

Sustained Clinical Remission and Rate of Relapse After Tocilizumab Withdrawal in Patients with Rheumatoid Arthritis

Luis Aguilar-Lozano, Jose Dionisio Castillo-Ortiz, Cesar Vargas-Serafin, Jorge Morales-Torres, Adriana Sanchez-Ortiz, Carlos Sandoval-Castro, Jorge Padilla-Ibarra, Claudia Hernandez-Cuevas, and Cesar Ramos-Remus

ABSTRACT. Objective. Data on when to stop use of biological agents in rheumatoid arthritis (RA) are scant. We assessed the length of remission and the rate of clinical relapse in patients with RA who had to discontinue treatment with tocilizumab (TCZ) because of the ending of longterm (5 yrs) open-label clinical trials.

Methods. All patients at 2 participating centers in Mexico were in remission, defined as Disease Activity Score $28 \leq 2.6$, with no swollen joints at the time of the last TCZ infusion. Patients were followed thereafter every 8 weeks for 12 months or until relapse. Relapse was defined as the presence of ≥ 1 swollen joint. Doses of methotrexate and antiinflammatory drugs were not changed during the followup period.

Results. Forty-five patients were analyzed, 87% were women (mean age 52 yrs, mean disease duration 14 yrs). During the 12 months of followup, 44% of patients maintained remission. Relapses occurred in 56% of patients: 14 during the first 3 months after the last TCZ administration. Retreatment using other agents achieved low disease activity or remission.

Conclusion. Longterm clinical remission is possible in a number of patients with RA after suspension of TCZ. This effect has also been reported with other biologic agents. Additional data are required to support recommendations for discontinuing a biological agent after achieving remission. (J Rheumatol First Release June 1 2013; doi:10.3899/jrheum.121427)

Key Indexing Terms:

REMISSION
BIOLOGICAL AGENT

RELAPSE
WITHDRAWAL

RHEUMATOID ARTHRITIS
TOCILIZUMAB

Rheumatoid arthritis (RA) produces a multidimensional effect ranging from pain, stiffness, progressive destruction of diarthrodial joints, and development of comorbid conditions such as cardiovascular disease or cancer to family distress and high societal costs^{1,2}. Although the incidence of RA peaks during the fifth decade of life, it can affect individuals in all age groups. Indeed, in some countries, in almost half of patients with RA the disease begins before the age of 35 years³. Spontaneous remissions may occur in some patients but most have a chronic progressive course.

From the Unidad de Investigación en Enfermedades Crónico-Degenerativas, Guadalajara; Hospital Aranda de la Parra, Leon; and Hospital General Regional 45, IMSS, Guadalajara, Mexico.

L. Aguilar-Lozano, MD; J.D. Castillo-Ortiz, MD, Rheumatologist; C. Vargas-Serafin, MD, Unidad de Enfermedades Crónico-Degenerativas; J. Morales-Torres, MD, Rheumatologist, CIMOVA, Hospital Aranda de La Parra; A. Sanchez-Ortiz, MD, Rheumatologist; C. Sandoval-Castro, MD; J. Padilla-Ibarra, MD, Unidad de Investigación en Enfermedades Crónico-Degenerativas; C. Hernandez-Cuevas, MD, Rheumatologist, CIMOVA, Hospital Aranda de La Parra; C. Ramos-Remus, MD, MSc, Unidad de Investigación en Enfermedades Crónico-Degenerativas, Attending Rheumatologist, Hospital General Regional 45, IMSS.

Address correspondence to Dr. C. Ramos-Remus, Unidad de Investigación en Enfermedades Crónico-Degenerativas, Colomos 2292, Providencia, Guadalajara, Jal. 44620, Mexico. E-mail: rramos@cencar.udg.mx

Accepted for publication March 12, 2013.

RA treatment has changed considerably during the last decade with the development and introduction into daily clinical practice of biological disease-modifying agents. When to initiate biological agents in the course of the disease has been an issue of much discussion^{4,5,6}, yet according to the new American College of Rheumatology guidelines⁷, biologic agents are recommended for early and established RA with moderate to high disease activity and/or poor prognosis features (e.g., positive rheumatoid factor or anticitrullinated protein antibodies), thus increasing the proportion of patients who are candidates for their use.

