epidermal loss of Jun B, which is linked to increased epidermal IL-6 secretion, is sufficient to induce an SLE phenotype in mice, and this suggests that defects in skin function may lead to systemic autoimmune diseases.

Conclusions

Lee and colleagues [1] revealed functional abnormalities in ATP synthesis and DNA repair in peripheral blood cells from patients with SLE. Further DNA microarray and bioinformatics analyses should provide interesting insights into the pathophysiology of autoimmune diseases.

Abbreviations

IFN, interferon; IL, interleukin; mtDNA, mitochondrial DNA; pDC, plasmacytoid dendritic cell; SLE, systemic lupus erythematosus; TGF-β, transforming growth factor-beta; TNF, tumor necrosis factor.

Competing interests

The author declares that he has no competing interests.

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Hepatitis B Virus Reactivation by Immunosuppressive Therapy in Patients with Autoimmune Diseases: Risk Analysis in Hepatitis B Surface Antigen-negative Cases

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ABSTRACT. ***Objective.*** To evaluate the risk of reactivation of resolved hepatitis B virus (HBV) by immunosuppressive therapy in patients with autoimmune diseases.

Methods. Thirty-five patients with autoimmune diseases were included in our study; all were hepatitis B surface antigen (HBsAg)-negative and antibody against hepatitis B core antigen-positive. They were followed for 8–124 weeks and clinical outcomes were analyzed, including serum levels of HBV-DNA and aminotransferase every 4 weeks during their immunosuppressive therapy for underlying autoimmune diseases. If HBV-DNA was detected during the immunosuppressive therapy, HBsAg, antibody against HBsAg (anti-HBs), hepatitis B e antigen (HBeAg), and antibody against HBeAg were also monitored every 4 weeks.

Results. HBV-DNA was detected in 6 out of 35 patients. Anti-HBs titer was significantly lower in the patients in whom HBV-DNA was detected compared with the others at baseline: 2.83 (range 0.24–168.50) mIU/ml vs 99.94 (range 0.00–5342.98) mIU/ml, respectively ($p = 0.036$). Outcomes of the 6 patients with HBV reactivation were as follows: HBV-DNA turned negative in 2 patients without nucleic acid analog (NAA) and 1 with NAA; 2 died due to bacterial sepsis; and 1 died due to autoimmune hemolytic anemia. Significant elevation of aminotransferase was found in only 1 patient, but HBsAg converted to positive in 2 patients and HBeAg converted to positive in 1 patient.

Conclusion. Reactivation of resolved HBV can occur during standard immunosuppressive therapy for autoimmune diseases. The low titer of baseline anti-HBs may carry its risk. (First Release Aug 15 2011; J Rheumatol 2011;38:2209–14; doi:10.3899/jrheum.110289)

Key Indexing Terms:
HEPATITIS B VIRUS IMMUNOSUPPRESSION AUTOIMMUNE DISEASES

Reactivation of hepatitis B virus (HBV) in patients undergoing cytotoxic chemotherapy or immunosuppressive therapy is considered one of the most important complications of such treatments affecting prognosis[1,2,3,4,5]. Prophylactic administration of nucleic acid analog (NAA) is recommended for HBV carriers during moderate or high intensity immunosuppressive therapies[6,7,8].

Clearance of hepatitis B surface antigen (HBsAg) with the appearance of antibody against HBsAg (anti-HBs) had been generally accepted as evidence of clinical cure of acute hepatitis B. However, in 2001 Dervite, *et al* first reported a possible relationship between HBV reactivation and use of rituximab in a patient with anti-HBs[9]. In 2006, a prospective study from Hong Kong revealed that 3.3% of patients who were HBsAg-negative developed HBV reactivation after chemotherapy[10]. HBV replication persists at low levels in the liver for decades after acute hepatitis B[11,12,13,14,15]. Hepatitis with reactivation of resolved HBV has frequently been reported[16,17,18,19,20,21,22]. From these data, negative HBsAg with positive antibody against hepatitis B core antigen (anti-HBc) has been recently accepted as occult HBV infection. High mortality is of great clinical significance in reactivation of resolved HBV. An epidemiological study revealed that reactivation of resolved HBV was found in 23 (4%) of 552 patients who were newly HBsAg-positive; fulminant hepatic failure developed in 5 (22%) of these 23 cases with 100% mortality, and all 5 patients had received a treatment regimen with rituximab[23].

Most of these reports have come from the fields of oncology and transplantation. There has been little evidence regarding reactivation of resolved HBV in the autoimmune diseases[24], including a few case reports of reactivation of resolved HBV during treatments with anti-tumor necrosis factor (TNF) or methotrexate (MTX)[25,26,27] and one prospective study suggesting the risk of reactivation of resolved HBV during biologic treatments[28]. We investigated the risk of HBV reactivation during diverse immunosup-

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pressive therapies for autoimmune diseases in patients who were HBsAg-negative.

MATERIALS AND METHODS

Study design and patients. A total of 414 patients with active autoimmune diseases who would have immunosuppressive therapy were screened for HBsAg, anti-HBc, and anti-HBs (all by the enzyme immunoassay method) in our institution during the period July 2007 through March 2010. A total of 35 HBsAg-negative and anti-HBc-positive patients were identified (Table 1). These 35 patients were followed for 24 (range 8–124) weeks and their clinical outcomes were analyzed including serum levels of HBV-DNA (by polymerase chain reaction method), aspartate aminotransferase (AST), and alanine aminotransferase (ALT) every 4 weeks during the immunosuppressive therapy for underlying autoimmune diseases. HBV-DNA was detected during the immunosuppressive therapy; HBsAg, anti-HBs, hepatitis B e antigen (HBeAg), and antibody against HBeAg (anti-HBe) were also monitored every 4 weeks (all by the enzyme immunoassay method). AST/ALT elevation was considered significant if elevated more than 3 times the upper limit of normal.

Our study was performed in accord with the Declaration of Helsinki and the Principles of Good Clinical Practice. Approval was obtained from the local ethics committee.

Statistical analysis. Statistical analysis was performed by Student's t test, Mann-Whitney U test, chi-square test, or Fisher's exact test, as appropriate. P values < 0.05 were considered significant.

RESULTS

Risk analysis of HBV-DNA detection (HBV reactivation). Out of 414 patients screened in this study, 35 patients (8%) had negative HBsAg and positive anti-HBc. HBV-DNA was detected in 6 of these 35 patients during the immunosuppressive therapy. HBV-DNA turned positive between 4 and 8 weeks after the initiation of immunosuppressive therapy.

Table 1. Patients' characteristics (N = 35).

