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ORIGINAL RESEARCH

Long-Term Safety and Effectiveness of Adalimumab in Japanese Patients with Noninfectious Intermediate, Posterior, or Panuveitis: Post-Marketing Surveillance of 251 Patients

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ABSTRACT

Introduction: The aim of this nationwide, prospective post-marketing surveillance was to assess the safety and effectiveness of up to 52 weeks of adalimumab treatment in patients with noninfectious intermediate, posterior, or panuveitis in Japanese clinical practice.

Methods: This post-marketing surveillance was conducted at 60 medical facilities in Japan from October 2016 to June 2020. Patients with noninfectious intermediate, posterior, or panuveitis who were administered adalimumab (Humira®, AbbVie Inc.) for the first time were eligible. Subcutaneous adalimumab was initially administered at 80 mg, followed by 40 mg 1 week later, then 40 mg every 2 weeks. Safety measures included the incidence of adverse events (AEs) and adverse drug reactions (ADRs; primary endpoint). Effectiveness measures included visual acuity, anterior chamber cell grade, vitreous haze, macular edema, foveal retinal thickness, uveitis recurrence rate, and oral corticosteroid dose. Health-related quality of life was evaluated using the 25-item National Eye Institute Visual Function Questionnaire (VFQ-25).

Results: During 52 weeks of surveillance, AEs and ADRs occurred in 70 (27.9%) and 47 (18.7%) of 251 patients, respectively. The most common ADR was infection (21/251 patients; 8.4%), including serious infections in eight (3.2%) patients. ADRs were more frequent in patients ≥ 65 years of age, those with concurrent diseases, and those with past medical history. Four patients developed tuberculosis. The uveitis recurrence rate was 24.8% (61/246 patients). All effectiveness measures tended to improve from baseline to week 52, and mean corticosteroid doses decreased. Clinically meaningful changes were observed for most VFQ-25 subscales.

Conclusions: The safety profile of adalimumab was generally consistent with previous reports, and no new safety concerns were identified.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s40123-022-00493-z.

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Key Summary Points

Why carry out this study?

Adalimumab is an anti-tumor necrosis factor-α monoclonal antibody approved for the treatment of noninfectious intermediate, posterior, or panuveitis; however, the long-term use of adalimumab in routine clinical practice needs to be evaluated prospectively in nationwide studies involving large numbers of patients.

This nationwide, prospective post-marketing surveillance study was conducted to assess the safety and effectiveness of up to 52 weeks of adalimumab treatment in 251 patients with noninfectious intermediate, posterior, or panuveitis in Japanese clinical practice.

What was learned from the study?

The safety profile of adalimumab was similar to that reported in clinical trials and in smaller, retrospective real-world studies, sustained improvements in uveitis symptoms and quality of life were achieved, and a corticosteroid-sparing effect was observed.

These results support the long-term use of adalimumab in Japanese patients with noninfectious uveitis.

INTRODUCTION

Noninfectious uveitis, which is common in Japan [1], is an ocular inflammatory condition associated with a number of systemic immune disorders, including sarcoidosis, Vogt-Koyanagi-Harada (VKH) disease, and Behçet's disease [2, 3]. Chronic inflammation from uveitis damages ocular structures and threatens vision, especially in patients with panuveitis. The standard initial treatment for noninfectious uveitis is oral or intravenous corticosteroids; however, long-term use of corticosteroids in patients with recurring uveitis can lead to serious side effects [4, 5]. Once inflammation subsides, corticosteroid doses can be tapered. In patients who experience recurrent flares after corticosteroid tapering or who require long-term control of inflammation, addition of immunosuppressants can further control inflammation without increasing the corticosteroid dose ("corticosteroid-sparing") [2, 4, 5]. However, some patients become refractory to or intolerant of corticosteroid and immunosuppressant therapy or have uveitis such as Behçet's disease where immediate use of immunosuppressants is warranted; for these patients, biologic drugs provide a molecularly targeted therapy as an effective, corticosteroid-sparing alternative [6].

Inhibitors of the proinflammatory cytokine tumor necrosis factor-α (TNF-α) are a major class of biologic drugs used to control inflammation in a range of diseases, including noninfectious uveitis. For example, the anti-TNF-α monoclonal antibody infliximab has been shown to suppress ocular inflammatory attacks in patients with Behçet's disease [7]. Adalimumab is a fully human anti-TNF-α monoclonal antibody that was approved for the treatment of noninfectious intermediate, posterior, or panuveitis in 2016 [8], including in Japan. Two global, randomized, placebo-controlled trials established the safety and efficacy of adalimumab for active (VISUAL I) and inactive (VISUAL II) noninfectious uveitis [9, 10]. In both trials, adalimumab significantly reduced the risk of treatment failure (a composite outcome based on changes in visual acuity, anterior chamber cell grade, and vitreous haze grade, and the appearance of new retinal lesions) compared with placebo [9, 10]. Adverse events (AEs) in the adalimumab group were consistent with those observed for other

indications, although VISUAL I reported a higher incidence of AEs with adalimumab than placebo, mainly due to injection site reactions. However, a small number of cases of tuberculosis and malignancy were noted in both trials, consistent with the known effects of TNF-α inhibitors on opportunistic infections [11, 12] and the potential risk for their influence on malignancies [8].