Despite advances in the field of biological agents and algorithms to use them, data about when to stop such treatment are scant. Emerging data indicate that discontinuing the biologic agent is more likely to be possible after achieving and maintaining remission^{4,5,6,8,9,10,11,12,13,14,15,16,17,18,19}; if confirmed, this possibility would have a remarkable influence medically and with regard to health economics. Disease activity outcomes after the ending of an industry-sponsored clinical trial may provide useful information to support the above concept.

We assessed the length of remission and the rate of clinical relapse in patients with RA who had to discontinue

the interleukin 6 (IL-6) blocker tocilizumab (TCZ) because of the ending of longterm open-label clinical trials, at 2 participating centers in Mexico.

MATERIALS AND METHODS

Study design. This was a prospective cohort study of patients with RA assembled at the last TCZ infusion because of the ending of 2 open-label, industry-sponsored longterm extension trials.

Patients. All patients were enrolled first in 1 of 4 multinational, industry-sponsored randomized clinical trials of TCZ^{20,21,22,23} at 2 participating centers in Mexico; these patients then continued into 1 of the 2 open-label extension studies^{24,25} using methotrexate (MTX) and TCZ 8 mg/kg every 4 weeks for 5 years. The entry criterion was that at the last TCZ infusion (Week 260) all these patients be in remission, as defined by a 28-joint Disease Activity Score < 2.6 and the absence of swollen joints.

Procedures and followup. After the ending of the extension studies, patients no longer received TCZ but continued with MTX on the same dose as before. All patients returned to their referral clinic to continue with standard of care. Referral rheumatologists have different intervals between appointments and variability in joint count. Thus, to ascertain relapse and the time it occurred, patients were monitored at our clinics for 12 months as follows: (1) each patient had a structured telephone interview based on the COPCORD core questionnaire²⁶ every 8 weeks by a senior medical student; (2) each patient was instructed to communicate with our centers without delay if they believed they had any swollen joint. In any case, if a patient reported a swelling joint or had the possibility of resurgence of RA, an appointment was made at our clinics no more than 1 week later; at that point physical examination and joint count were performed by the same rheumatologist (CRR, ASO, or JMT) as during the 5 years of the extension studies, using a similar template of 68 joints. (3) All patients were also assessed by the same rheumatologists, under the same procedures, at the end of the 12-month followup.

The primary outcome was relapse, defined as the time when the patient presented at least 1 swollen joint as assessed by a rheumatologist. Rates of relapses were calculated as the ratio of relapsed patients to the total number of patients in a given period of time. Length of remission was calculated by difference of time from last infusion to time of relapse. Data during the followup period were collected by senior medical students independent from the industry-sponsored clinical trials.

Statistics. Data are presented with means and 2-tailed SD. Differences between means were determined using nonparametric tests (Mann-Whitney U test or Kruskal-Wallis 1-way ANOVA). Cox's proportional hazard model was used to explore potential predictor variables for relapse or length of remission. Significance was set at $p \leq 0.05$ level.

All participating patients had provided signed informed consent for each clinical trial following protocols of the institutional ethics committees and regulatory agencies. All patients were informed in advance about the ending of the longterm extension studies, and all had agreed to be on a waiting list to try to find another biological treatment in case of relapse.

RESULTS

Forty-five patients participated in the study. Of these, 4 were first enrolled in the RADIATE trial because of failure to respond to an anti-tumor necrosis factor (TNF) agent²⁰, 6 were enrolled in the ROSE trial because of inadequate response to traditional disease-modifying antirheumatic drugs (DMARD)²¹, 20 were enrolled in the AMBITION trial and were MTX-naïve at the time of enrollment to assess TCZ monotherapy²², and 15 patients were enrolled in the OPTION trial because of inadequate response to MTX²³. After these trials that lasted 6 months, patients continued in

the open-label extension trials^{24,25} (Figure 1). All patients were receiving MTX, including those enrolled first in the AMBITION trial, at the same dose for the entire time of the open-label extension trials and during the followup. Those who participated in the open-label extension trials were also in remission at least for the last 4 years and at the time of the last TCZ infusion. Table 1 shows demographic and clinical characteristics of the 45 patients at the last TCZ infusion.

