Longterm Retention Rate and Risk Factors for Adalimumab Discontinuation Due To Efficacy and Safety in Japanese Patients with Rheumatoid Arthritis: An Observational Cohort Study

Yosuke Hattori, Toshihisa Kojima, Atsushi Kaneko, Daihei Kida, Yuji Hirano, Takayoshi Fujibayashi, Kenya Terabe, Yuichiro Yabe, Hiroyuki Miyake, Takefumi Kato, Hideki Takagi, Masatoshi Hayashi, Takayasu Ito, Yasuhide Kanayama, Takeshi Oguchi, Nobunori Takahashi, Hisato Ishikawa, Koji Funahashi, and Naoki Ishiguro

ABSTRACT. ***Objective.*** To evaluate the rates of retention and discontinuation of adalimumab (ADA) due to efficacy and safety in Japanese patients with rheumatoid arthritis (RA).

Methods. All patients with RA (n = 476) who were treated with ADA in the Tsurumai Biologics Communication Registry were enrolled.

Results. The retention rate of ADA was 46% at 5 years. When focusing on insufficient efficacy, previous biologics use and high baseline disease activity were significant risk factors for up to 1 year. Methotrexate (MTX) use was a significantly low risk factor after 1 year of treatment.

Conclusion. Concomitant MTX contributes to the longterm efficacy of ADA therapy. (First Release June 15; J Rheumatol 2016;43:1475–9; doi:10.3899/jrheum.151006)

Key Indexing Terms:

ADALIMUMAB | RHEUMATOID ARTHRITIS | EFFICACY
SAFETY | RETENTION RATE | DISCONTINUATION

Treatment of rheumatoid arthritis (RA) dramatically improved after the introduction of biological agents that targeted inflammatory cytokines such as tumor necrosis factor (TNF). Adalimumab (ADA) is the first fully human monoclonal antibody that binds to TNF with high specificity. ADA has been well established for RA treatment in multiple clinical trials conducted in Western countries, both with and without concomitant methotrexate (MTX)[1,2,3,4,5,6]. However, the unique genetic, environmental, and medical backgrounds of Japanese patients might alter the efficacy and safety of RA biological agents[7]. Therefore, evidence for the clinical use of ADA should be more thoroughly established for Japanese patients. In our study, we aimed to evaluate the rates of retention and risk factors for discontinuation of ADA due to efficacy and safety in Japanese patients with RA in daily practice.

From the National Hospital Organization Nagoya Medical Center, Orthopedic Surgery and Rheumatology; Orthopedic Surgery, Nagoya University Graduate School of Medicine; Orthopedic Surgery, Nagoya Central Hospital; Ito Seikeigeka; Orthopedic Surgery and Rheumatology, Toyota Kosei Hospital; Orthopedic Surgery, Japanese Red Cross Nagoya Daiichi Hospital, Nagoya; Rheumatology, Toyohashi Municipal Hospital, Toyohashi; Orthopedic Surgery, Konan Kosei Hospital, Konan; Rheumatology, Japan Community Healthcare Organization Tokyo Shinjuku Medical Center, Tokyo; Orthopedic Surgery, Ichinomiya Municipal Hospital, Ichinomiya; Kato Clinic, Okazaki; Rheumatology, Nagano Red Cross Hospital, Nagano; Orthopedic Surgery, Anjo Kosei Hospital, Anjo, Japan.