Characteristic	Value
Female, %	77 (27/35)
Age, yrs, median (range)	62 (30–80)
Diagnosis, n	
Systemic lupus erythematosus	12
Vasculitis syndrome	12
Rheumatoid arthritis	5
Polymyositis/dermatomyositis	2
Idiopathic thrombocytopenic purpura	2
Adult-onset Still's disease	1
Autoimmune hemolytic anemia	1
Prednisolone, mg/day, median (range)	60 (0–60)
Steroid pulse therapy, %	60 (21/35)
Immunosuppressant, %	60 (21/35)
Cyclophosphamide	13
Tacrolimus	4
Cyclophosphamide + tacrolimus	2
Methotrexate	1
Cyclosporin A	1
Biologics, %	17 (6/35)
Rituximab	3
Infliximab	1
Etanercept	1
Tocilizumab	1

There were no differences in sex, age, dose of prednisolone, and level of total serum immunoglobulin G between the patients in whom HBV-DNA was detected and the others (Table 2). Type of therapy, such as steroid pulse therapy, immunosuppressants, or biologics, did not correlate with the HBV reactivation. Baseline anti-HBs titer was significantly lower in the patients in whom HBV-DNA was detected compared with the other patients [2.83 (range 0.24–168.50) mIU/ml vs 99.94 (range 0.00–5342.98) mIU/ml, respectively; p = 0.036 by Mann-Whitney U test; Table 2].

Outcomes of patients with HBV reactivation. Outcomes of the 6 patients with HBV reactivation were as follows: HBV-DNA turned negative in 2 patients without NAA and one with NAA; 2 died due to bacterial sepsis; and 1 died due to autoimmune hemolytic anemia (Table 3). Significant elevation of AST and/or ALT was found in only 1 patient, but HBsAg converted to positive in 2 patients and HBeAg converted to positive in 1 patient (Table 3). The mortality rate was slightly higher in patients with HBV reactivation than in those without: 50% (3/6) versus 17% (5/29), respectively (p = 0.10, Fisher's exact test). Three representative clinical courses of patients with HBV reactivation are shown in Figure 1; a 77-year-old woman recovered with NAA (Figure 1A), a 78-year-old woman spontaneously recovered without NAA (Figure 1B), and a 58-year-old woman developed reverse seroconversions of both HBs and HBe (Figure 1C).

Anti-HBs titer. The titer of anti-HBs was monitored in each patient with HBV reactivation at baseline, at the time HBV-DNA was detected, and at the end of followup, but no particular fluctuation pattern was noted (Figure 2A). In patients without HBV reactivation, anti-HBs was measured at baseline and 8 weeks after the initiation of immunosuppressive therapy, showing persistent titers of anti-HBs: 99.4 (range 0.00–5342.98) mIU/ml versus 77.4 (range 0.00–2652.80) mIU/ml (p = 0.66, Mann-Whitney U test; Figure 2B).

Table 2. Comparison of patients in whom HBV-DNA was detected (HBV reactivation) or not detected.

Characteristic	HBV-DNA Detected, n = 6	HBV-DNA Not Detected, n = 29	p
Female, %	100 (6/6)	72 (21.29)	0.18
Age, yrs, median (range)	65 (30–78)	62 (34–80)	0.66
Prednisolone, mg/day, median (range)	60 (10–60)	60 (0–60)	0.80
Steroid pulse therapy, %	67 (4/6)	59 (17/29)	0.54
Immunosuppressant, %	83 (5/6)	55 (16/29)	0.21
Biologics, %	17 (1/6)	17 (5/29)	0.73
Total IgG at baseline, mg/dl, median (range)	1066 (787–4078)	1448 (192–2855)	0.36
Anti-HBs at baseline, mIU/ml, median (range)	2.83 (0.24–168.50)	99.94 (0.00–5342.98)	0.036*

* Mann-Whitney U test.

Table 3. Outcomes of patients with HBV reactivation.

Patient	Age/Sex	Diagnosis	Anti-HBs at Baseline, mIU/l	Immunosuppressive Regimen				Time to Detection of HBV, Weeks	AST/ALT Elevation	Outcome		
				PSL, mg	Steroid Pulse	Immuno-suppressant	Biologics			HBsAg	HBeAg	
1	77 F	RA + IP	168.5	60	+	TAC	–	4	–	–	–	Recovered with NAA
2	78 F	MPA	5.31	40	–	IVCY	–	8	–	–	–	Recovered without NAA
3	58 F	SLE	0.24	60	+	IVCY + TAC	–	4	–	+	+	Died due to sepsis
4	71 F	RA + EBV-LPD	0.28	10	–	–	RTX	4	–	–	–	Recovered without NAA
5	30 F	SLE	0.35	60	+	IVCY	–	8	+	–	–	Died due to sepsis
6	59 F	SLE	47.86	60	+	IVCY	–	4	–	+	–	Died due to hemolytic anemia

RA: rheumatoid arthritis; IP: interstitial pneumonia; MPA: microscopic polyangiitis; SLE: systemic lupus erythematosus; EBV-LPD: Epstein-Barr virus-related lymphoproliferative disease; PSL: prednisolone; TAC: tacrolimus; IVCY: intravenous cyclophosphamide; RTX: rituximab; NAA: nucleic acid analog; AST: aspartate aminotransferase; ALT: alanine aminotransferase.

DISCUSSION

We demonstrate the potential risk of HBV reactivation during standard immunosuppressive therapy for autoimmune diseases in patients who are HBsAg-negative. There have been 3 case reports of reactivation of resolved HBV during treatments with anti-TNF or MTX: a patient with Crohn's disease receiving infliximab[25], a patient with ankylosing spondylitis receiving etanercept[26], and a patient with rheumatoid arthritis receiving low doses of MTX[27]. In prospective studies, there have been conflicting results regarding the risk of reactivation of resolved HBV by biological agents; Charpin, *et al* reported the safety of anti-TNF agents in 21 patients with rheumatic diseases[29], and Vassilopoulos, *et al* reported the safety of anti-TNF agents in 19 patients with rheumatic diseases[30]. In contrast with these small prospective studies, Urata, *et al* reported that reactivation of resolved HBV occurred in 7 of 135 patients with rheumatoid arthritis and that use of biologic agents represented a risk for reactivation[28]. Therefore, the safety of immunosuppressive therapy in patients with resolved HBV with autoimmune diseases has not been established.

From our data, anti-HBs, the neutralizing antibody against HBV, may correlate with HBV reactivation. Anti-HBs titer was significantly lower in the patients with HBV reactivation than the others at baseline and tended to rise upon detection of HBV-DNA in some cases (Figure 1). Onozawa, *et al*[31] reported a correlation between progressive decrease of anti-HBs and reactivation of resolved HBV after allogeneic hematopoietic stem cell transplantation. In our study, a progressive decrease of anti-HBs was not seen. Compared with reports of treatments in the field of oncology or transplantation, the current therapy for autoimmune diseases is less aggressive in terms of immunosuppression, thus anti-HBs titers are persistent in patients with autoimmune diseases. In contrast, the low titer of anti-HBs at baseline may represent the risk of HBV reactivation and could be one of the markers for the management of those patients.

All the subjects investigated in our study had active heterogeneous autoimmune diseases requiring aggressive immunosuppressive therapy, thus it was difficult to analyze a correlation between underlying disease activity and HBV reactivation. However, patients receiving cyclophosphamide had relatively higher risk of having HBV reactivation than the other patients [31% (4/13) vs 9% (2/22); p = 0.12, Fisher's exact test]. It could reflect that patients who received cyclophosphamide because of high disease activity had more risk of HBV reactivation.