Table 2 shows a frequency distribution of relapses. Twenty patients (45%) maintained clinical remission at 12 months after last TCZ infusion: 9 (45%) of 20 patients from the AMBITION study, 7 (46.6%) of 15 patients from the OPTION study, 1 (25%) of 4 patients from the RADIATE study, and 3 (50%) from the ROSE study. Relapses occurred in 25 patients; patients from the AMBITION study relapsed steadily during the year of followup after last TCZ infusion; patients from the OPTION and RADIATE trials relapsed mostly during the first trimester; and patients from the ROSE trial relapsed during the first and second trimester.

We did not identify predictor variables for relapse or length of remission, including disease duration at entry to the core trials, age, or sex, using Cox's proportional hazard model.

Patients who relapsed were treated further based on their healthcare resources and preferences. The 25 patients who relapsed continued with MTX, but it was increased in 9 patients. A second DMARD was indicated in 5 other patients; glucocorticoids were added in 3, anti-TNF agents were prescribed in 4, rituximab was used in 3, and TCZ was restarted in another 4 patients. All patients achieved a low disease activity status or remission.

DISCUSSION

Achieving remission to maintain functional ability and prevent joint damage is the treatment goal in RA. The clinical outlook has changed considerably with the use of biological disease-modifying agents. However, these agents are not exempt from short- and longterm risks and have a high cost, and the longterm effects of suppressing a particular immunological signal remain unknown. If they are not essential to maintain suppression of rheumatoid inflammation, it would be beneficial if such therapies could be discontinued once the initial treatment goal had been achieved. This possibility would have notable effects in patient safety and health economics.

Our study shows that it is possible to maintain longterm clinical remission after withdrawal of the IL-6 blocker TCZ; 20 out of 45 patients maintained clinical remission at 12 months, and relapses, using a stringent criterion, occurred mostly during the first 5 months after the last TCZ infusion. However, our study should be viewed as a proof of concept, because several limitations must be considered. We studied a small convenience sample of patients in remission from 2 participating centers. Patients were enrolled in different core

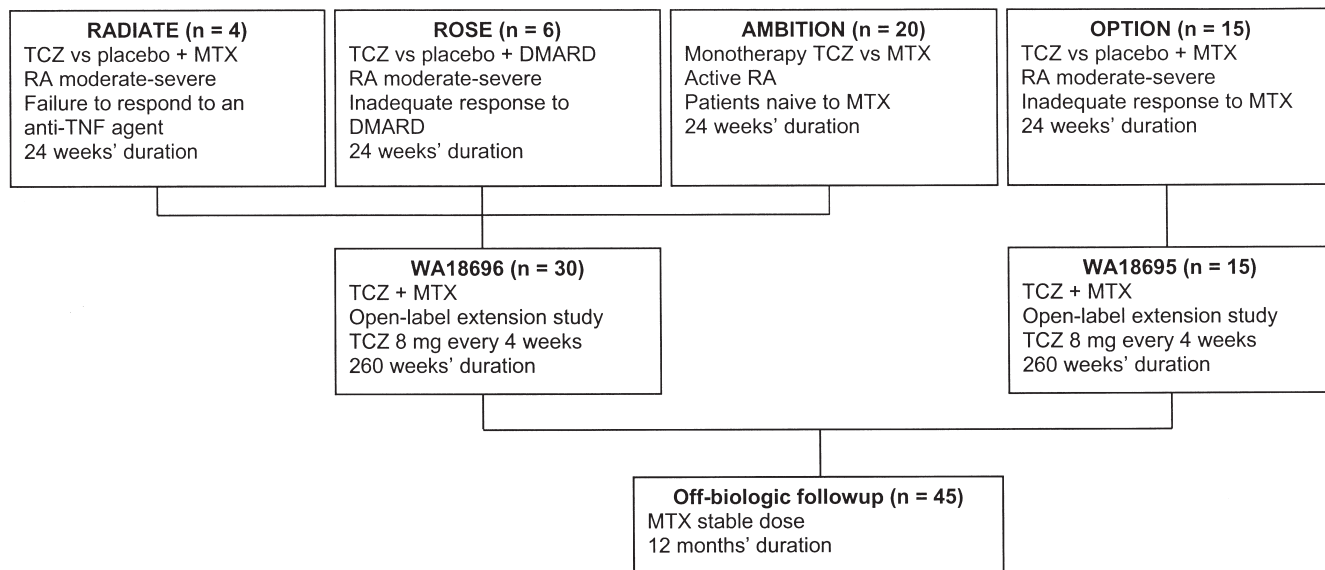


Figure 1. Core clinical trials where patients were first enrolled. TCZ: tocilizumab; MTX: methotrexate; RA: rheumatoid arthritis; TNF: tumor necrosis factor; DMARD: disease-modifying antirheumatic drug.