Y. Hattori, MD, PhD, Orthopedic Surgery and Rheumatology, National Hospital Organization Nagoya Medical Center; T. Kojima, MD, PhD, Department of Orthopedic Surgery, School of Medicine, Nagoya University; A. Kaneko, MD, Orthopedic Surgery and Rheumatology, National Hospital Organization Nagoya Medical Center; D. Kida, MD, PhD, Orthopedic Surgery and Rheumatology, National Hospital Organization Nagoya Medical Center; Y. Hirano, MD, PhD, Rheumatology Toyohashi Municipal Hospital; T. Fujibayashi, MD, PhD, Orthopedic Surgery, Konan Kosei Hospital; K. Terabe, MD, PhD, Orthopedic Surgery, Nagoya University Graduate School of Medicine; Y. Yabe, MD, PhD, Rheumatology, Japan Community Healthcare Organization Tokyo Shinjuku Medical Center; H. Miyake, MD, PhD, Orthopedic Surgery, Ichinomiya Municipal Hospital; T. Kato, MD, PhD, Kato Clinic; H. Takagi, MD, PhD, Orthopedic Surgery, Nagoya Central Hospital; M. Hayashi, MD, PhD, Rheumatology, Nagano Red Cross Hospital; T. Ito, MD, PhD, Ito Seikeigeka; Y. Kanayama, MD, PhD, Orthopedic Surgery and Rheumatology, Toyota Kosei Hospital; T. Oguchi, MD, PhD, Orthopedic Surgery, Anjo Kosei Hospital; N. Takahashi, MD, PhD, Orthopedic Surgery, Nagoya University Graduate School of Medicine; H. Ishikawa, MD, PhD, Orthopedic Surgery, Japanese Red Cross Nagoya Daiichi Hospital; K. Funahashi, MD, PhD, Orthopedic Surgery, Nagoya University Graduate School of Medicine; N. Ishiguro, MD, PhD, Orthopedic Surgery, Nagoya University Graduate School of Medicine.

Address correspondence to Dr. Y. Hattori, National Hospital Organization Nagoya Medical Center, Orthopedic Surgery and Rheumatology, 4-1-1 Sannomaru, Naka-ku, Nagoya, Aichi 460-000, Japan.
E-mail: yosuke-h@med.nagoya-u.ac.jp

Accepted for publication April 27, 2016.

Personal non-commercial use only. The Journal of Rheumatology Copyright © 2016. All rights reserved.

Downloaded on April 23, 2024 from www.jrheum.org

MATERIALS AND METHODS

Study population. All patients with RA (n = 476) treated with ADA in the Tsurumai Biologics Communication Registry (TBCR), a multicenter study group, were enrolled in our study. A registry of patients with RA starting treatment with biologics in 2008 was developed to analyze the longterm prognosis of treatment with biologics in clinical practice[8,9,10]. Data were collected prospectively from 2008, as well as retrospectively for patients who had been treated with biologics up until 2008. All 2827 patients registered in the TBCR as of April 2015 met the 1987 American College of Rheumatology classification criteria for RA. Information on medication history was collected at clinic visits to TBCR-affiliated institutions. Registry data are updated once per year and include information on drug continuation, reasons for discontinuation due to insufficient efficacy, and adverse events (AE). Patient anonymity was maintained during data collection, and security of personal information was strictly controlled. This study was approved by the Nagoya University Graduate School of Medicine Ethics Committee. Written informed consent was obtained from all participants in this study.

Treatment and evaluations. All patients were treated with ADA at a standard regimen of 40 mg every alternate week, with no dose escalation. Continuation rate, probabilities, and risk factors for discontinuation due to insufficient efficacy and AE were evaluated. After discontinuation, we confirmed that medication was not restarted for at least 1 year.

Statistical analysis. Demographic and disease characteristics are reported as descriptive statistics. All results are expressed as mean (SD) or as a percentage. Kaplan–Meier curves were generated to estimate the rates of continuation and discontinuation due to insufficient efficacy and AE. Risk factors for discontinuation due to insufficient efficacy and AE were analyzed using the Cox proportional hazards regression model with the backward stepwise method. Validity of the proportional hazards assumption was confirmed by the log-log survival function. $P < 0.05$ was considered statistically significant. Sensitivity and specificity for the best cutoff level were analyzed with receiver-operated characteristic (ROC) curves. SPSS 22 (SPSS Inc.) was used for statistical analysis.

RESULTS

Continuation rates of ADA therapy. ADA therapy was initiated in 476 Japanese patients with RA who enrolled in our study. Baseline characteristics of the study cohort are summarized in Table 1. Significant differences were found between the ADA continuation group and the discontinuation groups (the discontinuation due to insufficient efficacy group and the discontinuation due to AE group) for the following: previous biologics, MTX use, MTX dosage, and Disease Activity Score in 28 joints based on C-reactive protein (DAS28-CRP) at initiation of ADA therapy. Figure 1 (top panel) shows a Kaplan–Meier curve for ADA continuation with all patients over time. The retention rate for ADA was 46% at 5 years. The figure also shows that the retention rate was higher in patients who used biologics for the first time than in those who previously used biologics. Two patients discontinued for economic reasons, 7 for patient refusal, and 1 for remission maintenance.