The limitations of our study are the small sample size, large confidence intervals, and relatively short followup. In the published reports, reactivation of resolved HBV occurred 1 to 14 months after the initiation of immunosuppressive therapy[25,26,28], thus longer observation in large population studies may confirm our findings.

Our study suggests that reactivation of resolved HBV can occur during standard immunosuppressive therapy for autoimmune diseases, and that the low titer of baseline anti-HBs may carry its risk. Further study will be needed to establish the procedure for better management of HBV reactivation in the field of autoimmune diseases.

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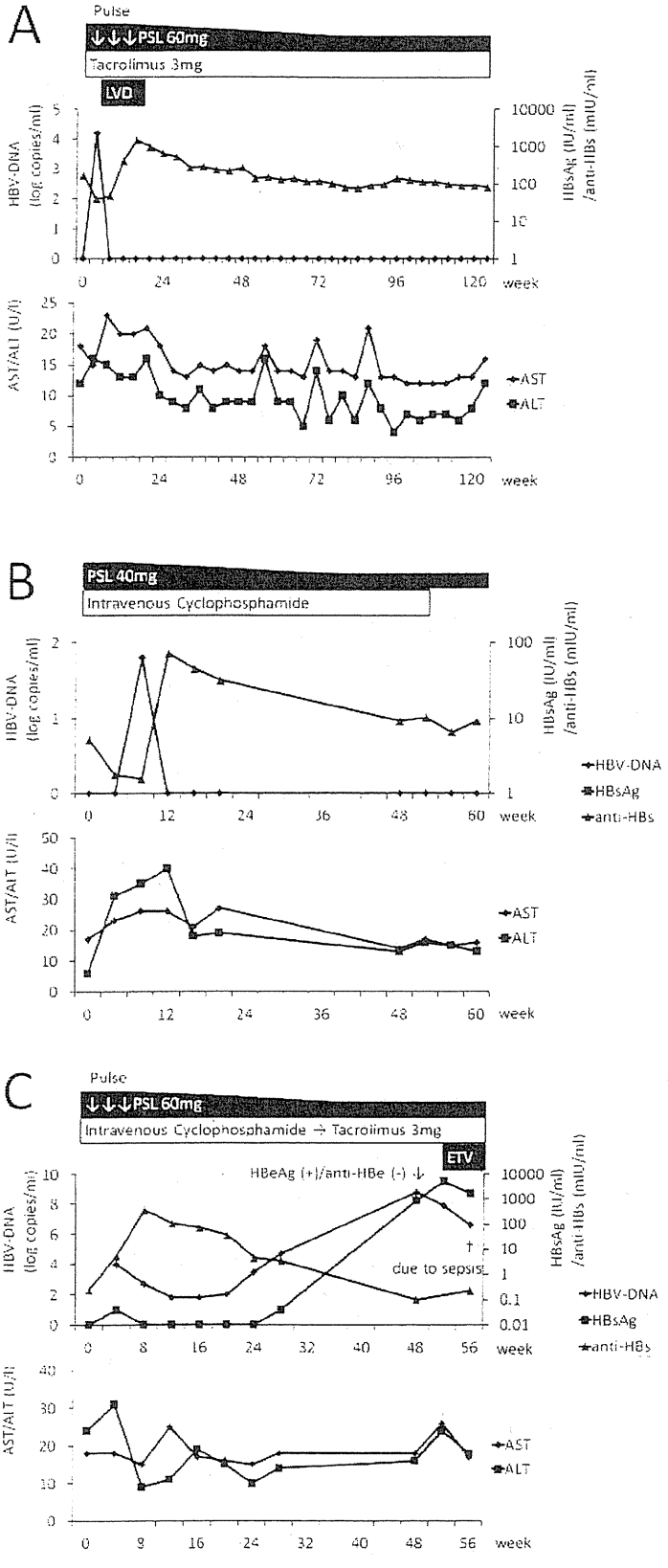

Figure 1. Representative clinical courses of patients with HBV reactivation. A. A 77-year-old woman treated with NAA. B. A 78-year-old woman who spontaneously recovered without NAA. C. A 58-year-old woman who developed reverse seroconversion of both HBs and HBe. PSL: prednisolone; LVD: lamivudine; ETV: entecavir; AST: aspartate aminotransferase; ALT: alanine aminotransferase.

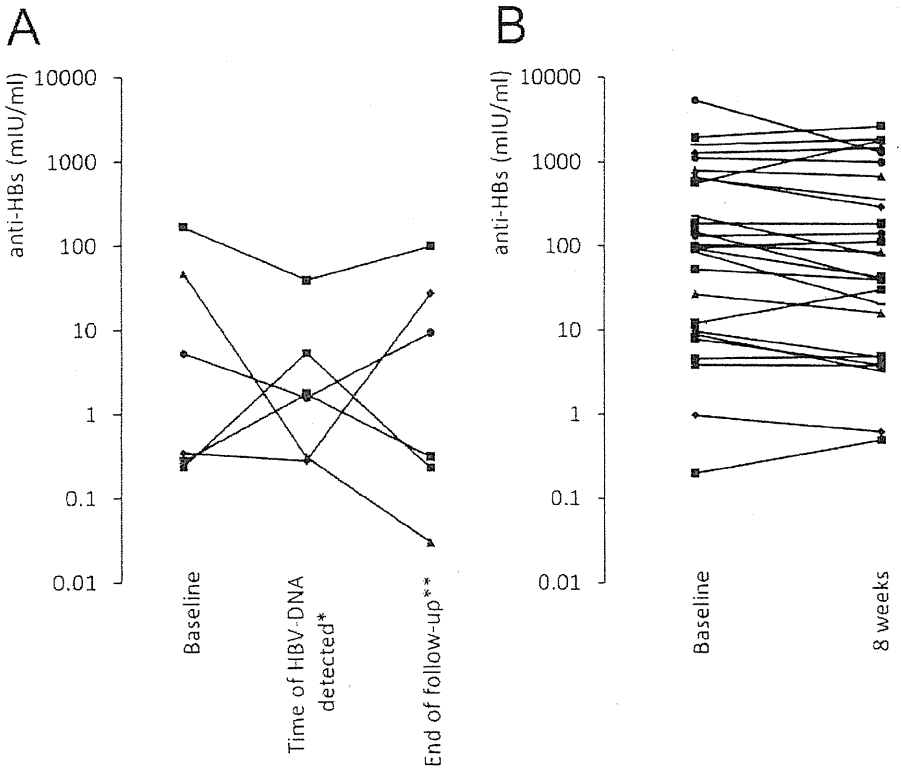

Figure 2. Change of anti-HBs titer in patients with HBV reactivation (A) and in those without reactivation (B). *4 to 8 weeks; **20 to 124 weeks.