Table 1. Demographic and clinical characteristics of the 45 studied patients at the last tocilizumab infusion.

Characteristic	
Female, n (%)	39 (87)
Age, yrs, mean ± SD	52 ± 13
Disease duration, yrs, mean ± SD	13.7 ± 6.9
Methotrexate dose, mg/wk, mean ± SD	12.7 ± 3
DAS28, mean ± SD	1.29 ± 0.5
ESR, mm/h, mean ± SD	8.2 ± 7.4
hsCRP, mg/l, mean ± SD	0.17 ± 0.4

DAS28: Disease Activity Score for 28 joints; ESR: erythrocyte sedimentation rate; hsCRP: high sensitivity C-reactive protein.

trials, with heterogeneous criteria, e.g., some were naive to MTX, others were enrolled because of failure of an anti-TNF agent, etc. The study design precludes proper calculations about predictors of relapse or the length of remission, and effect size.

However, it is possible that factors such as shorter disease duration⁵, negative rheumatoid factor, male sex, longer duration of biological treatment¹⁷, rapid achievement of remission, nonsmoking, absence of HLA shared epitope⁹, or initial treatment with biologicals rather than delayed treatment⁶ may be independent predictors of successful discontinuation of biological agents.

Although our definition of relapse was stringent and based on clinical grounds, the effect on the progression of structural damage was not assessed.

Our results are in accord with those of other investigations and it seems that this phenomenon is not specific to a given biological agent, as per similar reports with other

agents, such as abatacept¹⁸, adalimumab^{5,12,14,17,19}, infliximab^{5,8,9,10,16,17}, and etanercept^{5,17}. Maintaining remission after discontinuation of these agents was highly variable — it has been described in 0 to 97% of patients, in studies with different patient populations, diverse outcome definitions, and followup durations between 12 weeks and over 7 years. In patients who had a disease flare, retreatment with these agents was successful in 70% to 100%. There is only 1 previous report of 4 patients who relapsed after withdrawal of TCZ and who improved after retreatment with this agent²⁷. In our patients who relapsed, retreatment strategies achieved either remission or low disease activity.

We agree with the position stated by van den Broek, *et al*⁶ about a research agenda to support guidelines for stopping biological therapies in patients with RA. The concept that longterm remissions may happen in a proportion of patients after stopping several biologic agents has been proved. It is obvious that relapses can happen, but it may be acceptable to aim at a temporary drug “holiday” rather than permanent drug-free remission. Further research should focus on predictors of remission and relapse (e.g., shorter disease duration, duration of remission before discontinuation of the biologic therapy), definitions of how to detect relapses at very early stages, strategies for early restart of biological treatment, influence on structural damage, and the efficacy of retreatment.

REFERENCES

1. Badley EM. Rheumatic diseases: the unnoticed elephant in the room. *J Rheumatol* 2008;35:6-7.
2. Loza E, Abasolo L, Jover JA, Carmona L; EPISER Study Group. Burden of disease across chronic diseases: a health survey that measured prevalence, function, and quality of life. *J Rheumatol*

Table 2. Frequency distribution of relapses and retreatment after relapses of the 45 patients.

Followup Month	Continued in Remission n (%)	Relapses, n (%)	Patient Who Relapsed	Core Study	Treatment After Relapse
0	45 (100)	0 (0)			
1	43 (96)	2 (4)	1	AMBITION	MTX+CLQ+DFZ
2	40 (89)	3 (7)	2	AMBITION	ADA+MTX
			3	OPTION	TCZ+MTX
			4	OPTION	MTX↑
3	31 (69)	9 (20)	5	RADIATE	RTX+MTX
			6	ROSE	MTX↑
			7	OPTION	TCZ+MTX
			8	OPTION	MTX+CLQ
			9	OPTION	ETA+MTX
			10	OPTION	ETA+MTX
			11	OPTION	ETA+MTX
			12	AMBITION	MTX↑
			13	RADIATE	TCZ+MTX
			14	RADIATE	RTX+MTX
5	24 (53)	7 (16)	15	ROSE	MTX↑
			16	ROSE	MTX+CLQ+PDN
			17	OPTION	MTX↑
			18	AMBITION	MTX+CLQ+PDN+SFZ
			19	AMBITION	MTX↑
			20	AMBITION	MTX↑
			21	AMBITION	TCZ+MTX
7	23 (51)	1 (2)	22	AMBITION	MTX↑
9	22 (49)	1 (2)	23	AMBITION	MTX↑
10	20 (44)	2 (4)	24	AMBITION	MTX+CLQ+SFZ
			25	AMBITION	RTX+MTX
12	20 (44)	0 (0)	—	—	—
Total	20 (44)	25 (56)			

