in only two (9.5 %) patients (peak values 14.4 and 32.7 pg/ml, respectively). The patient with a peak value of 14.4 pg/ml developed PCP with the simultaneous elevation of serum KL-6 and BDG levels. In J-RAPID, of 32 patients who met criterion B by week 52, only 3 (9.4 %) patients (peak values 11.5, 12.3, and 18.1 pg/ml, respectively) showed abnormal, but modest, elevations of serum BDG levels that were observed in parallel with an elevation of serum KL-6 levels. These data and the favorable clinical courses of these patients indicate that the possibility of subclinical PCP was quite low in the majority of patients meeting criterion B.

Some important clinical questions arise from our findings. First, do we have to stop treatment with TNF inhibitors in RA patients with elevated serum KL-6 levels? The answer is no. We should search for reasons for the elevation, such as PCP, IP, and malignancy, as the first step, but when these adverse events are not identified, continuing treatment with TNF inhibitors under careful observation is a reasonable option for RA patients who have shown good response to the treatment. Second, is it worthwhile to monitor KL-6 every 4 weeks during treatment with TNF inhibitors? When we used criterion B to define the elevation of serum KL-6 levels, KL-6 had low positive predictive values for PCP and IP in RISING (5.9 %), HIKARI (14.3 %), and J-RAPID (0 %) and high negative predictive values (99–100 %) in all three trials. However, in these studies, there were only three PCP and three IP patients among those who met criterion B and three IP patients among those who did not met criterion B; there is, therefore, a possibility that more stringent criteria would have better predictive abilities for these adverse events. To clarify the usefulness of monitoring KL-6 serum levels during treatment with TNF inhibitors, a specifically designed clinical study is required. Therefore, we cannot provide a definite answer for the second question from our present analysis.

The potential contribution of concomitant MTX to the elevation of serum KL-6 levels in RA patients given TNF inhibitors should be mentioned. When we combined the MTX + placebo groups from J-RAPID and GO-FORTH, 3 (2.0 %) of 149 patients given MTX + placebo met criterion B by week 24 or 28 without associated pulmonary events. In our retrospective study [22], 5 (10.6 %) of 47 RA patients given MTX without biological DMARDs met criterion B, and 4 of these (8.5 %) did not have any clinical reasons for the elevation of serum KL-6 levels. These data indicate that we should consider a potential contribution of MTX to the elevation of serum KL-6 levels during treatment with TNF inhibitor + MTX.

The mechanisms of the elevation of serum KL-6 levels in RA patients given TNF inhibitors remain to be determined. Little is known about the molecular mechanisms of KL-6 expression and its transport mechanism through the alveolar–capillary barrier. Further studies are required to clarify the roles of TNF in these processes in both physiological and pathological conditions.

In summary, the transient elevation of serum KL-6 levels in patients meeting criterion B, without accompanying specific clinical events, was observed in 6.8–15.6 % of RA patients treated with TNF inhibitors by year 1 in five clinical trials. Continuing treatment with TNF inhibitors under careful observation is a clinically reasonable option when serum KL-6 levels rise.

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JAPANESE GUIDELINE FOR THE MANAGEMENT OF HYPERURICEMIA AND GOUT: SECOND EDITION

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□ *Gout is a urate deposition disease caused by persistent hyperuricemia. Because gout patients present with a variety of clinical symptoms, it is necessary to have a guideline for the standard management and care of gout and hyperuricemia. The Japanese Society of Gout and Nucleic Acid Metabolism, a scientific society committed to study nucleic acid metabolism and related diseases, established the first edition of the "Guideline for the Management of Hyperuricemia and Gout" in 2002, and published the revised version in January 2010. This second edition is not only evidence based on a search of systemic literature, but also includes consensus levels by a Delphi exercise to determine the strength of the recommendations. A draft version of this guideline was reviewed by internal and external reviewers as well as a patient. In this guideline, key messages from each chapter are listed as statements together with the evidence level, consensus level, and strength of the recommendation. In this proceeding, several selected chapters on the clinical management of gout and hyperuricemia are described. We hope this guideline is appropriately used for the standard management and care of patients with hyperuricemia and gout in daily practice.*

Keywords Guideline; gouty arthritis; hyperuricemia

INTRODUCTION

Gout is a urate deposition disease caused by persistent hyperuricemia. Because gout patients present with a variety of clinical symptoms, including acute arthritis, urinary stones, chronic kidney disease, and metabolic syndromes, they are often treated by physicians from a variety of subspecialties; thus, it is necessary to have a guideline for the management of gout and hyperuricemia. For this purpose, the Japanese Society of Gout and Nucleic Acid Metabolism, a scientific society established to study nucleic acid metabolism and related diseases, published the first edition of the "Guideline for the Management of Hyperuricemia and Gout" in 2002. Since its publication, additional data concerning the management of hyperuricemia

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and gout have accumulated, and the circumstances surrounding the clinical guidelines have also changed. Therefore, the Japanese Society of Gout and Nucleic Acid Metabolism established a committee to revise the guideline (Chairman: Hisashi Yamanaka, M.D.) in 2006. The committee actively collected data related to hyperuricemia and gout and discussed the significance of this information in daily practice. Ultimately, the second edition was published in January 2010.

MATERIALS AND METHODS

The guideline revising committee collected clinical questions for the management of gout and hyperuricemia, and based on 41 clinical questions, a systematic literature search was conducted. From the results of this search, 492 articles were selected and reviewed by committee members, and recommendations for the management of gout and hyperuricemia were proposed as statements with evidence levels. Next, a Delphi exercise[1] was conducted to determine the consensus level of each statement, and the strength of the recommendations in each statement was determined based on both the evidence level and the consensus level.

Evidence Levels

- Evidence level 1a: Evidence obtained by a meta-analysis of randomized comparative trials (RCTs) and results obtained by multiple RCTs are almost consistent.
- Evidence level 1b: Evidence obtained by at least one RCT.
- Evidence level 2a: Evidence obtained by well-designed, comparative studies (nonrandomized), including prospective cohort studies.
- Evidence level 2b: Evidence obtained by well-designed, semi-empirical studies, including retrospective studies.
- Evidence level 3: Evidence obtained by well-designed, nonempirical, descriptive studies, including case control studies.
- Evidence level 4: Evidence obtained from case reports, noncontrolled studies, low-quality cohort studies, and cross-sectional studies.
- Evidence level 5: Evidence obtained by expert's reports/opinions/experience, etc.

Consensus Levels

Consensus levels were assessed using a seven-rank rating, wherein rank 1 indicated a full consensus; rank 4, neutral; and rank 7, no consensus.

Recommendation Levels

On the epidemiology/diagnosis of gout/hyperuricemia (Chapters 1 and 2):

- Recommendation level A: Based on strong evidence for certainty.
- Recommendation level B: Based on evidence for certainty.
- Recommendation level C: Based on no evidence for certainty.

On the therapy for gout/hyperuricemia (Chapters 3 and 4):

- Recommendation level A: Therapy is strongly recommended.
- Recommendation level B: Therapy is recommended.
- Recommendation level C: Therapy may be considered for certain cases.