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EDITORIAL

Interferon-γ–Independent Suppression of Th17 Cell Differentiation by T-bet Expression in Mice With Autoimmune Arthritis

Takao Koike

Abundant evidence indicates that T cells are required for the initiation and/or chronicity of rheumatoid arthritis (RA) in humans as well as in mouse models of RA (1–3). Multiple animal models have demonstrated key roles of interleukin-17 (IL-17) and Th17 cells in the immunopathology and joint damage of arthritis (4). Further evidence of the role of IL-17 in RA is provided by its biologic properties in vitro and in vivo, as it induces monocyte- and fibroblast-derived proinflammatory cytokines (tumor necrosis factor α [TNFα], IL-1β, IL-8), mediators of bone and cartilage damage, such as matrix metalloproteinases and RANKL, neutrophil and monocyte recruitment, and osteoclastogenesis. Bone and synovial explants from RA joints exhibit increased production of functional IL-17, and IL-17+ CD4+ T cells can be found in RA synovial tissue. In early RA, the cytokine profile of synovial fluid is dominated by the presence of IL-17 as well as Th2 cytokines (5).

The differentiation of naive CD4+ T cells into effector populations is profoundly dependent on cytokines and specific transcription factors. Th1 cells are induced by IL-12 and interferon-γ (IFNγ) (including the transcription factor STAT-1) and by up-regulated expression of T-bet, which directly activates the IFNγ locus (6). Th17 cells in mice are induced by transforming growth factor β (TGFβ) and IL-6 (with STAT-3) or IL-21, which regulate the expression of the transcription factor retinoic acid receptor–related orphan nuclear receptor γt (RORγt) (7). Previous studies showed that these transcription factors negatively regulate the differentiation of other T cell subsets by direct co-interaction and/or by indirect effects of cytokines produced by each T cell subset. How the predominant differentiation of CD4+ T cells affects the development of autoimmune arthritis, however, remains unclear.

In this issue of *Arthritis & Rheumatism*, Kondo et al (8) provide evidence that overexpression of the T-bet gene on type II collagen (CII)–reactive CD4+ T cells regulates murine autoimmune arthritis in an IFNγ-independent manner. The investigators generated T-bet–transgenic (Tg) mice under the control of the CD2 promoter and then triggered collagen-induced arthritis (CIA) in them. They demonstrated complete suppression of CIA, a significant reduction in the level of anti-CII antibodies, and a decrease in CII-reactive IL-17 production in T-bet–Tg mice. Moreover, crisscross coculture experiments using CII-reactive CD4+ T cells from T-bet–Tg mice and splenic dendritic cells from C57BL/6 (B6) mice showed the dysfunction of CII-reactive CD4+ Th17 cells. A consensus of immunologic findings in mice indicates that IFNγ overproduction suppresses Th17 cell differentiation, as demonstrated by the exacerbation of arthritis and the production of high levels of IL-17 in IFNγ-deficient B6 mice with CIA (9). In experiments performed under Th17-polarizing conditions, Kondo et al confirmed that CD4+ T cells in T-bet–Tg mice differentiate weakly to Th17 cells, and unexpectedly, this suppression was not reversed in T cells from T-bet–Tg/IFNγ$^{-/-}$ mice. Their experiments thus support the notion that the suppression of autoimmune arthritis in T-bet–Tg mice might be due to the direct inhibition of Th17 differentiation by T-bet overexpression in CD4+ T cells.

In contrast to their role in mouse models, the role of IL-17 and Th17 cells and in RA is less clear, and several differences have been noted. For example, while Th17/Th1 (IL-17+IFNγ+) cells have been clearly identified in humans, including arthritis patients, this population of cells is rarely seen in mice. Human Th17 cells are thought to be converted to Th17/Th1 cells, whereas Th1 cells are not (10). Recent studies also show that the levels of IL-17 and the number of Th17 cells with increased RORC expression (such as the human counterpart of RORγt) are related to disease activity in RA,

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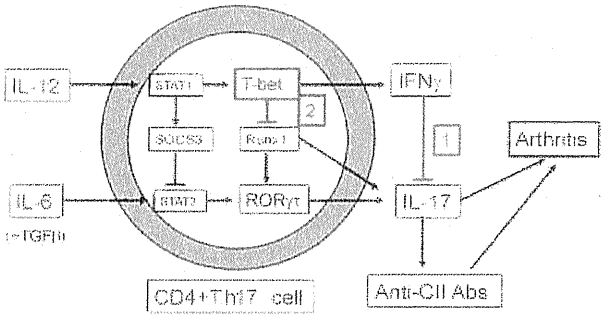

Figure 1. Possible mechanisms of T-bet regulation in autoimmune arthritis. Cytokines (interleukin-12 [IL-12] or IL-6 plus transforming growth factor β [TFGβ]) act as an activator of transcription factors, such as STAT-1 or STAT-3, resulting in the induced expression of T-bet or retinoic acid receptor–related orphan nuclear receptor γt (RORγt) for lineage commitment. **1,** T-bet may act on IL-17 through a direct suppressive pathway by affecting interferon-γ (IFNγ) production. **2,** T-bet may act on IL-17 through an indirect suppressive pathway by way of runt-related transcription factor 1 (RUNX-1) and/or RORγt down-regulation. SOCS-3 = suppressor of cytokine signaling 3; anti-CII = anti–type II collagen; Abs = antibodies.

whereas the level of IFNγ and T-bet is not (11). The mechanism of IFNγ-independent suppression of Th17 cells by T-bet identified by Kondo et al (8) seems to be an attractive target for regulating inflammatory Th17 cells in RA. Figure 1 illustrates the speculative mechanistic role of T-bet regulation.

Epigenetic regulation of T-bet and RORγt is undergoing intensive investigation. Previous studies have shown that RORγt expression is regulated positively by runt-related transcription factor 1 (RUNX-1) and STAT-3 (induced by IL-6 and TGFβ) (12). Moreover, Lazarevic et al (13) reported that expression of transfected T-bet under Th17-polarizing conditions (including neutralizing anti-IFNγ antibody) results in lower levels of RORγt expression. They also showed that T-bet inhibits RUNX-1 activity, and that RUNX-1 overexpression reverses the effect of T-bet on Th17 polarization. Therefore, T-bet inhibits IL-17 production in RORγt+ T cells by suppressing RUNX-1 (Figure 1). Several reports have suggested that single polymorphisms of RUNX-1 itself are associated with autoimmune diseases, including RA; therefore, the interaction of T-bet, RUNX-1, and RORγt should be intensively analyzed in future studies.

Kondo et al (8) further propose a new hypothesis that overexpression of T-bet transcription factors regulates autoimmune arthritis. This discovery should shed light on the molecular mechanisms of the generation of RA and assist in the development of new therapeutic strategies for RA.

AUTHOR CONTRIBUTIONS

Dr. Koike drafted the article, revised it critically for important intellectual content, and approved the final version to be published.