MTX: methotrexate; MTX↑: methotrexate dose increase; CLQ: chloroquine; DFZ: deflazacort; ADA: adalimumab; TCZ: tocilizumab; RTX: rituximab; ETA: etanercept; PDN: prednisone; SFZ: sulfasalazine.

- 2008;35:159-65.
- Ramos-Remus C, Sierra-Jimenez G, Skeith K, Aceves-Avila FJ, Russell AS, Offer R, et al. Latitude gradient influences the age of onset in rheumatoid arthritis patients. *Clin Rheumatol* 2007;26:1725-8.
- Chatzidionysiou K, van Vollenhoven RF. When to initiate and discontinue biologic treatments for rheumatoid arthritis? *J Intern Med* 2011;269:614-25.
- Saleem B, Keen H, Goeb V, Parmar R, Nizam S, Hensor EM, et al. Patients with RA in remission on TNF blockers: when and in whom can TNF blocker therapy be stopped? *Ann Rheum Dis* 2010;69:1636-42.
- van den Broek M, Lems WF, Allaart CF. Do we need guidelines to stop as well as to start biological therapies for rheumatoid arthritis? *Clin Exp Rheumatol* 2012;30 Suppl 73:S21-6.
- Singh JA, Furst DE, Bharat A, Curtis JR, Kavanaugh AF, Kremer JM, et al. 2012 update of the 2008 American College of Rheumatology recommendations for the use of disease-modifying antirheumatic drugs and biologic agents in the treatment of rheumatoid arthritis. *Arthritis Care Res* 2012;64:625-39.
- Quinn MA, Conaghan PG, O'Connor PJ, Karim Z, Greenstein A, Brown A, et al. Very early treatment with infliximab in addition to methotrexate in early, poor-prognosis rheumatoid arthritis reduces magnetic resonance imaging evidence of synovitis and damage, with sustained benefit after infliximab withdrawal: results from a twelve-month randomized, double-blind, placebo-controlled trial. *Arthritis Rheum* 2005;52:27-35.
- van den Broek M, Klarenbeek NB, Dirven L, van Schaardenburg D, Hulsmans HM, Kerstens PJ, et al. Discontinuation of infliximab and potential predictors of persistent low disease activity in patients with early rheumatoid arthritis and Disease Activity Score-steered therapy: subanalysis of the BeSt study. *Ann Rheum Dis* 2011;70:1389-94.
- Tanaka Y, Takeuchi T, Mimori T, Saito K, Nawata M, Kameda H, et al. Discontinuation of infliximab after attaining low disease activity in patients with rheumatoid arthritis, RRR (remission induction by remicade in RA) Study. *Ann Rheum Dis* 2010;69:1286-91.
- van der Maas A, Kievit W, van den Bemt BJ, van den Hoogen FH, van Riel PL, den Broeder AA. Down-titration and discontinuation of infliximab in rheumatoid arthritis patients with stable low disease activity and stable treatment: an observational cohort study. *Ann Rheum Dis* 2012;71:1849-54.
- Kavanaugh A, Emery P, Fleischmann R, van Vollenhoven RF, Pavelka K, Durez P, et al. Withdrawal of adalimumab in early rheumatoid arthritis patients who attained stable low disease activity with adalimumab plus methotrexate: results of a phase 4, double-blind, placebo-controlled study [abstract]. *Arthritis Rheum* 2011;63 Suppl:665-6.
- Harigai M, Takeuchi T, Tanaka Y, Matsubara T, Yamanaka H, Miyasaka N. Discontinuation of adalimumab treatment in rheumatoid arthritis patients after achieving low disease activity. *Mod Rheumatol* 2012;22:814-22.