The consistency of the contents of this guideline with those of other guidelines was reviewed and confirmed by liaison members of the committee. A draft version of this guideline was reviewed by trustee members of the Japanese Society of Gout and Nucleic Acid Metabolism, and subsequently, public comments were requested by external reviewers. Finally, the patient perspective was included based on the review of this guideline by a gout patient who works in the field of medical journalism. After these careful reviews, the Japanese Guideline for the Management of Hyperuricemia and Gout, second edition, was published in January 2010. The European League Against Rheumatism (EULAR) Standing Committee has published a recommendation for the management of gout[2,3]; however, a major difference between this guideline and the EULAR recommendation is that this guideline covers the management not only of gout but also of hyperuricemia.

RESULTS AND DISCUSSION

In this manuscript, the key messages from each chapter are listed together with the evidence level, consensus level, and strength of the recommendation. In this proceeding, several selected chapters on the clinical management of gout and hyperuricemia are presented.

Definition of Hyperuricemia

Statements:

1. Hyperuricemia is a major pathogenic factor for urate deposition diseases (gouty arthritis, renal disorder, etc.). It is defined as a disease condition in which patients have a serum urate level exceeding 7.0 mg/dL, regardless of sex and age—Evidence level 2a and Recommendation level B.

2. In women, the risks of lifestyle-related diseases increase with increases in the serum urate level, even when it is not more than 7.0 mg/dL. Examination for possible underlying diseases and lifestyle guidance should be given; however, drug therapy with urate-lowering drugs is not indicated—Evidence level 2a and Recommendation level B.

In the "Guideline for Therapy of Hyperuricemia/Gout (Version 2)", the significance of the serum urate level is evaluated from two viewpoints:

(1) Hyperuricemia as the cause of urate deposition diseases, such as gouty arthritis and renal impairment.
(2) Serum urate level as a clinically useful index (marker) of the pathology of various lifestyle-related diseases.

Hyperuricemia is a causative factor of urate deposition diseases, and the efficacy of therapeutic intervention has been confirmed. Hyperuricemia is a clear risk factor for gouty arthritis, the recurrence of which is suppressed by therapeutic interventions. Metabolic syndrome has attracted attention, and the results of an analysis focusing on the risks of cardiovascular diseases have demonstrated that a high serum urate level is also predictive of the onset of lifestyle-related diseases. However, the significance of urate in such pathologic conditions is unclear. Furthermore, reports indicating the improvement of these pathologic risks by therapeutic interventions are unavailable to date.

Taking these points into consideration, we suggest that attention should be given to the fact that the risks of lifestyle-related diseases increase with increases in serum urate level in both males and females, even if it is less than 7.0 mg/dL.[4] Examinations of potential diseases and lifestyle guidance are recommended at a lower serum urate level in females than in males. However, the risks increase linearly; thus, no clear threshold of serum urate level against the risk for diseases, including cardiovascular diseases, was determined. Also, urate-lowering drugs are currently not recommended for such cases (Figure 1).

Therapy of Gouty Arthritis/Gouty Tophus

Statements:

1) One tablet of colchicine (0.5 mg) is used in the aura phase of a gouty attack to stop further development of arthritis. In the case of frequent occurrences of gouty attacks, daily medication with one tablet of colchicine, "colchicine cover," is effective—Evidence level 3, Consensus level 1, and Recommendation level B.

2) Nonsteroidal anti-inflammatory drugs (NSAIDs) are effective in the acute phase of a gouty attack. NSAIDs are administered at a relatively high dose for a limited period to alleviate inflammation (NSAID pulse therapy). Accordingly, the occurrence of adverse drug reactions should be noted—Evidence level 3, Consensus level 1, and Advisability level B.
3) Oral corticosteroids are administered when NSAIDs cannot be administered, when NSAID administration is ineffective, or when polyarthritis occurs—Evidence level 1a, Consensus level 1, and Recommendation level A.
4) Since a gouty attack is exacerbated when the serum urate level is changed at the time of attack, in principle, medication with uric-acid-lowering drugs should not be initiated—Evidence level 3, Consensus level 1, and Advisability level B.
5) Surgical resection is considered necessary in the treatment of some cases of gouty tophus, but drug therapy is also necessary in such cases—Evidence level 3, Consensus level 1, and Recommendation level B.

A gouty attack is acute arthritis caused by urate crystals. Alleviating patients' pain and improvement of their quality of life (QOL) by appropriate therapy are the objectives of treatment.[5–7] In addition, the initiation of long-term therapy for hyperuricemia is important for patients who have

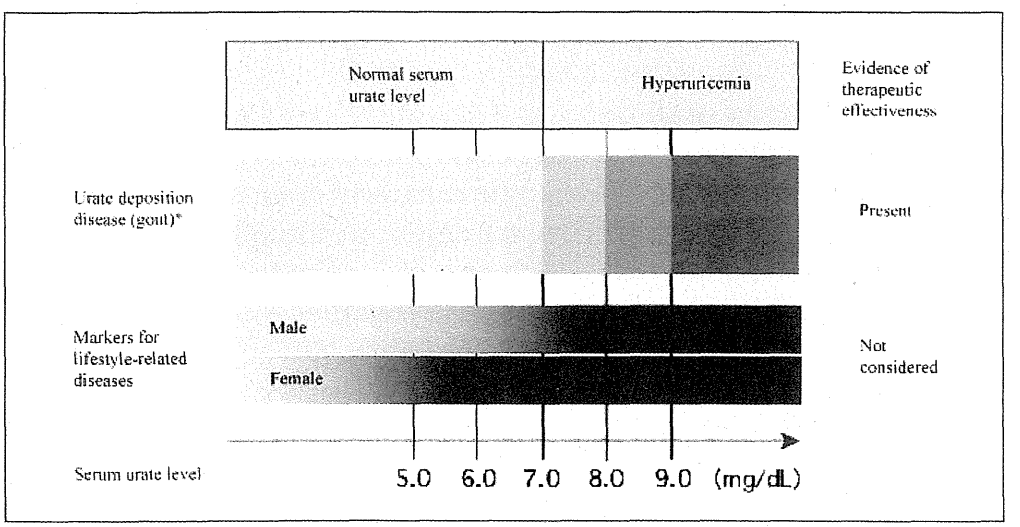


FIGURE 1 Definition of hyperuricemia.

experienced gouty attacks; however, quiescence of arthritis should not mean that therapy should be considered complete.

Therapy of Hyperuricemia

Therapeutic Goal

Statements:

1) The most important aim of treatment of hyperuricemia is to improve lifestyle changes that are related to the onset of hyperuricemia, in which prognosis-related complications, such as obesity, hypertension, glucose intolerance, and dyslipidemia, are prone to occur—Evidence level 2a, Consensus level 1, and Recommendation level A.
2) Urate-lowering therapy is indicated in patients with recurrent gouty arthritis or gouty tophi; thereby, it is desirable to maintain serum urate at a level of not more than 6.0 mg/dL—Evidence level 2a, Consensus level 1, and Recommendation level A.
3) Urate-lowering therapy may be indicated for asymptomatic hyperuricemia showing a serum urate level of not less than 8.0 mg/dL as a guide; however, it should be applied with caution—Evidence level 3, Consensus level 2, and Recommendation level C.