The long-term (150 weeks) safety and efficacy of adalimumab were confirmed in VISUAL III, an open-label extension study of VISUAL I and II [13]. Although the long-term use of adalimumab (or a biosimilar) in routine clinical practice has been evaluated in mainly retrospective studies conducted at ≤ 5 medical centers [14–21], larger, nationwide, prospective studies are needed. Such studies would include patients with complex treatment and medical histories who would have been excluded from clinical trials. In addition, it is important to assess the safety of adalimumab in Japan, where tuberculosis is more common than in most European and North American countries [22]. This nationwide, prospective post-marketing surveillance study was conducted to assess the safety and effectiveness of up to 52 weeks of adalimumab treatment in patients with noninfectious intermediate, posterior, or panuveitis in Japanese clinical practice.

METHODS

Study Design

This was an open-label, noncontrolled, multicenter, post-marketing surveillance conducted at 60 medical facilities in Japan from October 2016 to June 2020 (ClinicalTrials.gov identifier: NCT02916017). The surveillance was conducted in accordance with Good Post-marketing Study Practices for Drugs, and Japanese regulatory and legal requirements. The protocol was approved by the Pharmaceuticals and Medical Devices Agency of Japan. Patients provided written informed consent before any surveillance-specific procedures.

Study Population

Patients who were diagnosed with noninfectious intermediate uveitis, posterior uveitis, or panuveitis and who were administered adalimumab (Humira®, AbbVie Inc.) for the first time were eligible to register for this surveillance.

Treatment Protocol

Patient registration was managed by a central registration system (EPS Corporation, Tokyo, Japan). Patients received adalimumab by subcutaneous injection at 80 mg as an initial dose, followed by 40 mg 1 week later, and then 40 mg once every 2 weeks. As recommended by the Japanese Ocular Inflammation Society [23], patients were screened for serious infections, including tuberculosis and hepatitis B infection, before being administered adalimumab. The surveillance consisted of a 52-week treatment period (observational period). Patients who discontinued during the treatment period were observed until discontinuation; patients who had AEs were followed for up to 70 days after discontinuation. All data were entered into an electronic data capture system (Fujitsu FIP Corporation, now Fujitsu Japan Limited, Tokyo, Japan) by the investigators.

Outcome Measures

Information about patient demographics, disease characteristics (including primary disease underlying uveitis), medical history (including any concurrent diseases present at the time of first adalimumab administration and past medical history [diseases, conditions, procedures, etc.] that is no longer present at the time of first adalimumab administration), and treatment history was collected. Safety was evaluated by the incidence of AEs and adverse drug reactions (ADRs; primary endpoint). AEs were coded using version 23.0 of the Medical Dictionary for Regulatory Activities/Japanese version (MedDRA/J). ADRs were defined as AEs for which a causal relationship with adalimumab could not be ruled out. The incidence of ADRs

was also assessed in subgroups of patients with sarcoidosis, VKH disease, and Behçet's disease, which are three of the most common diseases underlying noninfectious uveitis in Japan [1]. Following the risk management plan for adalimumab, incidence rates of ADRs of interest and other important potential risks were assessed. ADRs of interest were specified from safety results of clinical studies and post-marketing surveillance studies in noninfectious uveitis and other indications and included infections, hepatitis B reactivation, tuberculosis, demyelinating diseases, lupus-like syndromes, serious allergic reactions, interstitial pneumonia, serious blood disorders, and fulminant hepatitis/liver disorders/jaundice/hepatic failure. Important potential risks are adverse events that are suspected to be related to adalimumab but that lack sufficient clinical data to be confirmed; these include malignancy, psoriasis or psoriasis aggravation, and sarcoidosis deterioration.

Effectiveness was evaluated at pre-dose (except uveitis recurrence rate) and all examination time points from treatment start (week 0) to week 52 or discontinuation. Effectiveness outcomes included visual acuity, anterior chamber cell grade by slit-lamp microscopy (Standardization of Uveitis Nomenclature [SUN] criteria [24]), vitreous haze by indirect ophthalmoscopy (National Eye Institute [25]/SUN working group [26] criteria), macular edema and foveal retinal thickness by optical coherence tomography, recurrence rate of uveitis, and oral corticosteroid dose as prednisolone equivalent.

Health-related quality of life (HR-QoL) was evaluated using the 25-item National Eye Institute Visual Function Questionnaire (VFQ-25; [27]) at pre-dose and week 52 or discontinuation. The VFQ-25 consists of 25 items in 12 subscales. Each item is assessed on a Likert scale from 0 to 100, with higher scores indicating better HR-QoL. Individual item scores are averaged to obtain subscale and total composite scores. Changes of approximately 4 points in the total score and 4–6 points in subscale scores have been suggested to be clinically meaningful [28].