14. Tanaka Y, Hirata S, Fukuyo S, Nawata M, Kubo S, Yamaoka K. Discontinuation of adalimumab without functional and structural progress after attaining remission in patients with rheumatoid arthritis [abstract]. *Arthritis Rheum* 2011;63 Suppl:962.
15. Nishimoto N. Drug free remission after cessation of actemra monotherapy (DREAM study) [abstract]. *Ann Rheum Dis Suppl* 2010;69 Suppl 3:98.
16. Buch MH, Marzo-Ortega H, Bingham SJ, Emery P. Long-term treatment of rheumatoid arthritis with tumor necrosis factor alpha blockade: outcome of ceasing and restarting biologicals. *Rheumatology* 2004;43:243-4.
17. Brocq O, Millasseau E, Albert C, Grisot C, Flory P, Roux CH, et al. Effect of discontinuing TNF-alpha antagonist therapy in patients with remission of rheumatoid arthritis. *Joint Bone Spine* 2009;76:350-5.
18. Kaine J, Gladstein G, Strusberg I, Robles M, Louw I, Gujrathi S, et al. Evaluation of abatacept administered subcutaneously in adults with active rheumatoid arthritis: impact of withdrawal and reintroduction on immunogenicity, efficacy and safety (phase Iiib ALLOW study). *Ann Rheum Dis* 2012;71:38-44.
19. Detert J, Bastian H, Listing J, Weiss A, Wassenberg S, Liebhaber A, et al. Induction therapy with adalimumab plus methotrexate for 24 weeks followed by methotrexate monotherapy up to week 48 versus methotrexate therapy alone for DMARD-naive patients with early rheumatoid arthritis: HIT HARD, an investigator-initiated study. *Ann Rheum Dis* 2012 Jul 10. [E-pub ahead of print]
20. Emery P, Keystone E, Tony HP, Cantagrel A, van Vollenhoven R, Sanchez A, et al. IL-6 receptor inhibition with tocilizumab improves treatment outcomes in patients with rheumatoid arthritis refractory to anti-tumor necrosis factor biologicals: results from a 24-week multicentre randomised placebo-controlled trial. *Ann Rheum Dis* 2008;67:1516-23.
21. Yazici Y, Curtis JR, Ince A, Baraf H, Malamet RL, Teng LL, et al. Efficacy of tocilizumab in patients with moderate to severe active rheumatoid arthritis and a previous inadequate response to disease-modifying antirheumatic drugs: the ROSE study. *Ann Rheum Dis* 2012;71:198-205.
22. Jones G, Sebba A, Gu J, Lowenstein MB, Calvo A, Gomez-Reino JJ, et al. Comparison of tocilizumab monotherapy versus methotrexate monotherapy in patients with moderate to severe rheumatoid arthritis: the AMBITION study. *Ann Rheum Dis* 2010;69:88-96.
23. Smolen JS, Beaulieu A, Rubbert-Roth A, Ramos-Remus C, Rovensky J, Alecock E, et al. Effect of interleukin-6 receptor inhibition with tocilizumab in patients with rheumatoid arthritis (OPTION study): a double-blind, placebo-controlled, randomised trial. *Lancet* 2008;371:989-97.
24. Hoffmann-La Roche. Long-term extension study of safety during treatment with tocilizumab in rheumatoid arthritis patients completing treatment in WA17822. [Internet. Accessed April 2, 2013.] Available from: <http://clinicaltrials.gov/show/NCT00721123>
25. Hoffmann-La Roche; Long-term extension study of safety during treatment with tocilizumab in rheumatoid arthritis patients completing treatment in tocilizumab core studies WA18062, WA18063 and WA17824. [Internet. Accessed April 2, 2013.] Available from: <http://clinicaltrials.gov/show/NCT00720798>
26. Goycochea-Robles MV, Sanin LH, Moreno-Montoya J, Alvarez-Nemegyei J, Burgos-Vargas R, Garza-Elizondo M, et al; Grupo de Estudio Epidemiológico de Enfermedades Músculo Articulares (GEEMA). Validity of the COPCORD core questionnaire as a classification tool for rheumatic diseases. *J Rheumatol Suppl.* 2011 Jan;86:31-5.
27. Sagawa A. The efficacy and safety of reinstitution of tocilizumab in patients with relapsed active rheumatoid arthritis after long-term withdrawal of tocilizumab: retreatment of patients with rheumatoid arthritis with a novel anti-IL-6 receptor antibody after a long-term interval following SAMURAI: the RONIN study. *Mod Rheumatol* 2011;21:352-8.