The elimination of urate deposited in body tissues due to sustained hyperuricemia and avoidance of urate deposition diseases, such as gouty arthritis, renal disorder, and so on, will become narrowly defined therapeutic goals for hyperuricemia. In addition, improvement in the prognosis for patients with hyperuricemia/gout with a high risk of cardiovascular events through improvements in lifestyle and attention to complications, such as obesity, hypertension, glucose intolerance, dyslipidemia, and so on, will become the ultimate therapeutic goal.

For the prevention of gouty arthritis recurrence by the removal of urate crystals through dissolution, serum urate should be maintained at a level of not more than 6.0 mg/dL. In the United States, where there are negative opinions regarding drug therapy for asymptomatic hyperuricemia without gouty arthritis or without gouty tophi, but with the serum urate level constantly exceeding 7.0 mg/dL, the number of patients with severe gout is greater than that in Japan; therefore, the treatment of asymptomatic hyperuricemia patients with a serum urate level higher than a certain concentration should be targeted for the prevention of gouty arthritis. Results of

a cohort study of healthy male subjects showed that the incidence of future gouty arthritis is significantly higher in those with a serum urate level exceeding 8.0 mg/dL, particularly 9.0 mg/dL, than in those with a lower serum urate level. Although this was a small-scale prospective clinical study, the results suggested that a decrease in renal function can be suppressed by administration of allopurinol in patients with renal failure.[8] Drug therapy aimed at renal protection with due attention to adverse drug reactions is also considered necessary for patients with serum urate higher than a certain level. Accumulated uric acid in the body will be difficult to dissolve by lifestyle adjustment only in patients with recurrent gouty arthritis or gouty tophi. Therefore, in such cases, it is desirable to use drug therapy to maintain the serum urate at a level of not more than 6.0 mg/dL.[9,10] For patients with a history of or with existing urinary calculus, the suppression of urinary uric acid excretion with allopurinol is necessary.

For asymptomatic hyperuricemia, a serum urate level of not less than 8.0 mg/dL is considered a criterion for the introduction of drug therapy in cases with complications, such as hypertension, ischemic heart disease, diabetes mellitus, and metabolic syndrome, which are considered risk factors for renal disorders, including urinary calculus, and cardiovascular disorders. However, the decision to initiate drug therapy should be based on current circumstances. Evidence obtained by intervention studies is currently limited, although observational studies have proven that the risk of cardiovascular disorders is heightened by high levels of uric acid in patients with such complications (Figure 2).

Therapy of Hyperuricemia Without Gouty Arthritis/Gouty Tophus (Asymptomatic Hyperuricemia)

Statements:

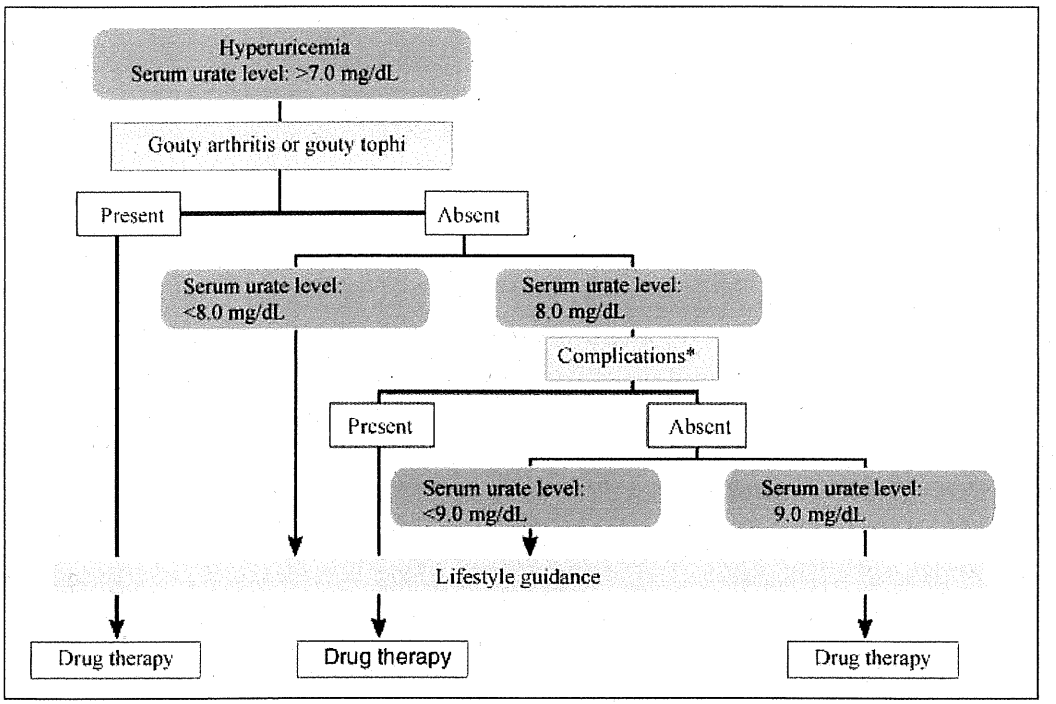
1) The serum urate level should be reduced in the asymptomatic stage of hyperuricemia to prevent the onset of gouty arthritis, gouty tophus, renal disorder, and urinary calculus, because hyperuricemia underlies these complications—Evidence level 3, Consensus level 2, and Recommendation level B.
2) Information and appropriate guidance considering lifestyle improvement, with the aim of reducing serum urate levels, should be provided; concrete instructions should be given to patients to avoid excessive consumption of alcoholic drinks, purines, fructose, sucrose, and calories, as well as to refrain from extreme exercises—Evidence level 3, Consensus level 1, and Advisability level A.

3) In cases of asymptomatic hyperuricemia with a serum urate level of not less than 9.0 mg/dL, drug therapy should be considered despite improvement in lifestyle. Further, drug therapy should be considered when the serum urate level reaches 8.0 mg/dL or more in cases with complications, such as urinary calculus, renal disease, hypertension, etc.—Evidence level 3, Consensus level 2, and Recommendation level B.

Hyperuricemia without clinical symptoms, such as gouty attack (acute gouty arthritis), gouty tophus, renal disorder, etc., is called "asymptomatic hyperuricemia."[11] It is desirable to reduce the serum urate level at this disease stage to prevent the onset of gouty arthritis, gouty tophus, renal disorder, and urinary calculus, which are caused by hyperuricemia as an underlying disease.

Guidance for improving lifestyle is important in decreasing the serum urate level. Particular attention should be given to alcohol and purine consumption and obesity.

There is a major difference in the management of asymptomatic hyperuricemia outlined in this Japanese guideline and that in Europe. In the



*Renal disorder, urinary calculus, hypertension, ischemic heart disease, diabetes, metabolic syndrome, etc. (No intervention studies were performed to consider decreasing events by lowering the serum uric acid level, except for renal disease and urinary calculus.)

