Utility of Dose Frequency Adjustment in Tocilizumab Administration for Rheumatoid Arthritis

Shuntaro Saito, Yuko Kaneko, Keisuke Izumi, and Tsutomu Takeuchi

ABSTRACT. ***Objective.*** To assess the utility of dose frequency adjustment of tocilizumab (TCZ) in rheumatoid arthritis (RA).

Methods. Patients who received TCZ at 3-week (n = 24) or 5-week (n = 61) interval were evaluated.

Results. Disease Activity Score at 28 joints based on erythrocyte sedimentation rate in the 3-week group significantly improved after 3 administrations at 3-week intervals (from 4.2 to 2.7, p = 0.001). Forty-five of the patients in the 5-week group (74%) successfully continued 5-week interval administration without disease exacerbation. Lower C-reactive protein level at TCZ initiation and shorter duration to remission achievement were key to successful dose frequency reduction.

Conclusion. Adjusting the dose frequency of intravenous TCZ is a useful strategy. (J Rheumatol First Release March 15 2017; doi:10.3899/jrheum.161047)

Key Indexing Terms:
TOCILIZUMAB RHEUMATOID ARTHRITIS

Interleukin 6 (IL-6) is a key cytokine in the pathogenesis of rheumatoid arthritis (RA)[1]. Tocilizumab (TCZ) is a humanized monoclonal antibody that binds to human IL-6 receptor, and has proven to be effective in the treatment of RA[2,3].

Although the standard dose of intravenous (IV) TCZ is 8 mg/kg every 4 weeks, adjusting dose frequency of TCZ is a promising strategy from the experience on tumor necrosis factor inhibitors and several basic studies[4,5]. However, there are few reports discussing the interval titration of TCZ. Here, we evaluated the usefulness of the dose frequency adjustment for TCZ in daily practice.

MATERIALS AND METHODS

Prospectively registered patients with RA who had initiated IV TCZ of 8 mg/kg for every 4 weeks and treated for more than 12 weeks in our institution since January 2008 to June 2015 were included in our observational study. Shortening or prolongation of TCZ interval was performed with patient consent. The study was approved by the ethics committee (Ethics Committee of Keio University School of Medicine, approval number: 20110136). Informed consent from the patients was waived according to the regulations in Japan.

The patients who were receiving TCZ at a 3-week interval more than 3× because of insufficient response to a 4-week TCZ [Clinical Disease Activity Index (CDAI) > 2.8] were assigned to the "3-week group." Those with a 5-week interval after achieving remission [Disease Activity Score for 28 joints using erythrocyte sedimentation rate (DAS28-ESR) < 2.6] were assigned to the "5-week group." The patients in the 5-week group were further classified into 2 groups: patients who experienced an RA flare within 3× of administration were defined as the "5-week failure group," and those without RA flare as the "5-week continued group." RA flare was defined as the increase of RA activity for which their attending physician shortened the administration interval.

Clinical information was collected from medical records, and the CDAI[6] and DAS28-ESR[7] were calculated. The time of dose frequency adjustment was set as Week 0, and the disease activity was collected for 3 continuous infusions. Clinical and laboratory assessments were performed on days of the TCZ administrations.

Descriptive values are expressed as median [interquartile range (IQR)]. The 3 groups were compared using the Kruskal-Wallis test and the chi-square test. Comparison between the 2 groups was conducted by paired or unpaired Wilcoxon test and Fisher's exact test. The factors related to the 5-week prolongation failure were identified by multivariate logistic regression analysis, and the threshold of variables was assessed by receiver-operating characteristic (ROC) curve with area under the curve (AUC). P values < 0.05 were regarded as significant. All statistical analyses were performed with JMP software 11.2.0.

RESULTS

Baseline patient characteristics in each group. A total of 331 patients were included in our study. Among them, 24 patients were in the 3-week group and 61 patients were in the 5-week group, whereas the remaining 246 patients were treated with 4-week TCZ administration. Characteristics of the 3 groups at TCZ initiation and at dose frequency adjustment are summarized in Table 1. The difference in the CDAI and DAS28-ESR at TCZ initiation between the 3 groups was not statistically significant; however, each of the levels of component, including tender joint count, swollen joint count, and C-reactive protein (CRP) and ESR in the 3-week group at TCZ initiation were higher than in the 4-week and the 5-week groups.

From the Division of Rheumatology, Department of Internal Medicine, Keio University School of Medicine, Tokyo, Japan.