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ORIGINAL ARTICLE

Effect of total arthroplasty combined with anti-tumor necrosis factor agents in attenuating systemic disease activity in patients with rheumatoid arthritis

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Abstract We assessed the effect of total large-joint arthroplasty combined with anti-tumor necrosis factor (TNF) therapy for rheumatoid arthritis (RA). We studied 45 RA patients (age 57.91 ± 12.74 years, RA duration 13.43 ± 8.28 years) who underwent total arthroplasty (35 knees, 19 hips, 3 elbows, and 1 ankle) between August 2002 and November 2009. All patients received anti-TNF agents (infliximab, 22; etanercept, 33; adalimumab, 3) during the period of the study (that is, they were being treated with the agents when operated on and postoperatively). The disease activity score 28 (DAS28)-erythrocyte sedimentation rate (mean ± standard deviation) in all patients improved significantly from baseline (just before the operation; 4.32 ± 0.99) to 1 year after the operation (3.35 ± 0.93) in contrast with the finding that the mean DAS28-ESR values had remained unchanged from 1 year before the operation to the baseline. Changes in clinical variables in the 58 cases were investigated at baseline, and at 4, 12, and 52 weeks after the operation. The patients were divided by a median split of baseline demographics into 2 groups for further evaluation. Compared with the high-value groups, those with low C-reactive protein and matrix metalloproteinase-3 values showed better results and had lower disease activity. Overall, the DAS28-ESR in both groups had improved 1 year after the operation. In RA patients who are being treated with anti-TNF agents, large-joint arthroplasty may be beneficial, not only for the relief of pain arising from joint destruction, but also for the systemic reduction of RA activity.

Keywords Anti-TNF agent · Disease activity · Rheumatoid arthritis · Surgical treatment · Total arthroplasty

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Introduction

Anti-tumor necrosis factor (TNF) therapy is beneficial for patients with rheumatoid arthritis (RA) because it suppresses inflammation and joint destruction [1, 2]. However, nowadays, many RA patients have long-term or high disease activity before they come to our attention. Consequently, some may have experienced joint destruction either before or after the use of biologics such as anti-TNF agents. In many such cases, orthopedic procedures such as total joint arthroplasty are required. For example, at our institute (Nagoya University Hospital, Japan), the percentage of RA patients who were treated with anti-TNF agents and who underwent orthopedic procedures on large joints increased from 11.5% in 2005 to 52.9% in 2008 [3]. Such surgical procedures in patients who are receiving biologics may become routine practice in future.

Of note, synovial cells in RA patients produce TNF. Hence, arthroscopic synovectomy and total knee

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arthroplasty (TKA) have been reported to be effective in patients in whom RA has been attenuated after the use of the anti-TNF agent infliximab (IFX) [4, 5]. In cases involving synovectomy, the synovium, the only site of TNF production, is removed surgically while degenerative cartilage and chondrocytes remain untouched. However, because chondrocytes can also produce TNF [6, 7], if we can completely resect almost all TNF-producing cells during orthopedic procedures such as total arthroplasty, the effect on disease activity in RA patients should be greater than that of synovectomy alone.

While we believe that systemic control of RA activity with medications is necessary, local control with surgical treatment such as total arthroplasty may have more comprehensive effects. Therefore, we hypothesized that total arthroplasty combined with anti-TNF therapy may not only improve the damaged joint itself but may also result in the attenuation of systemic disease activity. In this study, we evaluated the overall changes in RA patients who were receiving anti-TNF agents (including assessment of the disease activity score 28-erythrocyte sedimentation rate [DAS28-ESR]) 1 year after operation.

Patients, materials, and methods

Patients and study design

All patients fulfilled the American College of Rheumatology 1987 revised criteria for the diagnosis of RA [8]. We included total arthroplasties, performed consecutively from 2002, on knees, hips, elbows, and ankles, i.e., large joints, in patients being treated with anti-TNF agents. These agents included IFX, etanercept (ETN; including a clinical trial case, TNR001), and adalimumab (ADA). We predominantly included primary total arthroplasties, along with two revisions; total elbow arthroplasty (TEA) and total hip arthroplasty (THA). Neither of these two revisions presented with infection. Patients with only minor RA orthopedic operations, such as forefoot or wrist operations, were excluded from this study because such minor operations do not involve the excision of much synovium or degenerated cartilage. All patients required at least 1 year postoperative follow-up. Additional data recorded included: gender; age; RA duration; duration of use of anti-TNF agents; Steinbrocker Stage and Class; operations performed; the anti-TNF agents used; doses of methotrexate (MTX) and prednisolone (PSL) administered at baseline (just before the operation); DAS28-ESR at baseline, at 1 year before the operation (excluding the loading period, i.e., the maximum possible period when the duration between the start of anti-TNF agent therapy and the operation was less than 1 year), and at 1 year after the operation; and C-reactive protein (CRP), ESR, and matrix metalloproteinase-3 (MMP-3) at baseline and at 4 and 12 weeks and at 1 year after the operation. We permitted switching, adding, and dosage modifications of all drugs during this period. However, we excluded from our analysis non-responders and patients who dropped out within 1 year after the operation because they exhibited adverse events or secondary reductions in efficacy. After the exclusion criteria were applied, our study cohort consisted of 45 patients (35 knees, 19 hips, 3 elbows, and 1 ankle) who underwent TKA, THA, TEA, or total ankle arthroplasty (TAA) while being treated with anti-TNF agents between August 2002 and November 2009 at our institute. The resting periods for the anti-TNF agents, according to the guidelines of the Japanese College of Rheumatology [9], were 4 weeks before and after the operation for IFX and 2 weeks before and after the operation for both ETN and ADA. We performed as many synovectomies and cartilage excisions as possible at the time of the operations.

Finally, to evaluate the DAS28-ESR after the surgical procedures, we divided all 58 arthroplasties in the 45 patients into 2 equal groups ($n = 29$, each) based on the median values of certain characteristics at baseline, including CRP, MMP-3, age, RA duration, anti-TNF duration, tender joint count (TJC), and swollen joint count (SJC).

Statistical analysis

Data are expressed as means ± standard deviation. Postoperative values of CRP, ESR, MMP-3, and DAS28-ESR were compared to baseline values using paired *t*-tests. Within the baseline patient characteristics, the Mann–Whitney *U*-test was used to evaluate the significance of differences in continuous variables, and Fisher's exact test was used for proportions. $P < 0.05$ was considered to be significant.

Results

Forty-five RA patients (male 8, female 37; mean ± SD age, 57.91 ± 12.74 years; mean ± SD RA duration, 13.43 ± 8.28 years; Steinbrocker Stage III: 15, IV: 30, Class 2: 14, 3: 31; % MTX use, 77.6; MTX dosage, 7.00 ± 1.90 mg/week; % PSL use, 58.6; PSL dosage, 5.04 ± 2.36 mg/day) and 58 joints were treated with various anti-TNF agents (IFX, 22; ETN, 33; including 2 cases of TNR001; and ADA, 3) during the study period (THA, 19; TKA, 35; TEA, 3; TAA, 1) (Table 1). All the operated joints showed high-grade destruction and synovitis.