Discontinuation of ADA due to insufficient efficacy. Figure 1 (bottom panel) shows the cumulative frequency of discontinuation due to insufficient efficacy over time. ADA discontinuation primarily occurred during the first year, but also occurred as late as 5 years.

Significant risk factors for discontinuation of ADA due to insufficient efficacy included previous biologics use (HR 1.89, 95% CI 1.13–3.17, $p < 0.05$) and DAS28-CRP (HR 1.45, 95% CI 1.19–1.77, $p < 0.01$). ROC analysis of patients continuing ADA at 52 weeks revealed that the best cutoff level for DAS28-CRP for predicting discontinuation due to insufficient efficacy was 4.65 (50% sensitivity, 68% specificity, 61% accuracy).

Table 2A shows risk factors for discontinuation of ADA due to insufficient efficacy up to 1 year and after 1 year from the initiation of treatment. When focusing on insufficient efficacy up to 1 year, previous use of biologics (HR 2.40, 95% CI 1.30–4.42, $p < 0.01$) and a high DAS28-CRP (HR 1.61, 95% CI 1.28–2.02, $p < 0.0001$) were significant risk factors. When focusing on insufficient efficacy after 1 year, MTX use was a significantly low risk factor (HR 0.26, 95% CI 0.10–0.67, $p < 0.01$).

Discontinuation of ADA due to AE. Figure 1 (bottom panel) shows the cumulative rate of discontinuation due to AE over

Table 1. Baseline characteristics of the study cohort. Values are mean ± SD or % unless otherwise specified.

Characteristics	Total Patients Receiving ADA, n = 476	Continuation, n = 277	Discontinuation		p
			Insufficient Efficacy, n = 116	Adverse Events, n = 73	
Age, yrs	59 ± 14	58 ± 14	60 ± 12	61 ± 13	0.16**
Female	83	84	82	81	0.78*
Disease duration, yrs	10 ± 11	10 ± 11	8 ± 11	12 ± 12	0.11**
Stage, I and II/III and IV	51/49	28/72	31/69	29/71	—
Class, 1 and 2/3 and 4	66/34	56/44	57/43	58/42	—
Previous biologics	35	28	42	45	< 0.01*
Prednisolone use	57	55	60	61	0.52*
Prednisolone dose, mg/day	4.3 ± 2.4	4.1 ± 2.3	4.8 ± 2.9	4.2 ± 1.9	0.15**
MTX use	84	89	75	77	< 0.001*
MTX dose, mg/week	7.7 ± 2.5	7.9 ± 2.6	7.2 ± 2.0	7.4 ± 2.2	< 0.001**
DAS28-CRP	4.2 ± 1.4	4.0 ± 1.4	4.5 ± 1.4	4.2 ± 1.4	< 0.001**

P value calculated by using the * chi-square test or **Kruskal-Wallis test. ADA: adalimumab; MTX: methotrexate; DAS28-CRP: Disease Activity Score in 28 joints based on C-reactive protein.

Personal non-commercial use only. The Journal of Rheumatology Copyright © 2016. All rights reserved.