Statistical Analysis

A target sample size of 250 patients was set to provide at least 216 patients for the safety analysis, accounting for patient withdrawals, assuming an incidence rate of serious infections of approximately 2.3% (95% confidence interval ± 2.0%) based on previous safety data. All patients who met registration criteria were included in the safety analysis set. Of these, patients in whom effectiveness was evaluated at least once were included in the effectiveness analysis set. Data are summarized as numbers and percentages for categorical variables and mean ± standard deviation (SD) for continuous variables. Missing data were not imputed. A chi-square test was used to compare incidence rates between patient subgroups. Effectiveness outcomes are presented as descriptive statistics at baseline and last observation. Statistical analyses were performed using SAS® version 9.2 or later (SAS Institute, Cary, NC, USA).

RESULTS

Patient Disposition and Characteristics

Of 259 patients registered, case report forms were collected for 256 patients; 251 and 246 patients were included in the safety and effectiveness analysis sets, respectively (Fig. 1). Of 251 patients, 199 (79.3%) completed the 52-week treatment period and 52 (20.7%) discontinued participation. The most common reasons for discontinuation were AEs (n = 19), hospital transfer or not visiting a hospital (n = 13), lack of effectiveness (n = 8), and symptom improvement (n = 6).

Most patients were female (61.0%), aged from 40 to 64 years (49.8%), and had concurrent diseases (55.0%); 22.7% had a past medical history (Table 1). The most common primary diseases were Behçet's disease (27.5%), VKH disease (25.5%), and sarcoidosis (11.6%); 22.3% of patients had idiopathic noninfectious uveitis. A small percentage of patients (12.0%) had received previous treatment with infliximab; in contrast, most patients (94.8%) had been treated with other medications (Table 1).