FIGURE 2 Guidelines for therapy of hyperuricemia.

Japanese guideline, it is stated that asymptomatic hyperuricemia under certain conditions should be treated if lifestyle modification fails; on the other hand, in the United States and Europe, it is the general consensus that asymptomatic hyperuricemia should not be treated with drugs. Even if there is no large-scale comparative study to explore the beneficial effect of earlier intervention for asymptomatic hyperuricemia, it is noteworthy that the incidence of refractory gout and/or gouty tophi is much lower in Japan compared with that in Europe and the United States. Further study should be conducted to see whether this active management of asymptomatic hyperuricemia proposed in the Japanese guideline is beneficial for patients with hyperuricemia.

Treatments at Gouty Attack (Gouty Arthritis) and Interval Stage of Gout

Statements:

1) At the onset of gouty arthritis in untreated cases, gouty attack should be remitted by high doses of nonsteroidal anti-inflammatory drugs (NSAIDs) or NSAID pulse therapy, but not by urate-lowering drugs—Evidence level 2b, Consensus level 1, and Advisability level A.
2) The serum urate level should be reduced gradually to not more than 6.0 mg/dL over 3–6 months of drug therapy for hyperuricemia; thereafter, medication should be continued at the dose necessary to maintain serum urate at such a level—Evidence level 2b, Consensus level 2, and Recommendation level B.
3) Medication with urate-lowering drugs should be started at a low dose (benzbromarone: 12.5 mg, allopurinol: 50 mg) about 2 weeks after remission of gouty arthritis—Evidence level 2b, Consensus level 2, and Recommendation level B.
4) Concomitant administration of low-dose colchicine is recommended at an early stage after the start of administration of urate-lowering drugs for the prevention of gouty arthritis—Evidence level 1b, Consensus level 2, and Recommendation level B.
5) When gouty arthritis occurs after the administration of urate-lowering drugs at an appropriate dose, the concomitant use of NSAID pulse therapy according to the therapy of gouty arthritis, without discontinuation of urate-lowering drugs, is recommended—Evidence level 2b, Consensus level 2, and Recommendation level B.

Gouty attack is exacerbated by the change in serum urate level during gouty arthritis. Gouty arthritis often results from a drastic reduction in the serum urate level after the initiation of urate-lowering drugs.[12] Moreover,

hyperuricaciduria is caused by a drastic increase in uric acid excretion induced by uricosuric drugs, causing uric acid calculus and renal disorder. Accordingly, attention should be given to the means of administration of urate-lowering drugs.

After NSAID pulse therapy, remission of the attack should be awaited before the administration of urate-lowering drugs at the occurrence of gouty arthritis. From about 2 weeks after remission, urate-lowering drugs suited for the disease type should be selected; drug administration should be started at a low dose, and then the dose should be gradually increased. It is desirable to start with benzbromarone at 12.5 mg (25 mg tablet divided in half) or allopurinol at 50 mg (allopurinol 50 mg tablet, or 100 mg tablet divided in half). In addition, the onset of gouty arthritis can be prevented by concomitant administration of urate-lowering drugs with low-dose colchicine in the early stages after the start of administration.[5] A serum urate level of not more than 6.0 mg/dL, which is lower than the dissolution limit of uric acid in the body fluid (6.4 mg/dL), is set as a therapeutic goal. Thus, drug therapy over a period of 3–6 months is used to decrease the serum urate level gradually to not more than 6.0 mg/dL.

In addition, when gouty arthritis results from the administration of urate-lowering drugs, drug administration should be continued at the same dose with the concomitant use of NSAID pulse therapy according to the therapy of gouty arthritis. When the serum urate level does not reach the intended range, the dose of urate-lowering drugs should be increased gradually in the same manner from about 2 weeks after remission of gouty arthritis to keep the serum urate at a level of not more than 6.0 mg/dL. Thereafter, the dose of urate-lowering drugs should be continued so that the serum urate level is maintained at not more than 6.0 mg/dL.[9,10]

Therapy in Patients with Complications/Concurrent Diseases

Statements for the management of patients with renal disorder, urinary stones, hypertension/cardiovascular diseases, dyslipidemia, and metabolic syndrome are also listed in this guideline; however, because of the space limitations of this proceeding, these statements are not shown.

Lifestyle Intervention for Patients with Hyperuricemia/Gout

Statements:

1) Hyperuricemia and gout are lifestyle-related diseases. Education and proper guidance aimed at modifying the patients' lifestyle play a crucial role in improving the clinical course of the disease with or without drug therapy—Evidence level 2a, Consensus level 1, and Recommendation level B.

2) Lifestyle modification consists of three parts: nutrition therapy, restriction of alcohol consumption, and recommendation for physical training. Modest weight loss has been shown to reduce the serum urate level—Evidence level 2a, Consensus level 1, and Recommendation level B.
3) Nutrition therapy for hyperuricemia/gout includes appropriate consumption of calories and water and reduced consumption of dietary purines and fructose—Evidence level 2a, Consensus level 1, and Recommendation level B.
4) Patients with metabolic syndrome should be advised to perform physical activity to improve their clinical impairments—Evidence level 3, Consensus level 2, and Recommendation level C.

Lifestyle modification has an important role in improving the clinical course of hyperuricemia/gout based on the viewpoint that the diseases are typical lifestyle-related diseases.[13–16] The purposes of intervention are to motivate patients to self-correct their lifestyle by good contact with physicians and to help them resolve their lifestyle issues.

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ORIGINAL ARTICLE

Effectiveness and safety of adalimumab in Japanese patients with rheumatoid arthritis: retrospective analyses of data collected during the first year of adalimumab treatment in routine clinical practice (HARMONY study)

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Abstract We retrospectively investigated the ability of adalimumab (ADA) to reduce disease activity, improve physical function, and retard the progression of structural damage in 167 patients with rheumatoid arthritis. Clinical and functional outcomes were compared between patients with or without prior biologic treatment and those with or without concomitant methotrexate (MTX) treatment. At week 52, 38.3% achieved clinical remission: 42.4 and 28.6% of patients achieved remission in those without and with previous biologics, respectively, while 42.7 and 12.5% of patients achieved remission in those with and without concomitant MTX, respectively. ADA treatment significantly reduced the rate of radiographic progression from 27.1 ± 46.0 (median 13.6; 25th–75th percentiles 8.3 to 28.9) at baseline to 0.8 ± 5.0 (median 0.0; 25th–75th percentiles −0.9 to 2.0) at week 52 ($P < 0.0001$). Radiographic progression was absent in 59.8% of patients. Sixty adverse events (34.21/100 patient-years) were reported, 16 of which were serious (9.12/100 patient-years). ADA therapy is highly effective for reducing disease activity, improving physical function, and limiting radiographic progression. It is generally safe and well tolerated by Japanese RA patients in routine clinical practice.