All but one patient made a satisfactory postoperative recovery without surgical-site infection or delayed wound healing. One 68-year-old woman underwent right TKA

Table 1 Baseline (just before operation) characteristics of entire cohort ($n = 45$ patients, 58 operations)

Characteristics	
Gender	
Male	8
Female	37
% Female	82.2
Age at operation (years)	57.9 (12.7, 61.0, 55.0, 66.0)
RA duration (years)	13.4 (8.28, 12.0, 7.00, 18.8)
Biologics duration (months)	21.8 (16.6, 18.5, 12.0, 29.0)
Stage (Steinbrocker)	
% Stage III	33.3
% Stage IV	66.7
Class (Steinbrocker)	
% Class 2	31.1
% Class 3	68.9
Operations performed	
THA	19
TKA	35
TEA	3
TAA	1
Biologics	
IFX	22
ETN	33
ADA	3
% MTX use	77.6
Mean MTX dose (mg/week)	7.00 (1.90, 6.00, 6.00, 8.00)
% PSL use	58.6
Mean PSL dose (mg/day)	5.04 (2.36, 5.00, 3.50, 7.13)

Data are expressed as means (SD, median, 25th percentile, 75th percentile)

RA rheumatoid arthritis, *THA* total hip arthroplasty, *TKA* total knee arthroplasty, *TEA* total elbow arthroplasty, *TAA* total ankle arthroplasty, *IFX* infliximab, *ETN* etanercept, *ADA* adalimumab, *MTX* methotrexate, *PSL* prednisolone, *SD* standard deviation

while receiving IFX (RA duration of 33 years and IFX duration of 14 months) and experienced high fever just after the operation. We carried out wound debridement and synovectomy in combination with antibiotic treatment 4 weeks after the TKA and the infection subsided. The patient has received careful IFX therapy since that event. Including findings in this patient, the RA disease activity (DAS28-ESR) in almost all of the patients had improved 1 year after their arthroplasties.

In contrast with the finding that the mean DAS28-ESR values were unchanged from 1 year before the operation to the baseline (4.08 ± 0.89 and 4.32 ± 0.99, $P = 0.1496$), the mean DAS28-ESR values decreased dramatically from 4.32 ± 0.99 at baseline to 3.35 ± 0.93 at 1 year after the operation ($P = 0.0007$) (Fig. 1a), and the disease activity, estimated by DAS28-ESR classifications at baseline and at 1 year after operation, was attenuated (Fig. 1b). No procedures were performed within 14 weeks after the first IFX administration, i.e., during the loading period. Only 2 patients had their biologics switched after operations within this period; both patients were switched from IFX to ETN, at 4 and 24 weeks after their operations.

Average values of CRP, ESR, and MMP-3 in all operations improved relative to baseline in a time-dependent manner, and were lowest 1 year after the operation (Table 2). Improvement of CRP was statistically significant ($P = 0.016$).

To examine predictors of DAS28-ESR improvement, we divided all 58 operations in the 45 patients into 2 groups according to median values of CRP, MMP-3, age, RA duration, anti-TNF duration, TJC, and SJC at baseline, denoted as the high and low groups, and then we evaluated differences between these 2 groups in the DAS28-ESR at 1 year after operation in detail. The differences in the DAS28-ESR between the low and high groups were statistically significant only for CRP [3.00 ± 0.74 vs. 3.83 ± 0.99 ($P = 0.014$)] and MMP-3 [2.95 ± 0.72 vs. 3.80 ± 0.96 ($P = 0.023$)].

In evaluating the median split of CRP and MMP-3 at baseline, both groups contained the same breakdown of cases. For MMP-3, the baseline characteristics of the 2 median-split groups (136 ng/ml) were similar in gender, age, duration of use of anti-TNF agent, Steinbrocker Stage and Class, number of operations performed, anti-TNF agents being used, % of MTX use, % of PSL use, and doses of MTX administered. However, the RA duration was longer in the low MMP-3 group than that in the high MMP-3 group (16.9 ± 9.09 vs. 9.97 ± 5.67 years, $P = 0.0005$), and the mean PSL dosage (mg/day) was lower in the low MMP-3 group as well, (3.96 ± 2.03 vs. 5.80 ± 2.31, $P = 0.0102$).

Table 3 shows the DAS28-ESR for the low and high groups ($n = 29$, each) at baseline and at 1 year after operation, divided using a median split of CRP and MMP-3 at baseline; the differences in the DAS28-ESR between the groups were statistically significant: low group of CRP, 3.93 ± 0.87 and 3.00 ± 0.74 ($P = 0.0026$), high group of CRP, 4.96 ± 0.84 and 3.83 ± 0.99 ($P = 0.0100$), low group of MMP-3, 3.97 ± 0.92 and 2.95 ± 0.72 ($P = 0.0028$), high group of MMP-3, 4.65 ± 0.97 and 3.80 ± 0.96 ($P = 0.0260$). Interestingly, the mean DAS28-ESR in the low groups for both CRP and MMP-3 reached less than 3.2, representing low disease activity. Also, the percentages of remission or low disease activity in the low group exceeded those in the high group 1 year after the operations (70.0 vs. 11.1% in the CRP group, $P = 0.0036$; and 60.0 vs. 22.2% in the MMP-3 group, $P = 0.0532$).

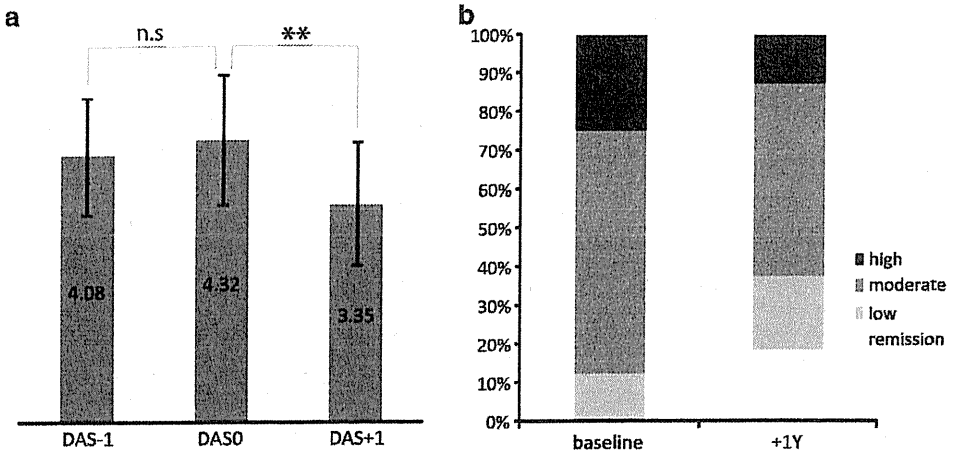

Fig. 1 **a** Average disease activity scores in 28 joints (DAS28-ESR) in all registered patients, all of whom were treated with anti-tumor necrosis factor (TNF) agents ($n = 45$ patients, 58 operations) at 1 year before the operation (*DAS-1*), at baseline (just before the operation; *DAS0*), and at 1 year after the operation (*DAS + 1*) (figure is a *bar graph* showing the standard deviation value for each mean). *n.s* Not significant. $^{**}P < 0.01$. **b** Disease activity for all patients (%) at baseline and at 1 year (*Y*) after the operation, estimated by DAS28-ESR

Discussion

In the new ACR/European League Against Rheumatism (EULAR) classification criteria in 2010, there is a focus on small joints [10] because generally these joints tend to be attacked in RA. Using these criteria, we can improve the detection of early RA and allow aggressive treatment under "treat-to-target" paradigms [11]. However, RA is a disease that also attacks large joints, and reductions in the activities of daily living (ADL) generally result after the destruction of large rather than small joints.