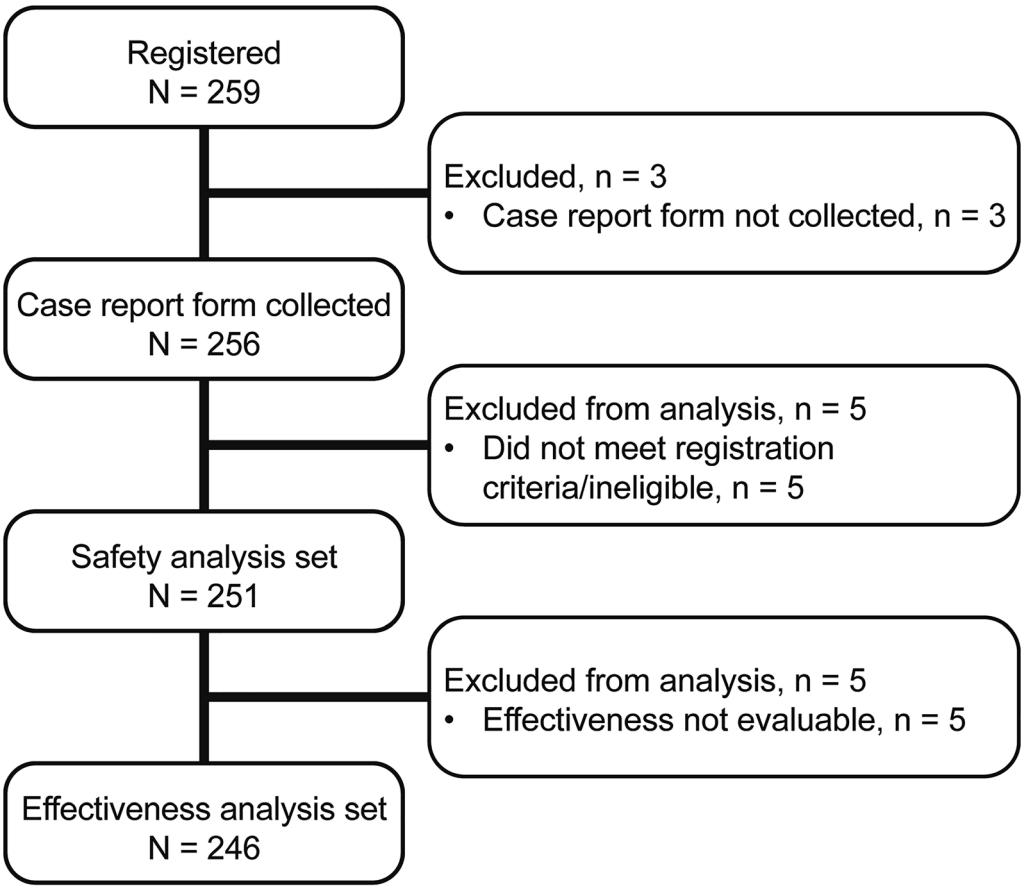


Fig. 1 Patient disposition

Approximately half (55.0%) of patients had at least one concurrent disease; the most common concurrent diseases were glaucoma (*n* = 29), hypertension (*n* = 26), diabetes mellitus (*n* = 19), cataract (*n* = 17), ocular hypertension (*n* = 10), hyperlipidemia (*n* = 9), rheumatoid arthritis (*n* = 8), osteoporosis (*n* = 6), dyslipidemia (*n* = 5), and dry eye (*n* = 5). Almost a quarter (22.7%) of patients had a past medical history, most commonly cataract (n = 13), gastric ulcer (n = 3), pneumonia, uterine leiomyoma, drug hypersensitivity, gout, asthma, cholecystitis, drug eruption, injection site reaction, open globe injury, and intraocular lens insertion (*n* = 2 each). Most patients were screened for tuberculosis (*n* = 234; 93.2%) and hepatitis B (*n* = 244; 97.2%; surface antigen test [HBsAg]: 92.8%, core antibody test [HBcAb]: 81.3%, surface antibody test [HBsAb]: 79.7%) at the first visit. The mean ± SD total VFQ-25 at baseline was 60.4 ± 21.1, with mean subscale scores ranging from 44.0 (general health) to 81.8 (color vision). Chest imaging was performed in 242 (96.4%) patients (X-ray: *n* = 183 [72.9%]; computed tomography: *n* = 131 [52.2%]).

Safety Outcomes

During the surveillance period, 70 of 251 patients (27.9%) reported at least one AE and 24 (9.6%) reported at least one serious AE (Table 2). Forty-seven patients (18.7%) reported at least one ADR and 14 (5.6%) reported at least one serious ADR (Table 2). The most common ADR was an infection (any infection: 21 patients,

Table 1 Patient characteristics (safety analysis set)

Patient characteristics		Number of patients (%) $N = 251$
Age, years	< 15	7 (2.8)
	≥ 15, < 40	60 (23.9)
	≥ 40, < 65	125 (49.8)
	≥ 65	59 (23.5)
Weight, kg	< 40	8 (3.2)
	≥ 40, < 60	87 (34.7)
	≥ 60	89 (35.5)
	Unknown	67 (26.7)
Sex	Male	98 (39.0)
	Female	153 (61.0)
Reasons for use	Noninfectious intermediate uveitis	12 (4.8)
	Noninfectious posterior uveitis	34 (13.5)
	Noninfectious panuveitis	205 (81.7)
Primary disease	Sarcoidosis	29 (11.6)
	Vogt-Koyanagi-Harada disease	64 (25.5)
	Behçet's disease	69 (27.5)
	Sclerouveitis	7 (2.8)
	Sympathetic ophthalmia	5 (2.0)
	Psoriasis	4 (1.6)
	Others	17 (6.8)
	Idiopathic	56 (22.3)
Duration of uveitis, years	< 1	33 (13.1)
	≥ 1, < 3	48 (19.1)
	≥ 3, < 5	42 (16.7)
	≥ 5	90 (35.9)
	Unknown	38 (15.1)
Affected eyes	Right	20 (8.0)
	Left	18 (7.2)
	Both	213 (84.9)
Concurrent disease	Yes	138 (55.0)
Past medical history	Yes	57 (22.7)
Prior treatment (infliximab)	Yes	30 (12.0)
	Lack of efficacy[a]	8 (26.7)
	Adverse event[a]	15 (50.0)
	Patient request[a]	3 (10.0)
	Others[a]	4 (13.3)
Prior treatment (others)	Yes	238 (94.8)
	Topical corticosteroid[b]	185 (73.7)
	Oral corticosteroid[b]	160 (63.7)
	Topical mydriatics[b]	70 (27.9)
	Corticosteroid injection (intraocular or periocular)[b]	68 (27.1)
	Cyclosporine[b]	64 (25.5)
	NSAIDs[b]	12 (4.8)
Concomitant drugs	Prednisolone	127 (50.6)
	Cyclosporine	34 (13.5)
	Methotrexate	26 (10.4)
	Colchicine	17 (6.8)
Clinical characteristics		**Mean ± SD**
Anterior chamber cell grade		
	Right eyes, $n = 220$	0.32 ± 0.61
	Left eyes, $n = 217$	0.41 ± 0.78
Vitreous haze grade		
	Right eyes, $n = 215$	0.52 ± 0.75
	Left eyes, $n = 207$	0.64 ± 0.83
Number of previous recurrences within previous year		
	Right eyes, $n = 195$	1.5 ± 1.6
	Left eyes, $n = 190$	1.4 ± 1.4

NSAID nonsteroidal anti-inflammatory drug, *SD* standard deviation

[a]Reason for discontinuation. Percentages are based on the number of patients who had been treated with infliximab, i.e., 30

[b]Details of prior treatment

Table 2 Summary of adverse events, adverse drug reactions, and important potential risks (safety analysis set)[a]

Events	Number of patients (%) $N = 251$	
	Any AE/ADR	Serious AE/ADR
AEs	70 (27.9)	24 (9.6)
ADRs	47 (18.7)	14 (5.6)
ADRs of interest		
Infections	21 (8.4)	8 (3.2)
Tuberculosis[b]	4 (1.6)	4 (1.6)
Interstitial pneumonia	1 (0.4)	1 (0.4)
Hepatitis B reactivation	0 (0)	0 (0)
Demyelinating diseases	0 (0)	0 (0)
Lupus-like syndromes	0 (0)	0 (0)
Allergic reactions	0 (0)	0 (0)
Blood disorders	0 (0)	0 (0)
Fulminant hepatitis/liver disorders/jaundice/hepatic failure	0 (0)	0 (0)
Important potential risks		
Malignancy	2 (0.8)	2 (0.8)
Psoriasis or psoriasis aggravation	1 (0.4)	0 (0)
Sarcoidosis deterioration	0 (0)	0 (0)