Keywords Adalimumab · Japanese · Retrospective study · Radiographic outcome · Rheumatoid arthritis

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Introduction

Rheumatoid arthritis (RA) is characterized by progressive inflammatory synovitis and subsequent articular matrix degradation, which may result in joint destruction [1]. Disability and premature death result if the aggressive form of the disease goes untreated [2]. Over the last decade, management of RA has evolved radically because of the development of aggressive therapies for early stages of the disease and the advent of molecular targeted therapies [3, 4]. Although the pathophysiology of RA is not completely understood, tumor necrosis factor (TNF) plays a critical role in mediating the inflammatory synovitis, articular matrix degradation, and bony erosions in RA. Hence, TNF is recognized to be an important molecular target for directed biologic intervention [5].

Adalimumab (ADA) is a fully human immunoglobulin G_1 (IgG_1) monoclonal antibody with a high specificity for TNF-α [6]. ADA's efficacy and safety are well established both with and without concomitant methotrexate (MTX) treatment, based on randomized controlled clinical trials with RA patients conducted in Western countries [7–11]. In Japan, ADA was approved in 2008, making it the third TNF blocker to earn approval. Infliximab (a chimeric

monoclonal antibody to TNFα) [12] and etanercept (a recombinant human TNF receptor-Fc fusion protein) [13] were the first two TNF blockers to be approved. Recently, these biological agents have been reported to be effective and safe for Japanese RA patients encountered during routine clinical practice [14–17]. For ADA, the CHANGE study served as the bridging study for extrapolating data obtained for patients of Western origin to Japanese patients, in whom only the effects of monotherapy had previously been investigated [18]. However, the overseas clinical data obtained so far suggest that ADA monotherapy has only limited effectiveness compared to combination therapies with DMARDs, and in particular MTX.

Therefore, it is of clinical importance to further investigate the effects of ADA, particularly when it is administered concomitantly with MTX to Japanese RA patients. This study aimed to retrospectively investigate the clinical, functional, and radiographic responses to ADA as well as safety in Japanese RA patients encountered in routine clinical practice. This is the first study to evaluate the radiographic response to ADA in Japanese RA patients.

Patients and methods

Patients

Patients with available baseline components for the 28-joint Disease Activity Score based on erythrocyte sedimentation rate (DAS28-ESR) who started treatment with ADA between July 15, 2008 and June 15, 2009 at the following 4 medical institutions were enrolled in this study: (1) the Division of Rheumatology and Clinical Immunology, Department of Internal Medicine, Saitama Medical Center, Saitama Medical University, Saitama; (2) the Division of Rheumatology, Department of Internal Medicine, Faculty of Medicine, Keio University, Tokyo; (3) the First Department of Internal Medicine of the School of Medicine, University of Occupational and Environmental Health, Kitakyushu; and (4) the Institute of Rheumatology, Tokyo Women's Medical University, Tokyo. All of the patients satisfied the classification criteria of the American College of Rheumatology [19]. Information on patient characteristics was obtained from medical records and pooled for retrospective analyses; the demographic data included age, gender, disease duration, concomitant medications, co-morbidity, and other variables. For subanalyses, patients were divided into subsets based on whether they had or had not received the following: (1) previous biologic treatment; (2) concomitant MTX treatment at baseline.

This study was a retrospective observational study using anonymized information, and it conformed to the standard anti-TNF treatment guideline proposed by the Japan College of Rheumatology (JCR). Written consent was obtained from the patients according to the Declaration of Helsinki.

ADA treatment

ADA treatment was started in accordance with the Japan College of Rheumatology guidelines for adalimumab therapy [20]. We administered 40 mg ADA every other week, in keeping with the dosage instructions on the Japanese drug label. Concomitant use of MTX, disease-modifying antirheumatic drugs (DMARDs) other than MTX, and/or oral steroids was at the discretion of the attending physician. Dose adjustment was carried out according to standard medical practice for controlling disease activity.

Clinical efficacy

Disease activity was assessed using the DAS28-ESR [21]. Functional disability was assessed using the disability index of the Health Assessment Questionnaire (HAQ-DI) [22]. Radiographs of the hands/wrists and feet at baseline and at week 52 were available for 71 patients. The images were scored using van der Heijde's modified Sharp method [23] independently by 2 readers.

Safety

Safety was assessed based on the adverse events reported by patients as well as on the findings of physical examinations and standard clinical laboratory tests recorded from the start of July 15, 2008 through to the data cut-off date of June 15, 2010. All adverse events were summarized according to the Medical Dictionary for Regulatory Activities system organ class (MedDRA SOC) and reported as events per 100 patient-years. Adverse events judged to be serious by the attending physicians were individually listed.

Retention rate

Kaplan–Meier analysis was used to estimate retention rates during the first 52 weeks; 2 patients were excluded because their exact discontinuation dates were unknown. Reasons for discontinuation were categorized for all patients who withdrew at any time, even after 52 weeks.

Statistical analysis

Patient baseline characteristics were summarized using mean (standard deviation), median (interquartile range), or n (%), as appropriate, for the entire patient population and for patient subgroups stratified by previous use of biological agents (previous biologics + or −) and

concomitant use of MTX (concomitant MTX + or −). Demographic and baseline characteristics were analyzed using the Mann–Whitney U test for continuous variables and Pearson's chi-square test for discrete variables for the previous biologics (+) versus (−) and the concomitant MTX (+) versus (−) groups. For patients who withdrew before week 52, the last observation carried forward (LOCF) method, including baseline values, was employed to evaluate all efficacy parameters other than the radiographic endpoint. Missing radiographic values at week 52 were determined by linear extrapolation using data at baseline and at the last observation point (where available) if the patients had received ADA treatment for at least 180 days. Patients who withdrew before the 180th day of treatment were not considered in the calculation. The Wilcoxon signed rank test was used to detect statistically significant differences in disease activity and functional outcomes between baseline and week 52. The impact of previous biologic treatment or concomitant MTX treatment on the patient's response to ADA was examined using Pearson's chi-square test. Kaplan–Meier analysis was used to estimate retention rates during the first 52 weeks, and the difference in retention curves was examined by means of a log-rank test. All reported P values are two-sided and not adjusted for multiple testing. P values <0.05 were considered significant. Data were analyzed with StatView for Windows Version 5.0 (SAS Institute Inc., Cary, NC, USA).

Endpoints

Co-primary endpoints were the percentages of patients achieving remission, as defined by a DAS28-ESR of <2.6 at week 52, and of patients with no radiographic progression, as defined by a change in the total Sharp score (TSS) ≤0.5 from baseline to week 52. Other endpoints include the proportion of patients achieving functional remission (HAQ score ≤0.5) and safety.