S. Saito, MD, Rheumatologist, Division of Rheumatology, Department of Internal Medicine, Keio University School of Medicine; Y. Kaneko, MD, PhD, Rheumatologist, Division of Rheumatology, Department of Internal Medicine, Keio University School of Medicine; K. Izumi, MD, PhD, Rheumatologist, Division of Rheumatology, Department of Internal Medicine, Keio University School of Medicine; T. Takeuchi, MD, PhD, Rheumatologist, Professor, Division of Rheumatology, Department of Internal Medicine, Keio University School of Medicine.

Address correspondence to Dr. T. Takeuchi, Division of Rheumatology, Department of Internal Medicine, Keio University School of Medicine, 35 Shinanomachi, Shinjuku-ku, Tokyo, Japan. E-mail: tsutake@z5.keio.jp

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Table 1. Characteristics of TCZ administration group at the initiation of TCZ and at the start of dose frequency adjustment. Values are median (interquartile range) unless otherwise indicated.

Characteristics	4-week Interval, n = 246	3-week Interval, n = 24	5-week Interval, n = 61	4-week vs 3-week, p	4-week vs 5-week, p	3-week vs 5-week, p
At the TCZ initiation						
Age, yrs	62 (50–69)	61 (44–67)	59 (50–67)	0.57	0.19	0.77
Female, n (%)	217/246 (88)	18/24 (74)	52/61 (85)	0.10	0.53	0.26
Disease duration, mos	73 (29–168)	35 (12–107)	52 (25–137)	0.03	0.28	0.20
RF-positive, n (%)	217/246 (88)	22/24 (92)	52/61 (85)	0.83	0.73	0.42
Anti-CCP–positive, n (%)	184/212 (87)	16/20 (80)	45/52 (87)	0.42	0.96	0.49
MTX use, n (%)	138/246 (56)	12/24 (50)	34/61 (56)	0.57	0.96	0.63
MTX dose, mg/week*	8 (6–10)	8 (6–10)	8 (6–10)	0.87	0.18	0.51
PSL use, n (%)	102/246 (41)	11/24 (46)	19/61 (31)	0.67	0.14	0.20
PSL dose, mg/day*	5 (4–8)	6 (4–9)	5 (3–5)	0.61	0.21	0.16
Patients with previous biologic treatment, n (%)	121/246 (49)	15/24 (63)	28/61 (46)	0.21	0.65	0.17
No. previous biologic treatment*	1 (1–2)	1 (1–2)	1 (1–2)	0.47	0.58	0.85
TJC	5 (2–9)	5 (3–12)	3 (1–8)	0.24	0.06	0.03
SJC	5 (3–9)	5 (2–10)	4 (3–7)	0.47	0.02	0.55
PtGA	51 (29–72)	40 (24–64)	60 (34–78)	0.19	0.19	0.07
PGA	37 (24–57)	52 (35–73)	52 (34–63)	< 0.01	0.13	0.41
CRP, mg/dl	1.55 (0.5–3.39)	3.24 (1.21–5.49)	1.5 (0.28–2.76)	< 0.01	0.26	< 0.01
ESR, mm/h	49 (32–77)	75 (38–108)	46 (23–74)	0.03	0.37	0.02
CDAI	20.2 (12.0–28.4)	20.2 (13.4–35.9)	19.4 (15.3–27.3)	0.32	0.24	0.93
DAS28-ESR	5.13 (4.40–6.27)	5.69 (4.60–6.90)	4.98 (3.96–6.33)	0.08	0.53	0.06
HAQ-DI	1 (0.5–1.75)	1.125 (0.375–2.0)	1.125 (0.75–1.63)	0.90	0.44	0.96
At the dose frequency adjustment						
TJC	—	3 (1–10)	0 (0–1)	—	—	< 0.01
SJC	—	4 (1–9)	0 (0–0)	—	—	< 0.01
PtGA	—	27 (13–64)	5 (2–11)	—	—	< 0.01
PGA	—	61 (23–80)	0 (0–5)	—	—	< 0.01
CRP, mg/dl	—	0.33 (0.01–3.20)	0.01 (0.01–0.02)	—	—	< 0.01
ESR, mm/h	—	22 (8–101)	5 (2–7)	—	—	< 0.01
CDAI	—	14.5 (7.9–34.0)	1.1 (0.3–2.4)	—	—	< 0.01
DAS28-ESR	—	4.2 (2.8–6.5)	1.3 (0.8–1.8)	—	—	< 0.01
HAQ-DI	—	1.625 (0.5–2.25)	0.125 (0–0.5)	—	—	< 0.01

* Median (interquartile range) of PSL/MTX dose; no. previous biologic treatments are calculated from patients who had PSL/MTX or previous biologic treatment. TCZ: tocilizumab; RF: rheumatoid factor; anti-CCP: anticyclic citrullinated peptide antibodies; MTX: methotrexate; PSL: prednisolone; TJC: tender joint count; SJC: swollen joint count; PtGA: patient's global assessment; PGA: physician's global assessment; CRP: C-reactive protein; ESR: erythrocyte sedimentation rate; CDAI: Clinical Disease Activity Index; DAS28-ESR: 28-joint Disease Activity Score based on ESR; HAQ-DI: Health Assessment Questionnaire–Disability Index.