ADR adverse drug reaction, *AE* adverse event
[a]Medical Dictionary for Regulatory Activities/Japanese version 23.0
[b]Includes tuberculosis ($n = 2$), miliary tuberculosis ($n = 1$), and brain tuberculoma ($n = 1$)

8.4%; serious infection: eight patients, 3.2%) (Table 2, Table S1). Among the three most common primary diseases, the incidence of ADRs was higher in patients with sarcoidosis (any: 27.6%; serious: 13.8%) than in those with VKH disease (any: 18.8%; serious: 4.7%) or Behçet's disease (any: 15.9%; serious: 2.9%) (Table S2). Infection was the most common ADR in all three primary disease groups. The incidence rate of ADRs was significantly higher in patients aged ≥ 65 years than in those < 65 years, in patients with concurrent diseases than in those without concurrent diseases, and in patients with a past medical history than in those without a past medical history (Table 3).

Table 3 Incidence of adverse drug reactions by patient characteristics

Baseline factor	Number of patients	Number of patients with ADR	Incidence (%)	*p* value
Age, years				0.0231
< 65	192	30	15.6	
≥ 65	59	17	28.8	
Concurrent disease				0.0028
No	113	12	10.6	
Yes	138	35	25.4	
Past medical history				0.0067
No	172	24	14.0	
Yes	57	17	29.8	

p values were calculated using the chi-square test
ADR adverse drug reaction

Serious infections, tuberculosis, and interstitial pneumonia were reported ADRs of interest (Table 2). Four patients developed active tuberculosis during the surveillance period (tuberculosis in two patients, miliary tuberculosis in one patient, and brain tuberculoma in one patient); of these, three patients had tested negative and one patient's test was inconclusive (interferon-γ release assay test) before treatment. As important potential risks, two patients (0.8%) had a serious malignancy (colon cancer, breast cancer) and one patient (0.4%) had nonserious psoriasis aggravation (Table 2). One patient died because of a putaminal hemorrhage that was considered treatment-related. The patient was refractory to treatment with prednisolone, methotrexate, and cyclosporine and received adalimumab after a negative tuberculosis screen was confirmed. An adverse reaction of personality change occurred after the start of

adalimumab administration, which was then discontinued. Subsequently, the patient was diagnosed with intracranial tuberculoma and died of putaminal hemorrhage.

Effectiveness Outcomes

The recurrence rate of uveitis was 24.8% (61/246 patients) (Table 4). Recurrence rates were 37.0% in patients with sarcoidosis, 28.1% in patients with VKH disease, 23.5% in patients with Behçet's disease, and 21.4% in patients with idiopathic uveitis.

Visual acuity and foveal retinal thickness tended to be improved at final observation compared with pre-dose, and the percentage of patients with macular edema tended to be lower at final observation than at pre-dose (Table 5). Both anterior chamber cell grade and vitreous haze grade tended to shift to lower grades (i.e., improved) at final observation compared with pre-dose (Fig. 2). The proportion of patients with anterior chamber cell grade or vitreous haze grade of 0 increased from pre-dose to final observation.

At week 0, 121 patients were receiving concomitant oral corticosteroids; at week 52, 93 of these patients were still receiving adalimumab, and 69 were receiving both adalimumab and corticosteroids. The mean dose of oral corticosteroids (prednisolone equivalent) decreased from 14.6 mg/day at week 0 to 7.2 mg/day at week 52 (Fig. 3). Patients who were also receiving immunosuppressants had a mean corticosteroid dose of 12.6 mg/day at week 0 and 7.5 mg/day at week 52. Patients without immunosuppressants had a mean corticosteroid dose of 15.3 mg/day at week 0 and 7.1 mg/day at week 52. By week 52, 25.8% (24/93) of patients were corticosteroid-free; the percentage was 30.0% (6/20) in patients who were receiving immunosuppressants and 24.7% (18/73) in those who were not.

The mean change in total VFQ-25 score was 5.71, indicating improvement, and mean changes of 4 points or more in the VFQ-25 were observed in most subscales (Fig. 4). Changes greater than 6 points were seen in mental health (10.01), near vision (8.89), dependency (6.93), and general vision (6.73). Moderate changes of approximately 4–6 points were observed in ocular pain, distance vision, social functioning, role difficulties, color vision, and peripheral vision. In contrast, changes of < 2 points were seen in general health and driving.