Results

Baseline characteristics of the patients

A total of 167 patients for whom ADA therapy was initiated between June 2008 and June 2009 at the 4 medical institutions had all of the DAS28-ESR components at baseline. Baseline demographic and disease characteristics are summarized in Table 1. The mean age of all 167 patients included in this study was 58.4 years, and the majority of the subjects were women (82.6%). The mean duration of disease was 9.0 ± 9.5 years. The baseline mean DAS28-ESR and HAQ scores were 5.3 ± 1.3 (n = 167) and 1.24 ± 0.78 (n = 149), respectively. The initial mean TSS was 89.7 ± 83.1 (median 65.5; 25th–75th percentiles 36.0–115.0) (n = 87), and yearly progression before the initiation of ADA therapy was estimated to be 27.1 ± 46.0 (median 13.6; 25th–75th percentiles 8.3–28.9) (n = 87). Among the 167 patients, 118 (70.7%) were naïve to biologic treatment, whereas 49 (29.3%) had been treated with biologics prior to ADA. In total, 143 (85.6%) received concomitant MTX and 69 (41.3%) received concomitant oral steroid, with mean doses of 8.5 ± 2.9 mg/week and 4.8 ± 2.7 mg/day (prednisolone equivalents), respectively, at the beginning of ADA treatment. A comparison of the baseline demographics for different patient subgroups is provided in Table 1. When compared within subsets, patients who had received previous biologic therapy (+) were younger (P < 0.05) and had a more severe disease by stage (P < 0.05), a longer duration of disease (P < 0.05), and a higher rate and dose of concomitant prednisolone (P < 0.05 for both) than patients who had not received previous biologic therapy (−). The duration of disease was longer in the concomitant MTX (−) group than in the concomitant MTX (+) group (P < 0.05). Moreover, a higher proportion of the patients received concomitant prednisolone in the concomitant MTX (−) group than in the concomitant MTX (+) group (P < 0.05). The baseline yearly radiographic progression was greater in the previous biologics (−) group (28.9 ± 50.2) (median 13.2; 25th–75th percentiles 7.9–31.0) than in the previous biologics (+) group (18.3 ± 10.7) (median 14.0; 25th–75th percentiles 11.2–26.5), while it was greater in the concomitant MTX (+) group (28.7 ± 48.0) (median 14.0; 25th–75th percentiles 8.5–30.9) than in the concomitant MTX (−) group (11.1 ± 7.1) (median 10.2; 25th–75th percentiles 7.1–14.4). There were no differences in other baseline demographic and disease characteristics between the previous biologics (+) and (−) groups and between the concomitant MTX (+) and (−) groups.

Clinical efficacy of ADA

DAS28-ESR

Overall, the mean DAS28-ESR score decreased from 5.3 ± 1.3 at baseline to 3.5 ± 1.5 at week 52 (P < 0.0001 vs. baseline) (Fig. 1). In the previous biologics (+) and (−) groups, the mean DAS28-ESR scores decreased from 5.3 ± 1.2 to 4.0 ± 1.7 and from 5.3 ± 1.3 to 3.3 ± 1.4, respectively. Although the decreases were statistically significant in both previous biologics (+) and (−) groups, it was more substantial in the previous biologics (−) group (P < 0.0001 vs. baseline) than the previous biologics (+) group (P < 0.05 vs. baseline). Similarly, in the concomitant MTX (+) and (−) groups, the DAS28-ESR scores decreased from 5.3 ± 1.3 to 3.3 ± 1.4 (P < 0.0001 vs.

Table 1 Baseline characteristics of patients

Variables	Total ($n = 167$)	Previous biologics			Concomitant MTX		
		(+) ($n = 49$)	(−) ($n = 118$)	P value	(+) ($n = 143$)	(−) ($n = 24$)	P value
Age (years)	58.4 ± 13.0	55.1 ± 11.5	59.7 ± 13.4	<0.05	58.2 ± 12.9	59.1 ± 14.1	0.5560
Gender, n (% female)	138 (82.6)	43 (87.8)	95 (80.5)	0.2603	118 (82.5)	20 (83.3)	0.9222
Disease duration (years)	9.0 ± 9.5	9.9 ± 8.1	8.7 ± 10.0	<0.05	8.6 ± 9.5	11.8 ± 8.9	<0.05
Stage (I/II/III/IV %)	(15.0/33.5/ 18.6/32.9)	(10.2/24.5/ 16.3/49.0)	(16.9/37.3/ 19.5/26.3)	<0.05	(16.1/34.3/ 18.9/30.8)	(8.3/29.2/ 16.7/45.8)	0.4836
Class (I/II/III/IV %)	(11.4/74.3/ 14.4/0.0)	(12.2/69.4/ 18.4/0.0)	(11.0/76.3/ 12.7/0.0)	0.5953	(11.2/72.7/ 16.1/0.0)	(12.5/83.3/ 4.2/0.0)	0.3052
Prior use of biologics, n (%)	49 (29.3)	49 (100.0)	0 (0.0)	–	39 (27.3)	10 (41.7)	0.1518
RF positive, n (%)	158 (94.6)	46 (93.9)	112 (94.9)	0.7868	136 (95.1)	22 (91.7)	0.4900
MTX use, n (%)	143 (85.6)	39 (79.6)	104 (88.1)	0.1518	143 (100.0)	0 (0.0)	–
MTX dose (mg/week)	8.5 ± 2.9	9.9 ± 8.1	8.1 ± 3.0	0.2153	8.5 ± 2.9	0.0 ± 0.0	–
Oral steroid use, n (%)	69 (41.3)	26 (53.1)	43 (36.4)	<0.05	54 (37.8)	15 (62.5)	<0.05
Oral steroid dose (mg/day[a])	4.8 ± 2.7	5.7 ± 2.6	4.2 ± 2.6	<0.05	4.7 ± 2.6	4.9 ± 3.1	0.9590
MMP-3 (ng/mL[b])	297.6 ± 344.3	292.4 ± 250.7	299.8 ± 377.5	0.2757	312.3 ± 366.1	208.1 ± 127.9	0.7895
SJC, 0-28	6.5 ± 5.6	6.2 ± 6.2	6.6 ± 5.4	0.2307	6.3 ± 4.9	7.6 ± 8.8	0.6004
TJC, 0-28	7.3 ± 6.9	6.7 ± 6.8	7.6 ± 6.9	0.3585	7.4 ± 6.5	7.2 ± 9.1	0.1809
ESR (mm/h)	54.0 ± 31.3	54.4 ± 28.8	53.8 ± 32.4	0.7544	54.0 ± 31.4	53.6 ± 31.2	0.9582
CRP (mg/dL)	2.8 ± 3.9	2.9 ± 3.4	2.8 ± 4.1	0.4068	2.9 ± 4.1	2.3 ± 2.5	0.7391
GH, VAS 0–100 mm	50.7 ± 25.1	56.2 ± 24.5	48.4 ± 25.1	0.0932	49.6 ± 25.1	57.3 ± 25.1	0.1192
DAS28-ESR	5.3 ± 1.3	5.3 ± 1.2	5.3 ± 1.3	0.8398	5.3 ± 1.3	5.2 ± 1.5	0.6598
HAQ-DI[c]	1.24 ± 0.78	1.24 ± 0.85	1.25 ± 0.76	0.8833	1.24 ± 0.78	1.27 ± 0.84	0.8360
TSS[d]	89.7 ± 83.1	98.8 ± 66.0	87.9 ± 86.6	0.2757	88.9 ± 80.5	98.3 ± 112.5	0.6648
Median (IQR)	65.5 (36.0–115.0)	73.5 (52.5–141.5)	65.3 (32.6–109.6)		66.5 (39.8–113.3)	44.3 (22.0–153.5)	
Estimated YP (ΔTSS)[d]	27.1 ± 46.0	18.3 ± 10.7	28.9 ± 50.2	0.2795	28.7 ± 48.0	11.1 ± 7.1	0.1542
Median (IQR)	13.6 (8.3–28.9)	14.0 (11.2–26.5)	13.2 (7.9–31.0)		14.0 (8.5–30.9)	10.2 (7.1–14.4)	