Although anti-TNF drugs are now widely used, there are still many patients whose disease activities cannot be kept at a low level. In addition, there are many RA patients who suffered extensive disease before anti-TNF therapies became available; and similarly, higher disease activity can be found in patients whose disease onset occurred when they were already elderly and their joints had already undergone changes due to osteoarthritis, or patients whose disease control was poor for a long time and thus led to damaged joints.

Anti-TNF agents have been reported to show effects on joint destruction, sometimes including the "repair" of joint erosion and radiographic inhibition [12, 13]. However, this assessment of joint damage is mainly limited to studies of small joints in the hands and feet, and in these studies the effect of treatment with anti-TNF agents on large joints was unclear. Patients can possibly endure the pain in small non-load-bearing joints, but the pain in large load-bearing joints such as the knee or hip can be severe; hence, early pain reduction is needed. Once problems with these joints have become progressively worse, sharp pain and functional problems may not improve even if inflammation of the joints has been suppressed by strong drug therapy.Hip and knee joints with pre-existing damage have shown disease progression even in patients with a good response to TNF blockers [14]. In such cases, a combination of surgical management with strong medical therapy may be effective [15]. From this perspective, the unsatisfactory decrease in the DAS28-ESR scores of our patients before their operations may be attributed to the presence of painful, destroyed large joints; long duration of RA; and the limited plateau state of response to TNF therapy after an initial responsive phase. Therefore, additional treatment apart from pharmacological treatment with TNF blockers may be required in such patients.

Excellent clinical results have been reported for total arthroplasty in RA [16]. However, evaluation of the effect of total arthroplasty has been discussed only with reference to the operated joints, and no studies evaluating RA disease activity after total arthroplasty in patients using biologic agents have been reported. Thus, this is the first study reporting the effect of total arthroplasty on RA systemic disease activity in patients using biologic agents. Some researchers have stated that RA disease activity was attenuated further after synovectomy in RA patients in whom IFX-induced attenuation of disease activity was observed [4]. We therefore hypothesized that the effect of total arthroplasty would be greater than that of synovectomy, due to complete surgical removal of not only the synovial tissues but also the denatured chondrocytes. Therefore, in the present study, we included only large-joint arthroplasty because we could then remove a large quantity of synovium and denatured cartilage. Only two revisions were included. These patients had active synovitis that extended over a large area, although cartilage had already been resected in the initial operation.

Except for the case of the 68-year-old woman mentioned above, no infection or delay in wound healing occurred in

Table 2 Values of CRP, ESR, and MMP-3 in entire cohort taking TNF blockers ($n = 58$ operations) at baseline, and at 4, 12, and 52 weeks after operations

	Baseline	4 Weeks	12 Weeks	52 Weeks
CRP (mg/dl)	1.71 (2.48, 0.52, 0.12, 2.48)	1.72 (2.35, 0.61, 0.21, 2.17)	1.28 (2.03, 0.45, 0.09, 1.34)	0.90* (1.08, 0.37, 0.07, 1.62)
ESR (mm/h)	40.3 (28.8, 38.0, 14.5, 58.3)	44.8 (25.9, 40.0, 25.5, 61.5)	39.1 (25.7, 41.3, 17.0, 56.5)	34.4 (23.0, 37.4, 18.0, 47.2)
MMP-3 (ng/ml)	231 (242, 136, 87.9, 312)	181 (175, 110, 65.6, 256)	198 (210, 117, 72.2, 251)	166 (146, 95.5, 65.5, 256)

Data are expressed as means (SD, median, 25th percentile, 75th percentile)

CRP C-reactive protein, *ESR* erythrocyte sedimentation rate, *MMP-3* matrix metalloproteinase-3, *TNF* tumor necrosis factor

* Denotes significant difference from baseline; $P < 0.05$

other patients/operations in the present study, presumably due to the use of preventive antimicrobial treatment for 3 days. Of course, safety is paramount, and with regard to operations in patients treated with anti-TNF agents, surgical-site infections are a serious problem. Some studies have concluded that anti-TNF agents are unrelated to infection during the perioperative period in orthopedic surgery [17–19]; conversely, other studies have found a strong relationship between these agents and such infection [20, 21].

We believe that the decreases in MMP-3 values at 4 weeks after operation relative to baseline were due to the effects of synovectomy and the excision of denatured cartilage in the total arthroplasty (Table 2). A small but surprising increase in MMP-3 values occurred 12 weeks after the operation, though we had expected MMP-3 values to continue to decline. We can say that even if the synovium and degenerative cartilage are completely resected by total arthroplasty, only the synovium would temporarily re-grow after the operation and produce MMPs. In this study, however, MMP-3 values had decreased at 1 year after the operation, and this may be because synovitis occurring after surgical intervention is not permanent.

In the present study, we observed the effect of total arthroplasty on systemic disease activity in RA patients who were all using anti-TNF agents. Subanalyses indicated that regardless of the presence of high or low CRP or MMP-3 at baseline, the DAS28-ESR had decreased 1 year after the operation (Table 3). In spite of the already low DAS28-ESR at baseline in the low CRP and MMP-3 groups, changes in DAS28-ESR between baseline and the 1-year postoperative follow-up in the low groups were similar to those found in the high groups, and the mean values of disease activity were low (<3.2) (Table 3). Thus, the data cumulatively suggest that there are strong advantages in total arthroplasty not only for those patients whose disease activity remains high but also for those whose disease activity is already low, because these patients with disease that is well controlled by anti-TNF agents may achieve even lower disease activity without painful joints by total arthroplasty.

Our patients generally had less improvement in their DAS28-ESR compared to those reported by Kanbe and Inoue [4]. The reason for this may be that we included consecutive patients; in other words, we did not exclusively study only those patients who experienced a flare in RA activity or those who had symptoms of high disease activity. We also included patients with low and moderate disease activity at baseline. Conversely, our data may show the effects of total arthroplasties in patients using anti-TNF agents in an actual clinical setting.