Downloaded on April 23, 2024 from www.jrheum.org

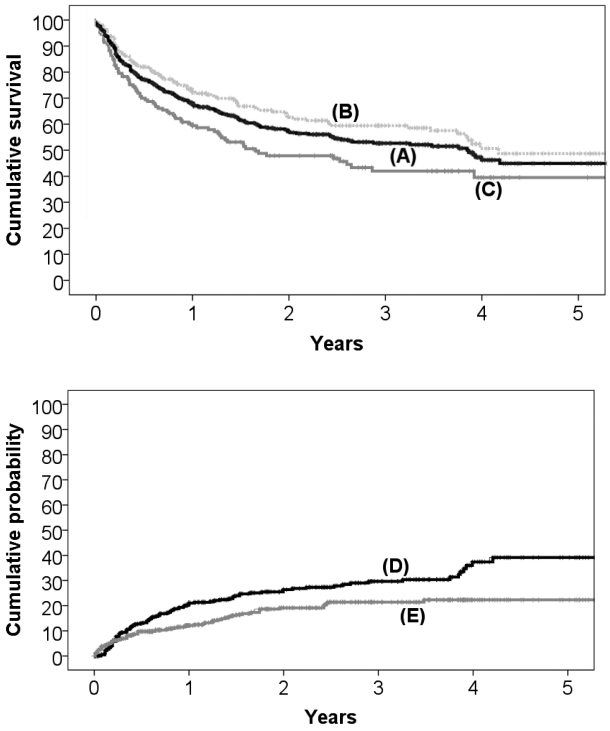

Figure 1. Kaplan-Meier plot showing overall therapy survival over time. A. Drug survival for all patients treated with ADA. B. Drug survival for patients treated with ADA as the first biologic. C. Drug survival for patients who previously used biologics. Cumulative incidence for patients discontinuing ADA due to (D) insufficient efficacy and (E) adverse events. ADA: adalimumab.

time. The majority of AE that led to discontinuation of ADA occurred during the first 6 months after initiation of treatment. When focusing on AE in general, there were no significant baseline risk factors for discontinuation of ADA due to AE.

Table 2B shows risk factors for discontinuation of ADA due to AE up to 1 year and after 1 year from the initiation of treatment. When focusing on AE up to 1 year, previous use of biologics was a significant risk factor (HR 2.50, 95% CI 1.13–5.52, $p < 0.05$).

Table 3 shows the incidence rate of AE involved in discontinuation of ADA. The 476 patients who received at least 1 dose of ADA accounted for 812 per 100 patient-years (PY). The incidence rate of discontinuation of ADA therapy due to all AE was 9.00/100PY, skin disorders 1.97/100PY, blood disorders 0.49/100PY, infectious diseases 2.59/100PY, tuberculosis 0.37/100PY, pneumocystis pneumonia 0.12/100PY, organizing pneumonia 0.25/100PY, interstitial pneumonia 0.37/100PY, liver disorders 0.37/100PY, malignant lymphoma 0.12/100PY, and solid cancer 0.25/100PY. A delay in ADA injections due to infection or in the context of surgery was not considered discontinuation due to AE. Only patients who stopped and did not restart therapy were considered for our analysis.

DISCUSSION

In our study, the retention rate for ADA was 46% at 5 years. This rate is consistent with data extrapolated from other registries, i.e., about 48% at 5 years[11]. When focusing on insufficient efficacy, we found MTX use to be a significantly low risk factor. This result is similar to that reported in a comparable Western registry[12]. In an ADA monotherapy trial[13], however, a higher occurrence of antibody against ADA (AAA) production was observed among Japanese patients after 24 weeks of treatment than was detected in a similar study among Western patients[14]. A metaanalysis revealed that the use of immunosuppressive agents, primarily MTX, reduced the proportion of patients receiving infliximab and ADA with detectable antidrug antibodies[15]. When focusing on insufficient efficacy after 1 year from the initiation of treatment, MTX use was a significant low risk factor in our study. Concomitant MTX is thus necessary for the longterm stable efficacy of ADA, which may also contribute to the suppression of AAA production. Similar to past reports, previous use of biologics and high baseline DAS28-CRP were risk factors for discontinuation due to insufficient efficacy[16,17].

The 3 most commonly reported AE during the first 6 months of ADA therapy in Japanese patients with RA were skin allergies, infections, and respiratory disorders[10,18]. Several Western studies have reported a high incidence of injection site reactions and erythema[1,3,5]. Injection site reactions appear to have an even higher incidence rate in Japan than Western countries[13]. Skin disorders also occurred frequently in our present study. Discontinuation of ADA due to AE was most frequently observed during the first 6 months of therapy. Discontinuation increased among a large proportion of study patients who started ADA therapy with no MTX use and who had a history of previous use of biologics. These findings could be attributed to the long duration of disease in elderly patients. The incidence of infections was high in our study, but none of the infections were fatal. In addition, there were no deaths directly related to ADA. The incidence of AE was equal to that reported in the PREMIER study[19].

Our study has some limitations worth noting. First, the multicenter study design raises the possibility of selection bias because administration of ADA with or without MTX is at the discretion of rheumatologists at each institute. Second, the degree of insufficient efficacy and AE, which was determined by each rheumatologist, was not clearly defined. One final limitation of our study was that we collected data only annually and therefore, if a patient had discontinued a medication but then restarted it before the next annual visit, this would be considered as continuous treatment.