Mean ± SD unless otherwise indicated

Demographic and baseline characteristics were analyzed by the Mann–Whitney U test for continuous variables and Pearson's chi-square test for discrete variables for previous biologics (+) versus (−) and concomitant MTX (+) versus (−)

RF rheumatoid factor, *MTX*, methotrexate, *MMP-3* matrix metalloproteinase 3, *SJC* swollen joint count, *TJC* tender joint count, *ESR* erythrocyte sedimentation rate, *CRP* C-reactive protein, *GH* patient's global assessment of disease activity, *VAS* visual analogue scale, *DAS* disease activity score, *HAQ-DI* health assessment questionnaire disability index, *TSS* total Sharp score, *YP* yearly progression, *IQR* interquartile range

[a] Prednisolone equivalents

[b] Total $n = 163$; previous biologics (+) $n = 48$; previous biologics (−) $n = 115$; concomitant MTX (+) $n = 140$; concomitant MTX (−) $n = 23$

[c] Total $n = 149$; previous biologics (+) $n = 41$; previous biologics (−) $n = 108$; concomitant MTX (+) $n = 131$; concomitant MTX (−) $n = 18$

[d] Total $n = 87$; previous biologics (+) $n = 15$; previous biologics (−) $n = 72$; concomitant MTX (+) $n = 79$; concomitant MTX (−) $n = 8$

baseline) and from 5.2 ± 1.5 to 4.6 ± 1.5 ($P < 0.05$ vs. baseline), respectively. In all groups, rapid improvement was achieved during the first 4 weeks of ADA treatment.

Figure 2 shows the percentages of patients who achieved different disease statuses (high, DAS28 > 5.1; moderate, 3.2 ≤ DAS28 ≤ 5.1; low, 2.6 ≤ DAS28 < 3.2; and remission, DAS28 < 2.6) over the time course of treatment. The percentages of patients who achieved clinical remission using the criterion of DAS28 < 2.6 were 31.7% at week 24 and 38.3% at week 52. At week 52, 28.6 and 42.4% of patients in the previous biologics (+) and (−) groups, respectively, achieved remission. The difference in the remission rate was more pronounced between the concomitant MTX (+) and (−) groups ($P < 0.01$) than between the previous biologics (+) and (−) groups ($P = 0.0948$) at week 52. In the concomitant MTX (+) group, the proportion of patients who achieved remission increased over time and reached 42.7% at week 52, while

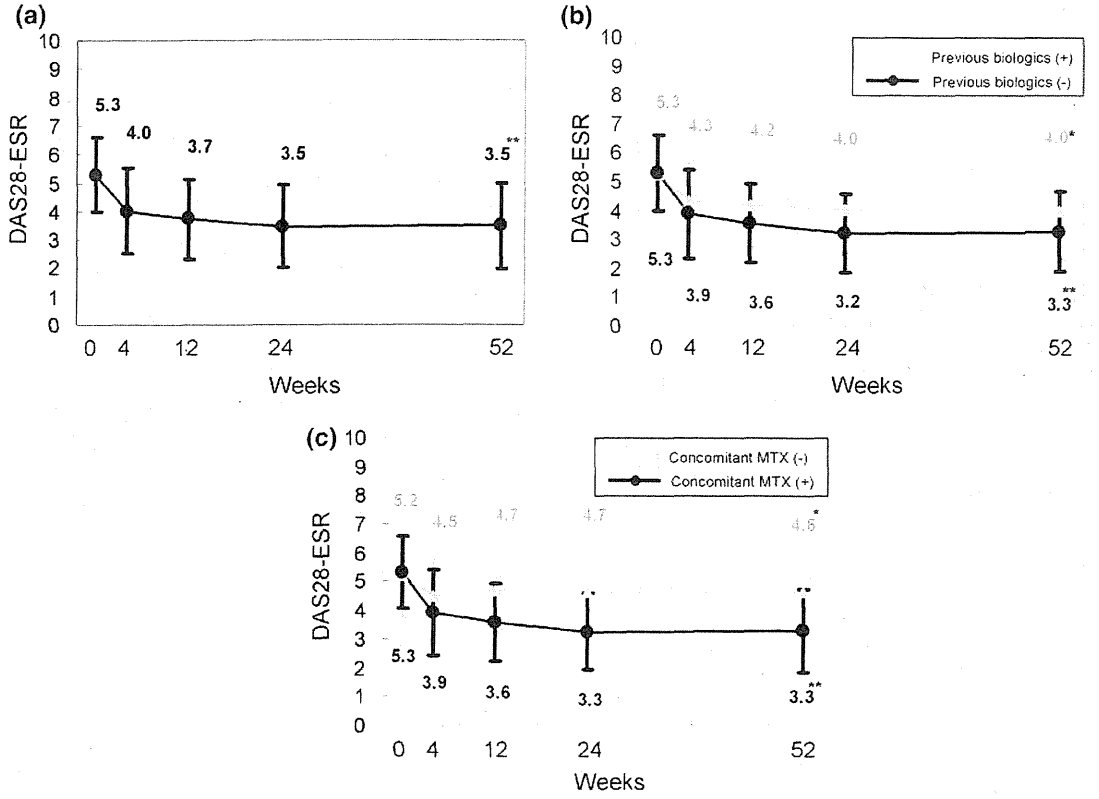

Fig. 1 Time course of the disease activity score over 52 weeks following the initiation of adalimumab treatment. Data were analyzed by the last observation carried forward (LOCF) method. *Points* and *bars* represent means and standard deviations, respectively. **a** All patients ($n = 167$), **b** previous biologics (+) ($n = 49$) and (−) ($n = 118$), **c** concomitant MTX (+) ($n = 143$) and (−) ($n = 24$). *$P < 0.05$ and **$P < 0.0001$ versus baseline by the Wilcoxon signed rank test

in the concomitant MTX (−) group, the baseline value shifted steadily around 12.5% after 4 weeks.

HAQ

The mean HAQ score of 1.24 ± 0.78 at baseline decreased to 0.92 ± 0.77 at week 52 (Fig. 3). The improvement was moderate but significant ($P < 0.0001$ vs. baseline). At week 4, the mean change was −0.22, which has been associated with meaningful clinical improvements and can be considered to represent the minimum clinically important difference (MCID) [24]. Although the baseline HAQ scores were comparable between the previous biologics (+) and (−) groups on average (1.24 ± 0.85 vs. 1.25 ± 0.76), patients without previous biologic therapy (−) showed a greater improvement than those with previous biologic treatment (+) (0.83 ± 0.72 vs. 1.16 ± 0.86) at week 52. In addition, the difference at week 52 was even more striking between the concomitant MTX treatment (+) and (−) groups (0.87 ± 0.75 vs. 1.29 ± 0.85). A significant improvement in the HAQ score as compared to baseline was detected only in the previous biologics (−) and concomitant MTX (+) groups ($P < 0.0001$ for both groups).