Table 4 Recurrence rate of uveitis (effectiveness analysis set)

	Number of patients[a]	Number of patients with recurrences	Recurrence rate (%)
Effectiveness analysis set	246	61	24.8
Primary disease			
Sarcoidosis	27	10	37.0
Vogt-Koyanagi-Harada disease	64	18	28.1
Behçet's disease	68	16	23.5
Others	31	5	16.1
Idiopathic	56	12	21.4
Prior treatment with biologic agents in patients with Behçet's disease			
No	40	9	22.5
Yes	27	7	25.9
Unknown	1	0	0

[a]Excludes patients whose recurrences were "unknown"

DISCUSSION

This is the first nationwide, prospective post-marketing evaluation of the long-term safety and effectiveness of adalimumab for the treatment of noninfectious uveitis in Japanese clinical practice. The safety profile of adalimumab was generally similar to that reported in previous clinical trials in noninfectious uveitis

Table 5 Summary of other effectiveness outcomes

	N	Pre-dose	Final observation
Visual acuity (logMAR), mean ± SD[a]			
Right eyes	220	0.37 ± 0.58	0.27 ± 0.54
Left eyes	218	0.37 ± 0.56	0.29 ± 0.53
Foveal retinal thickness (μm), mean ± SD[a]			
Right eyes	90	296.8 ± 102.0	266.0 ± 83.7
Left eyes	87	296.7 ± 132.4	257.8 ± 85.6
Macular edema, *n* (%)			
Right eyes	216	49 (22.7)	24 (11.1)
Left eyes	203	44 (21.7)	22 (10.8)

logMAR logarithm of the minimum angle of resolution, *SD* standard deviation

[a]Patients with both pre-dose and final observation data

[9, 10, 13, 29] and other diseases [30], in observational studies in both Japan [17, 18] and other countries [14–16, 19–21], and in Japanese post-marketing surveillance studies in other inflammatory diseases [31–34]. Importantly, the incidence rates of serious infections, including tuberculosis, and malignancy were low. Moreover, sustained improvements were seen in visual acuity, macular edema, anterior chamber cell grade, vitreous haze, and HR-QoL, and the daily dose of oral corticosteroids decreased. These results support the long-term use of adalimumab in Japanese patients with noninfectious uveitis.

The long-term safety profile of adalimumab in Japanese clinical practice was consistent with the known effects of TNF-α inhibitors, and no new ADRs were identified. As expected based on extensive experience with adalimumab in other indications [12, 30–34], infections were the most common of the ADRs of interest and other important potential risks, and increased susceptibility to infections is typical of TNF-α inhibitors [6]. Similar results have been reported in Japanese post-marketing surveillance studies of the TNF-α inhibitor infliximab in refractory uveoretinitis associated with Behçet's disease [7] and in rheumatoid arthritis [35]. Not surprisingly, the incidence of ADRs was higher in older patients and in patients with concurrent diseases or a past medical history; as with most treatments, these patients require additional care and safety monitoring during adalimumab treatment. ADRs were also more frequent in patients with sarcoidosis than in patients with VKH disease or Behçet's disease, although the reason for this is unknown and may be related to the smaller sample size of patients with sarcoidosis. Serious cases of tuberculosis and malignancy were observed in four and two patients, respectively. These AEs also occurred at low rates in the VISUAL I–III trials [9, 10, 13, 29], as well as in post-marketing surveillance studies in other indications [30, 31, 33, 34]. Despite the higher prevalence of tuberculosis in Japan compared with European and North American countries [22], the overall incidence of tuberculosis in this post-marketing surveillance study (1.6%; 4/251 patients) was consistent with the incidence seen in the global VISUAL I (1/111 patients) and VISUAL II (3/115 patients) trials [9, 10]. The Japanese Ocular Inflammation Society recommends screening for tuberculosis and hepatitis B virus, as well as other serious infectious diseases, before initiating treatment with a TNF inhibitor [23]. Unfortunately, this screening was not conducted in a small proportion of patients in this study of clinical practice. The guidelines also note that false negative results may occur if the patient is currently treated with corticosteroids or immunosuppressants; therefore, monitoring should be repeated periodically after starting adalimumab treatment. Although the rate of malignancy was low, comparison with reference populations is needed to evaluate whether adalimumab increases the risk. The potential effect of TNF inhibitors on newly developed or recurrent cancer is currently unclear [8]. Psoriasis or psoriasis aggravation was observed in one patient (0.4%), a rate similar to that reported in VISUAL III (0.44 per 100 patient-years) [13]. Although sarcoidosis deterioration occurred at a rate of 0.35 per 100 patient-years in VISUAL III [13], it was not observed in this study.