Our study described the followup of a cohort of 476 Japanese patients with RA who were treated with ADA. The retention rate for ADA was 46% at 5 years. MTX use was found to be a significantly low risk factor after 1 year from

Personal non-commercial use only. The Journal of Rheumatology Copyright © 2016. All rights reserved.

Downloaded on April 23, 2024 from www.jrheum.org

Table 2A. Risk factors for discontinuation of ADA due to insufficient efficacy up to 1 year and after 1 year from initiation of treatment.

Variables	Up to 1 Yr				After 1 Yr			
	Univariate Analysis		Multivariate Analysis		Univariate Analysis		Multivariate Analysis	
	HR (95% CI)	p	HR (95% CI)	p	HR (95% CI)	p	HR (95% CI)	p
Age, yrs	1.01 (0.99–1.02)	0.46	1.00 (0.98–1.02)	0.89	1.00 (0.98–1.04)	0.56	1.00 (0.95–1.03)	0.60
Sex	0.84 (0.49–1.44)	0.52	1.02 (0.48–2.17)	0.96	0.78 (0.34–1.80)	0.56	1.13 (0.33–3.86)	0.85
Disease duration, yrs	0.96 (0.93–1.01)	0.056	0.97 (0.93–1.01)	0.082	1.01 (0.98–1.04)	0.39	0.99 (0.94–1.04)	0.60
Stage	0.85 (0.66–1.08)	0.17	0.91 (0.65–1.29)	0.60	1.20 (0.76–1.90)	0.43	1.13 (0.61–2.11)	0.69
Class	1.26 (0.88–1.80)	0.21	1.20 (0.76–1.91)	0.44	1.22 (0.71–2.09)	0.47	2.03 (0.92–4.46)	0.08
Previous biologics	1.58 (1.03–2.45)	< 0.05	2.40 (1.30–4.42)	< 0.01	1.37 (0.68–2.76)	0.37	1.28 (0.49–3.37)	0.62
Prednisolone use	1.04 (0.67–1.63)	0.85	1.00 (0.55–1.82)	0.99	1.69 (0.76–3.76)	0.19	1.24 (0.47–3.26)	0.66
Methotrexate use	0.76 (0.44–1.32)	0.33	1.00 (0.47–2.15)	0.996	0.26 (0.12–0.55)	< 0.001	0.26 (0.10–0.67)	< 0.01
DAS28-CRP	1.24 (1.06–1.45)	< 0.01	1.61 (1.28–2.02)	< 0.0001	1.19 (0.90–1.57)	0.21	0.97 (0.63–1.50)	0.89

HR and 95% CI for discontinuation of ADA were estimated with Cox proportional hazards regression analysis. ADA: adalimumab; DAS28-CRP: Disease Activity Score in 28 joints based on C-reactive protein.

Table 2B. Risk factors for discontinuation of ADA due to adverse events up to 1 year and after 1 year from initiation of treatment.

Variables	Up to 1 Yr				After 1 Yr			
	Univariate Analysis		Multivariate Analysis		Univariate Analysis		Multivariate Analysis	
	HR (95% CI)	p	HR (95% CI)	p	HR (95% CI)	p	HR (95% CI)	p
Age, yrs	1.01 (0.99–1.04)	0.20	1.00 (0.97–1.03)	0.90	1.01 (0.98–1.05)	0.47	1.01 (0.96–1.07)	0.74
Sex	0.85 (0.43–1.70)	0.65	1.75 (0.59–5.24)	0.32	1.32 (0.39–4.48)	0.65	0.48 (0.11–2.00)	0.31
Disease duration, yrs	1.01 (0.98–1.03)	0.69	1.01 (0.98–1.05)	0.54	1.01 (0.98–1.05)	0.44	1.02 (0.97–1.07)	0.39
Stage	0.91 (0.68–1.22)	0.52	0.72 (0.47–1.10)	0.13	1.36 (0.74–2.48)	0.33	1.11 (0.49–2.52)	0.80
Class	1.10 (0.71–1.70)	0.67	0.88 (0.49–1.55)	0.65	0.84 (0.42–1.68)	0.63	0.81 (0.31–2.11)	0.67
Previous biologics	1.73 (1.01–2.99)	< 0.05	2.50 (1.13–5.52)	< 0.05	1.43 (0.61–3.35)	0.41	0.79 (0.19–3.29)	0.75
Prednisolone use	1.43 (0.79–2.59)	0.23	1.55 (0.66–3.69)	0.32	0.81 (0.31–2.11)	0.67	1.56 (0.45–5.36)	0.48
Methotrexate use	0.55 (0.29–1.04)	0.064	0.52 (0.22–1.21)	0.13	0.89 (0.26–3.04)	0.85	0.92 (0.18–4.79)	0.92
DAS28-CRP	1.05 (0.86–1.30)	0.62	1.10 (0.82–1.49)	0.52	1.07 (0.77–1.50)	0.68	0.88 (0.53–1.46)	0.61