The limitations of this study are as follows: small sample size; ignorance of the influence of clinical interventions such as a switch in disease-modifying anti-rheumatic drugs (DMARDs) after operations; the lack of

Table 3 DAS28-ESR in low and high groups stratified by medians of CRP and MMP-3 at baseline

	Median	Group	DAS0	DAS + 1	DAS + 1 < 3.2 (%)
CRP	0.52 (mg/dl)	Low	3.93 (0.87, 3.89, 3.27, 4.20)	3.00** (0.73, 2.99, 2.42, 3.64)	70$^{\#\#}$
		High	4.96 (0.84, 5.17, 4.38, 5.66)	3.83* (0.99, 3.53, 3.28, 4.35)	11.1
MMP-3	136 (ng/ml)	Low	3.97 (0.92, 3.73, 3.27, 4.16)	2.95** (0.72, 2.99, 2.35, 3.48)	60
		High	4.65 (0.97, 4.65, 4.04, 5.57)	3.80* (0.96, 3.74, 3.30, 4.18)	22.2

Data are expressed as means (SD, median, 25th percentile, 75th percentile)

DAS disease activity score, *DAS0* DAS28-ESR just before operation, *DAS + 1* DAS28-ESR 1 year after operation

* $P < 0.05$, ** $P < 0.01$ Denotes significant difference from baseline

$^{\#\#}$ $P < 0.01$ Denotes significant difference from high group

separation of MMP-3 values in males from those in females; and the retrospective cohort. Our study had no control group, but Yano et al. [15], in their study with a control group, reported that the postoperative DAS28-ESR after 3 years had decreased from 4.85 to 3.97 in their sample of 130 TKAs performed for patients with established RA, most of whom used DMARDs. While their cases do not completely match with ours, our finding of an average decrease in the DAS28-ESR from 4.32 to 3.35 was superior to theirs. In addition, we examined the DAS28-ESR 1 year before the operation and observed that the mean DAS28-ESR values remained unchanged for that year despite the patients maintaining the same anti-TNF therapy. This unchanging DAS28 value may have been due to temporary disease control in these patients.

In conclusion, the present findings suggest that total arthroplasty for RA in patients using anti-TNF agents is effective not only for the restoration of damaged joints but also for its systemic RA disease-attenuating activity.

Conflict of interest None.

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ORIGINAL ARTICLE

Early aggressive intervention with tocilizumab for rheumatoid arthritis increases remission rate defined using a Boolean approach in clinical practice

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Abstract The goal of treating rheumatoid arthritis (RA) should be remission, for which a new definition was proposed in 2011. To determine which patients can achieve the new Boolean-based definition of remission in clinical practice, we analyzed factors associated with remission in 123 patients who received tocilizumab for 52 weeks. We found that patients with short disease duration (<4.8 years) had a significantly higher rate of remission (31.7%) than those with longer disease duration, and patient global assessment was the most important factor for achieving remission. Multivariate analysis revealed the following predictors of remission: short disease duration [<4.8 years; odds ratio (OR) 2.5, 95% confidence interval (CI) 1.4–4.7] and lower disease activity [28-joint disease activity score–erythrocyte sedimentation rate (DAS28-ESR) <5.23; OR 2.5, 95% CI 1.2–5.1). In this study, we showed that remission, as newly defined using a Boolean approach, is a realistic goal for patients treated with tocilizumab with short disease duration in real-world clinical practice.

Keywords Rheumatoid arthritis · Remission · Tocilizumab · Patient-reported outcome · Interleukin 6

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Introduction

The goal of treating rheumatoid arthritis (RA) is remission [1]. Clinical trials report that early intervention is associated with better outcomes for patients treated with biologics [2–4]. Accordingly, early intervention is recommended by the European League Against Rheumatism (EULAR) and American College of Rheumatology (ACR) [5, 6]. Remission is now defined using a Boolean approach [swollen joints ≤1, tender joints ≤1, C-reactive protein (CRP) ≤1 mg/dl, and patient global assessment ≤1 cm on a 10-cm visual analog scale (VAS)] or index-based definition [Simplified Disease Activity Index (SDAI) <3.3] [7]. Because treatments should be evaluated based on these criteria for remission, it is important to know whether this is a realistic goal in real-world clinical practice.

Tocilizumab, a humanized monoclonal antibody that binds to and inhibits the interleukin-6 (IL-6) receptor, was approved in 2008 in Japan. The efficacy of tocilizumab for RA was demonstrated in several clinical trials [8–11], and its effectiveness in clinical practice is under investigation [12]. We focused on the importance of short disease duration at initiation of aggressive treatment with tocilizumab for achieving new remission (Boolean approach) in actual clinical practice.

Methods

Tsurumai Biologics Communication Registry

A new registry of patients starting treatment with biologics in 2008, named Tsurumai Biologics Communication (TBC), was developed to explore the long-term prognosis of treatment with biologics in clinical practice. Data were collected prospectively from 2008, as well as retrospectively for patients who had been treated with biologics up until 2008. This study was approved by the Ethics Committee of Nagoya University, School of Medicine. Patient anonymity was maintained during data collection, and the security of personal information was strictly controlled. All patients (n = 134) who underwent tocilizumab treatment between May 2008 and September 2009 at Nagoya University Hospital and 12 other institutes (Tsurumai Biologics Communication Study Group) and were registered in Tsurumai Biologics Communication Registry (TBCR) were enrolled. All patients analyzed in this study were registered in TBCR prospectively.

All patients met the 1987 ACR classification criteria for RA. Tocilizumab (8 mg/kg) was infused every 4 weeks according to the drug label and the Japan College of Rheumatology guidelines for tocilizumab therapy. Demographic data, including disease duration, concomitant treatments (methotrexate and prednisolone), joint damage (Steinblocker stage), and daily dysfunction (Steinblocker class) were recorded at the initiation of treatment (baseline). The following parameters were recorded at baseline and 52 weeks later: tender joint count (TJC) on 28 joints, swollen joint count (SJC) on 28 joints, patient global assessment of disease activity [VAS–general health (VAS-GH)], erythrocyte sedimentation rate (ESR), and serum CRP levels. We evaluated remission at 52 weeks using the 2011 definition of remission developed for use in RA clinical trials (Boolean approach) as well as the 28-joint disease activity score (DAS28)-ESR definition of remission. We analyzed baseline characteristics to determine those associated with remission.

Statistical analyses

Continuous variables are expressed as mean ± standard deviation (SD) and categorical variables as percentages. We categorized patients into three groups based on tertile values of disease duration: short (<4.8 years), medium (<12 years), and long (>12 years). We evaluated differences in patient characteristics among the groups using the Kruskal–Wallis test for continuous variables and chi-square test for categorical variables. For cases in which tocilizumab therapy was discontinued, the last observation carried forward method was used. To determine predictors of Boolean-defined remission, we performed univariate followed by multivariate logistic regression analyses in which we dichotomized age, DAS28-ESR, and serum CRP levels based on lowest tertile values. All data were analyzed using JMP version 8.0 (SAS Institute Japan, Tokyo, Japan). $P < 0.05$ was considered significant.

Results

Of 134 patients, 11 who moved while undergoing tocilizumab therapy were excluded from the analysis because we were unable to determine the final treatment status within 52 weeks. Nineteen patients discontinued treatment and were included in the analysis using the last observation carried forward method. We thus analyzed results for 123 patients. Of 19 patients who discontinued treatment, five cases were in the short-duration (insufficient effectiveness n = 2; adverse event n = 1; patient convenience n = 2); six in the medium-duration (adverse events n = 3; inadequate response n = 2; pregnancy n = 1); and eight in the long-duration (adverse events n = 7; insufficient effectiveness n = 1) groups. Baseline characteristics of the 123 patients are shown in Table 1 by patient group. There was a significant difference in the proportion of those with low joint damage grade (Steinblocker stage I and II; short