Treatment with adalimumab was associated with improvements in the ocular symptoms of uveitis, visual acuity, and a broad range of HR-QoL categories. These results are consistent with

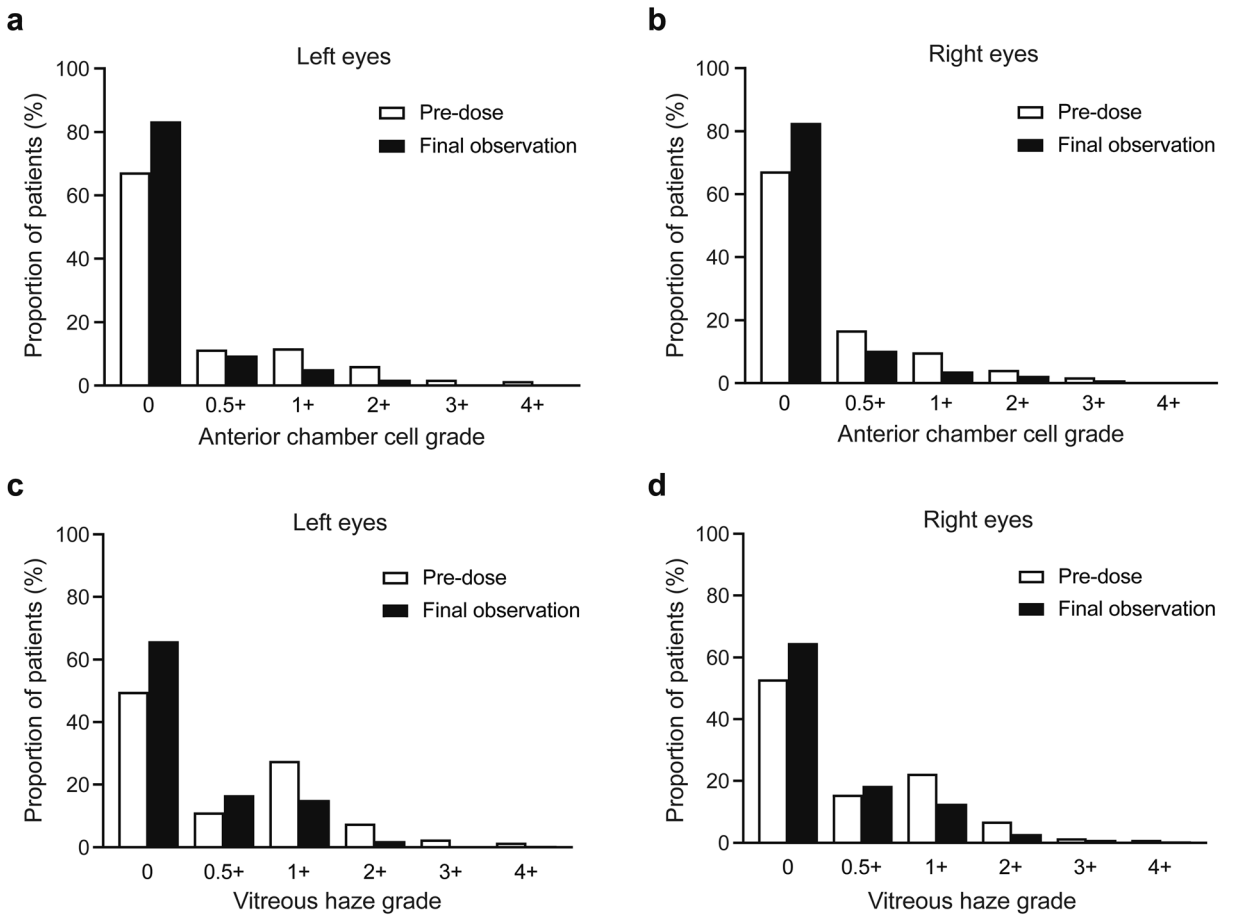
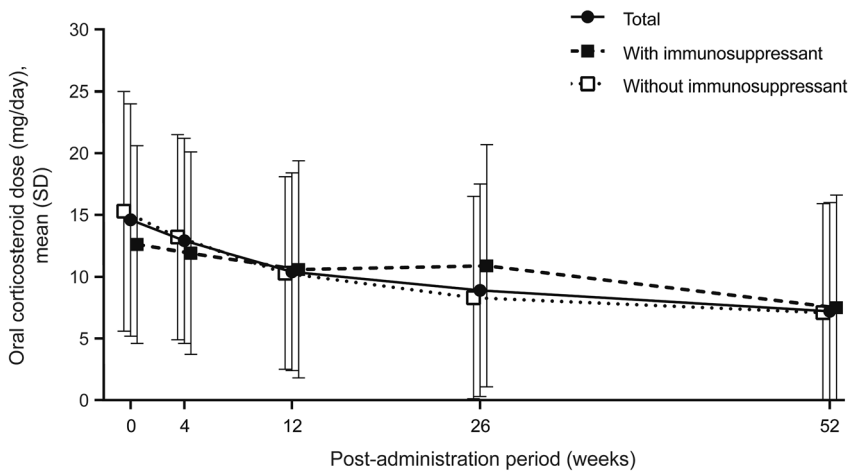


Fig. 2 Changes in the anterior chamber cell grade in **a** left eyes and **b** right eyes; changes in vitreous haze grade in **c** left eyes and **d** right eyes

those of the long-term VISUAL III extension study [13] and previous observational studies [14–21] and indicate that continued adalimumab treatment results in sustained control of uveitis. By week 52 of this study, > 90% of eyes had an anterior chamber cell grade of 0 or 0.5+, and > 80% had a vitreous haze grade of 0 or 0.5+. Foveal retinal thickness had also decreased, and the proportion of eyes with macular edema had approximately halved. In addition, the recurrence rate of uveitis was 24.8%, which is lower than the treatment failure rate seen in the VISUAL II trial (39% [45/115] of patients receiving adalimumab compared with 55% [61/111] of patients receiving placebo) [10], but similar to the 26 relapses per 100 patient-years seen over 12 months of treatment in a retrospective study conducted in Italy [16]. Interestingly, another Italian retrospective study reported an even lower rate of four relapses per 100 patient-years during the first 12 months of treatment with SB5, an adalimumab biosimilar [20]. These results suggest that adalimumab is at least as effective, and possibly more effective, at preventing uveitis recurrence in real-world clinical practice as in clinical trials.