HR and 95% CI for discontinuation of ADA were estimated with Cox proportional hazards regression analysis. ADA: adalimumab; DAS28-CRP: Disease Activity Score in 28 joints based on C-reactive protein.

Table 3. Incidence rate of discontinuation of adalimumab due to adverse events. PY = 811.5.

Adverse Events	Events	Events/100PY
Total adverse events leading to discontinuation	73	9.00
Skin disorders	16	1.97
Blood disorders	4	0.49
Infectious diseases	21	2.59
Tuberculosis	3	0.37
Pneumocystis pneumonia	1	0.12
Organizing pneumonia	2	0.25
Interstitial pneumonia	3	0.37
Liver disorders	3	0.37
Malignant lymphoma	1	0.12
Solid cancer	2	0.25

PY: patient-years.

the initiation of treatment. We believe concomitant MTX to be necessary for the longterm stable efficacy of ADA.

ACKNOWLEDGMENT

We thank Dr. Toshihisa Kanamono (Department of Orthopedic Surgery, Nagano Red Cross Hospital, Nagano, Japan), Dr. Yukiyoshi Ohishi (Department of Rheumatology, Toyohashi Municipal Hospital, Toyohashi, Japan), Dr. Naoki Fukaya (Department of Orthopedic Surgery, Kariya Toyota General Hospital, Kariya, Japan), and Seiji Tsuboi (Department of Rheumatology, Shizuoka Kosei Hospital, Shizuoka, Japan) for their kind suggestions.

REFERENCES

1. van de Putte LB, Atkins C, Malaise M, Sany J, Russell AS, van Riel PL, et al. Efficacy and safety of adalimumab as monotherapy in patients with rheumatoid arthritis for whom previous disease modifying antirheumatic drug treatment has failed. Ann Rheum Dis 2004;63:508-16.
2. Weinblatt ME, Keystone EC, Furst DE, Moreland LW, Weisman MH, Birbara CA, et al. Adalimumab, a fully human anti-tumor necrosis factor alpha monoclonal antibody, for the treatment of rheumatoid arthritis in patients taking concomitant methotrexate: the ARMADA trial. Arthritis Rheum 2003;48:35-45.
3. Keystone EC, Kavanaugh AF, Sharp JT, Tannenbaum H, Hua Y, Teoh LS, et al. Radiographic, clinical, and functional outcomes of treatment with adalimumab (a human anti-tumor necrosis factor monoclonal antibody) in patients with active rheumatoid arthritis receiving concomitant methotrexate therapy: a randomized,

Personal non-commercial use only. The Journal of Rheumatology Copyright © 2016. All rights reserved.