Dose frequency increase. Twenty-four patients (73%) were administered TCZ at a 3-week interval. The median (IQR) duration from TCZ initiation to dose frequency increase was 20 weeks (12–52 weeks). The DAS28-ESR at TCZ initiation was 5.7, and decreased from 4.2 at Week 0 to 2.7 at Week 9 (p = 0.001; Figure 1A). Changes in CDAI were similar (Supplementary Figure 1A, available with the online version of this article). Notably, the levels of CRP and ESR at dose frequency increase were higher than the normal range in almost half of the patients despite TCZ treatment, but were quickly normalized after the 3-week interval administration (Supplementary Figures 2A and 2C, respectively, available with the online version of this article). No serious adverse event was reported during the dose frequency increase.

Dose frequency reduction. Sixty-one patients (18.4%) were administered TCZ at a 5-week interval. The median (IQR) duration from TCZ initiation to remission achievement was 16 weeks (12–40) and to interval prolongation was 80 weeks (36–108). Overall, after 3 cycles of 5-week TCZ administrations, the DAS28-ESR slightly but significantly increased from 1.3 at Week 0 to 1.6 at Week 15 (p = 0.027; Figure 1B). The CRP and ESR levels were slightly elevated after dose frequency reduction (Supplementary Figures 2B and 2D, respectively, available with the online version of this article).

Of the 61 patients in this group, 16 patients (26.2%) went to the 5-week failure group while the remaining 45 patients (73.8%) went to the 5-week continued group. Changes in the DAS28-ESR in both groups are shown in Figure 1C. The DAS28-ESR did not change (from 1.2 to 1.3, p = 0.56) in the 5-week continued group, but increased from 1.8 to 3.4 in the 5-week failure group (p < 0.001). Changes in the CDAI were similar (Supplementary Figures 1B and 1C, available with