Figure 4 shows the time course of HAQ-DI categorized by increments of 0.5 units from 0.0 to 3.0. At baseline, 23.5% of all patients had HAQ scores ≤0.5, suggesting that about a quarter of the patients had normal function at the time of entry. At week 52, the percentage increased to 43.0%. Although in general the functional profile was consistently better in the previous biologics (−) group at all the time points, there was no difference in the percentage of patients with a HAQ score of ≤0.5 from the previous biologic (+) group at week 52 (44.4 vs. 39.0%, $P = 0.5506$). In the concomitant MTX (+) group, the proportion of patients with a HAQ score of ≤0.5 at baseline (22.9%) increased steadily and almost doubled to 45.0% at week 52. In contrast, there was no increase in the proportion of patients who did not receive concomitant MTX (−) at week 52 when compared to the baseline, though it was not significantly different from the concomitant MTX (+) group ($P = 0.1654$) at week 52.

Radiographic outcomes

Radiographic data at both the baseline and week 52 were available for 71 patients. Linear imputation was employed

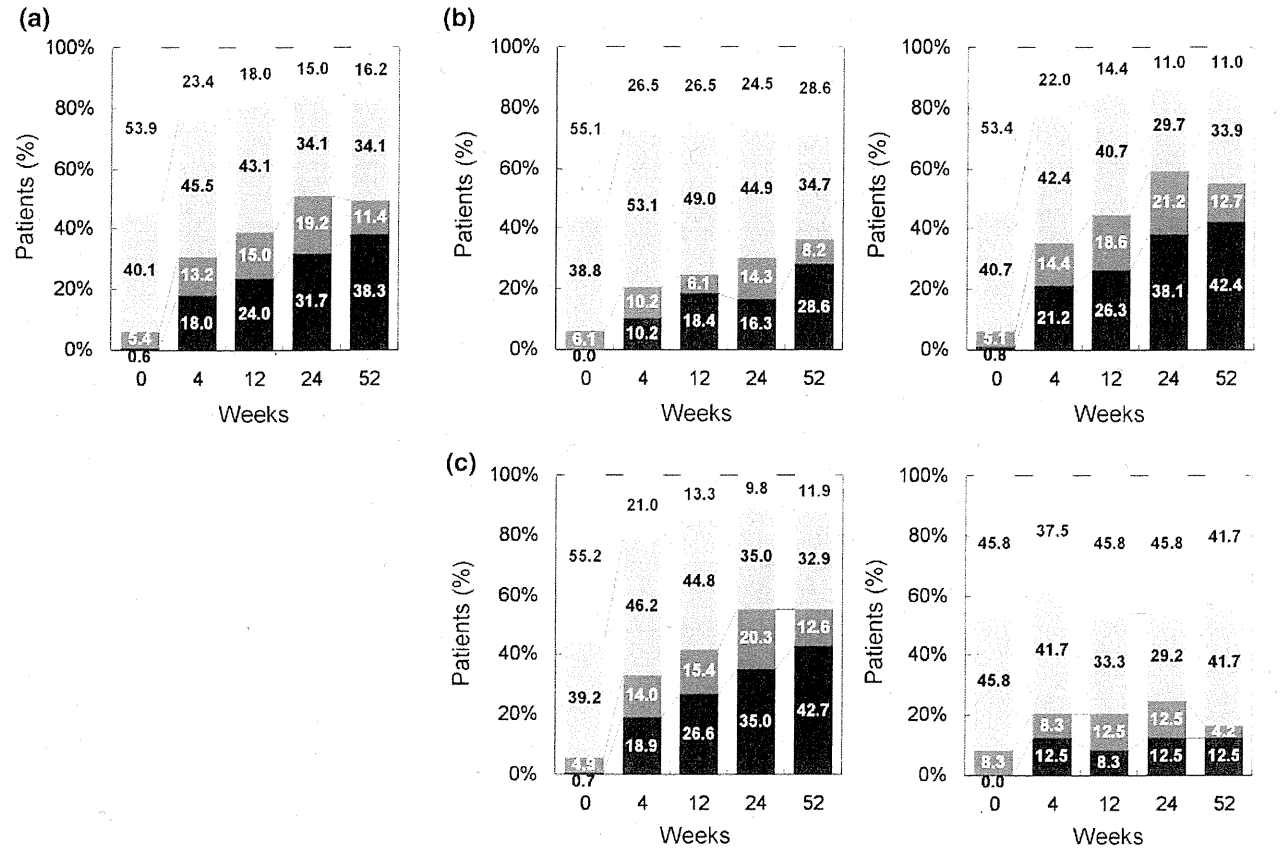

Fig. 2 Time course of disease activity over 52 weeks following initiation of adalimumab treatment. Data were analyzed by the last observation carried forward (LOCF) method. **a** All patients ($n = 167$), **b** previous biologics (+, *left*) ($n = 49$) and (−, *right*) ($n = 118$), and **c** concomitant MTX (+, *left*) ($n = 143$) and (−, *right*) ($n = 24$). Disease activity was categorized as follows

- 5.1 < DAS28-ESR
- 3.2 ≦ DAS28-ESR ≦ 5.1
- 2.6 ≦ DAS28-ESR < 3.2
- DAS28-ESR < 2.6

to determine missing data at week 52 for 16 patients who received ADA treatment for at least 180 days. A total of 87 patients were, therefore, subject to an evaluation of radiographic response to ADA. The mean estimated yearly progression was 27.1 ± 46.0 (median 13.6; 25th–75th percentiles 8.3–28.9) at baseline (Fig. 5), which is indicative of a great risk of further joint damage. After 52 weeks of ADA treatment, the mean change was significantly reduced to 0.8 ± 5.0 (median 0.0; 25th–75th percentiles −0.9 to 2.0) ($P < 0.0001$) (Fig. 5). It is particularly worth noting that ADA also suppressed the most aggressive progression in individuals with baseline changes of >100 TSS units/year. The results clearly indicate the ability of ADA to prevent further joint damage as assessed by a reduction in the rate of radiographic disease progression. A cumulative probability plot of changes in TSS was used to illustrate these findings (Fig. 6) [29]. The percentage of patients with no radiographic progression (as defined by a change in TSS of ≤0.5 units) over 52 weeks was 59.8%. However, there were 4 patients with a change in TSS of >10 despite ADA treatment (range 11.0–26.5), 2 of whom discontinued treatment before 52 weeks, and their radiographic data were therefore imputed.

Safety

The overall exposure time to ADA used for the safety evaluation was conservatively estimated to be 175.4 patient-years (as of June 15, 2010), using the last visit records for the 2 patients whose exact discontinuation dates were unknown. ADA was generally well tolerated. A total of 60 adverse events (34.21/100 patient-years) were reported (Table 2).