Downloaded on April 23, 2024 from www.jrheum.org

placebo-controlled, 52-week trial. Arthritis Rheum 2004;50:1400-11.
4. Breedveld FC, Weisman MH, Kavanaugh AF, Cohen SB, Pavelka K, van Vollenhoven R, et al. The PREMIER study: A multicenter, randomized, double-blind clinical trial of combination therapy with adalimumab plus methotrexate versus methotrexate alone or adalimumab alone in patients with early, aggressive rheumatoid arthritis who had not had previous methotrexate treatment. Arthritis Rheum 2006;54:26-37.
5. Furst DE, Schiff MH, Fleischmann RM, Strand V, Birbara CA, Compagnone D, et al. Adalimumab, a fully human anti tumor necrosis factor-alpha monoclonal antibody, and concomitant standard antirheumatic therapy for the treatment of rheumatoid arthritis: results of STAR (Safety Trial of Adalimumab in Rheumatoid Arthritis). J Rheumatol 2003;30:2563-71.
6. Weinblatt ME, Keystone EC, Furst DE, Kavanaugh AF, Chartash EK, Segurado OG. Long term efficacy and safety of adalimumab plus methotrexate in patients with rheumatoid arthritis: ARMADA 4 year extended study. Ann Rheum Dis 2006;65:753-9.
7. Takeuchi T, Kameda H. The Japanese experience with biologic therapies for rheumatoid arthritis. Nature Rev Rheumatol 2010;6:644-52.
8. Kojima T, Kaneko A, Hirano Y, Ishikawa H, Miyake H, Oguchi T, et al; TBC. Study protocol of a multicenter registry of patients with rheumatoid arthritis starting biologic therapy in Japan: Tsurumai Biologics Communication Registry (TBCR) Study. Mod Rheumatol 2012;22:339-45.
9. Matsubara H, Kojima T, Kaneko A, Hirano Y, Ishikawa H, Hattori Y, et al. Longterm retention rate and risk factor for discontinuation due to insufficient efficacy and adverse events in Japanese patients with rheumatoid arthritis receiving etanercept therapy. J Rheumatol 2014;41:1583-9.
10. Kaneko A, Hirano Y, Fujibayashi T, Hattori Y, Terabe K, Kojima T, et al. Twenty-four-week clinical results of adalimumab therapy in Japanese patients with rheumatoid arthritis: retrospective analysis for the best use of adalimumab in daily practice. Mod Rheumatol 2013;23:466-77.
11. Arora A, Mahajan A, Spurden D, Boyd H, Porter D. Long-term drug survival of TNF inhibitor therapy in RA Patients: a systematic review of European National Drug Registers. Int J Rheumatol 2013;2013:764518.
12. Soliman MM, Ashcroft DM, Watson KD, Lunt M, Symmons DP, Hyrich KL. Impact of concomitant use of DMARDs on the persistence with anti-TNF therapies in patients with rheumatoid arthritis: results from the British Society for Rheumatology Biologics Register. Ann Rheum Dis 2011;70:583-9.
13. Miyasaka N; CHANGE Study Investigators. Clinical investigation in highly disease-affected rheumatoid arthritis patients in Japan with adalimumab applying standard and general evaluation: the CHANGE study. Mod Rheumatol 2008;18:252-62.
14. Bartelds GM, Wijbrandts CA, Nurmohamed MT, Stapel S, Lems WF, Aarden L, et al. Clinical response to adalimumab: relationship to anti-adalimumab antibodies and serum adalimumab concentrations in rheumatoid arthritis. Ann Rheum Dis 2007;66:921-6.
15. Garcês S, Demengeot J, Benito-Garcia E. The immunogenicity of anti-TNF therapy in immune-mediated inflammatory diseases: a systematic review of the literature with a meta-analysis. Ann Rheum Dis 2013;72:1947-55.
16. Du Pan SM, Dehler S, Ciurea A, Ziswiler HR, Gabay C, Finckh A; Swiss Clinical Quality Management Physicians. Comparison of drug retention rates and causes of drug discontinuation between anti-tumor necrosis factor agents in rheumatoid arthritis. Arthritis Rheum 2009;61:560-8.
17. Smolen JS, Aletaha D. Rheumatoid arthritis therapy reappraisal: strategies, opportunities and challenges. Nat Rev Rheumatol 2015;11:276-89.
18. Koike T, Harigai M, Ishiguro N, Inokuma S, Takei S, Takeuchi T, et al. Safety and effectiveness of adalimumab in Japanese rheumatoid arthritis patients: postmarketing surveillance report of 7740 patients. Mod Rheumatol 2014;24:390-8.
19. van der Heijde D, Breedveld FC, Kavanaugh A, Keystone EC, Landewé R, Patra K, et al. Disease activity, physical function, and radiographic progression after longterm therapy with adalimumab plus methotrexate: 5-year results of PREMIER. J Rheumatol 2010;37:2237-46.

Personal non-commercial use only. The Journal of Rheumatology Copyright © 2016. All rights reserved.

Downloaded on April 23, 2024 from www.jrheum.org