Importantly, the observed improvements in ocular symptoms were accompanied by improvements in visual acuity and VFQ-25 scores, indicating better vision and less negative impact on quality of life. Noninfectious uveitis adversely affects all aspects of HR-QoL, as shown by worse scores on all VFQ-25 subscales



Patients with concomitant corticosteroids/total patients, (n/N)

Total	121/121	114/118	106/114	96/110	69/93
With immunosuppressant	29/29	27/28	25/26	23/25	14/20
Without immunosuppressant	92/92	87/90	81/88	73/85	55/73

Fig. 3 Mean changes in the daily oral corticosteroid dose (prednisolone equivalent) from week 0 to week 52. Week 0 was the start of adalimumab administration. The number of patients at each time point, expressed as the number receiving concomitant corticosteroids over the total number of patients receiving adalimumab (n/N), is shown under the graph. In patients who stopped using oral corticosteroids between time points, a corticosteroid dose of 0 mg/day was used for the subsequent time point

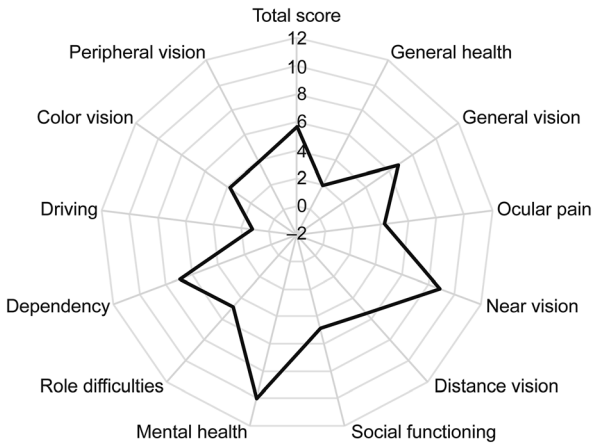


Fig. 4 Mean changes from week 0 to week 52 in the 25-item National Eye Institute Visual Function Questionnaire total score and 12 subscale scores. Patients with both pre-dose and final observation data were included

compared with a population with normal vision [36]. In VISUAL I and II, adalimumab was associated with greater improvements in VFQ-25 total, general vision, and mental health scores, as well as in ocular pain and near vision scores in VISUAL I, compared with placebo [37]. In this post-marketing surveillance study, clinically meaningful improvements were observed in the total VFQ-25 score and in 10 of 12 subscales, indicating that the benefits of adalimumab extend beyond visual acuity alone. Further, adalimumab allowed the daily dose of oral corticosteroids to be reduced and a greater percentage of patients to be corticosteroid-free, even among patients who were receiving other immunosuppressants at baseline. This suggests that adalimumab has a corticosteroid-sparing effect in patients who have become refractory to corticosteroids and/or immunosuppressants. To minimize the potential for adverse effects with extended corticosteroid use, guidelines recommend doses < 10 mg/day for the treatment of noninfectious uveitis, as well as other inflammatory diseases [5, 38–40]. Despite these recommendations, reducing corticosteroid doses is sometimes difficult in patients with persistent

inflammation, and adalimumab may be an option that allows corticosteroid doses to be further reduced.

This study provides real-world evidence of the use of adalimumab for noninfectious uveitis, including in patients who may have been excluded from clinical trials. In addition to evaluating safety, the study assessed a broad range of effectiveness measures, including patient-reported HR-QoL. However, changes in effectiveness parameters from week 0 to week 52 were not examined using inferential statistics and, given the observational nature of the study, there was no control group for comparison. Further, we did not collect or assess image data of fundus examination such as by fluorescein angiography and indocyanine angiography. In addition, the results may only be applicable to Japanese patients. Finally, longer-term follow-up and/or larger sample size may be needed to accurately assess rare events, such as malignancies.

CONCLUSIONS

In conclusion, this post-marketing surveillance study confirmed the long-term (52 weeks) safety and effectiveness of adalimumab for noninfectious uveitis in Japanese clinical practice. No new safety concerns were identified, sustained improvements in uveitis symptoms and HR-QoL were achieved, and a corticosteroid-sparing effect was observed.

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Compliance with Ethics Guidelines. This post-marketing surveillance was conducted in accordance with Good Post-marketing Study Practices for Drugs, and Japanese regulatory and legal requirements. The protocol was approved by the Pharmaceuticals and Medical Devices Agency of Japan. Patients provided written informed consent before any surveillance-specific procedures.

Data Availability. The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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