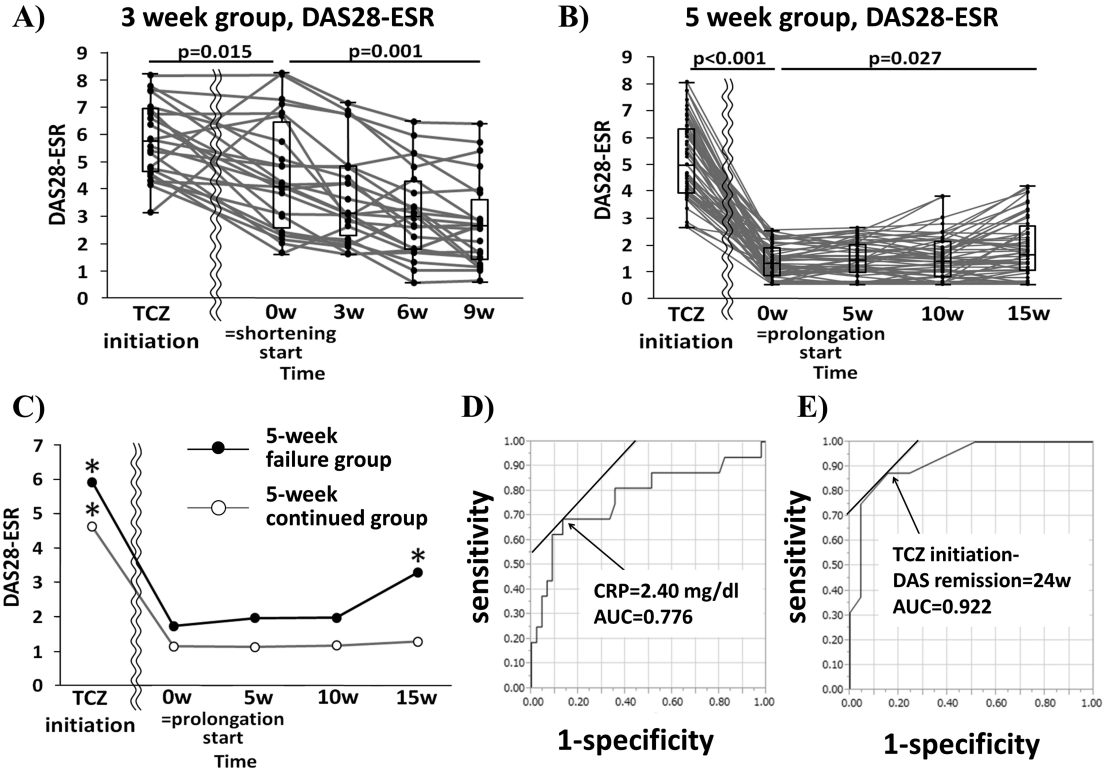

Figure 1. Transition of DAS28-ESR in (A) the 3-week group, (B) the 5-week group, and (C) the 5-week continued and failure groups. ROC curve showing (D) a cutoff of CRP level and (E) the duration of TCZ administration to achieve remission, for prolongation failure. * $p < 0.01$ for the comparison with the value at Week 0 in each group. ESR: erythrocyte sedimentation rate; DAS28-ESR: 28-joint Disease Activity Score based on ESR; ROC: receiver-operating characteristic; CRP: C-reactive protein; TCZ: tocilizumab; AUC: area under the curve.

the online version of this article). The disease activity in all the 5-week failure patients returned to remission levels after several re-administration cycles of 4-week TCZ (data not shown).

The number of patients with further dose frequency reduction is summarized in Supplementary Figure 3 (available with the online version of this article).

Predictors of prolongation failure. Although no significant difference in demographic characteristics between the 5-week continued and failure groups was found (Table 2), the CRP and ESR levels at TCZ initiation were significantly lower, and the duration from TCZ initiation to remission achievement was significantly shorter in the 5-week continued group than the 5-week failure group (CRP 1.16 mg/dl vs 3.33 mg/dl, $p < 0.01$; ESR 33 mm/h vs 74 mm/h, $p < 0.01$; duration 12 weeks vs 32 weeks, $p < 0.01$). The DAS28-ESR at the initiation of prolongation was higher in the 5-week failure group than in the 5-week continued group.

Multivariable logistic regression analysis with possible variables including CRP at TCZ initiation, the duration to remission achievement, and DAS28-ESR at dose frequency reduction identified higher CRP level at TCZ initiation (OR 3.16, 95% CI 1.47–9.92, $p < 0.01$), and longer duration to remission achievement (OR 1.23, 95% CI 1.10–1.48, $p < 0.01$) as independent factors for prolongation failure (Supplementary Table 1, available with the online version of this article). In addition, in another multivariate analysis including TCZ monotherapy, the number of previous biologics treatment, prednisolone dose, and methotrexate dose as a covariate did not identify them as a statistically significant risk (data not shown).

ROC analysis determined the level of CRP at TCZ initiation and the duration to remission achievement to be 2.40 mg/ml (69% sensitivity, 87% specificity, AUC = 0.78) and 24 weeks (85% sensitivity, 88% specificity, AUC = 0.93) as the threshold to discriminate the 5-week failure group from the 5-week continued group, respectively (Figures 1D and 1E, respectively).

DISCUSSION

Throughout our study, we demonstrated the utility of adjusting dose frequency of IV TCZ. Dose frequency increase to 3-week interval was useful to control disease activity in patients with insufficient response to 4-week administration. Dose frequency reduction was feasible in the majority of patients who achieved DAS28-ESR remission. A

Table 2. Characteristics of the 5-week continued group and the 5-week failure group. Values are median (interquartile range) unless otherwise indicated.

Characteristics	5-week Continued Group, n = 45	5-week Failure Group, n = 16	p
At the TCZ initiation			
Age, yrs	60 (30–76)	57 (35–71)	0.51
Female, n (%)	38/45 (84)	14/16 (88)	0.76
RA duration, mos	62 (2–367)	43 (4–233)	0.23
RF-positive, n (%)	37/45 (82)	15/16 (94)	0.26
Anti-CCP–positive, n (%)	32/37 (86)	13/15 (87)	0.98
MTX use, n (%)	23/45 (51)	11/16 (69)	0.22
MTX dose, mg/week*	8 (6–10)	10 (8–15)	0.20
PSL use, n (%)	12/45 (27)	7/16 (44)	0.21
PSL dose, mg/day*	5 (3–5)	5 (4–7)	0.33
Patients with previous biologic treatment, n (%)	23/45 (51)	5/16 (31)	0.17
No. previous biologic treatment*	1 (1–2)	1 (1–2)	0.57
CRP, mg/dl	1.16 (0.01–4.65)	3.33 (0.02–5.2)	< 0.01
ESR, mm/h	37 (8–124)	74 (13–132)	< 0.01
CDAI	19.2 (7.9–48.8)	19.6 (9.9–51.9)	0.38
DAS28-ESR	4.63 (2.63–7.75)	5.92 (3.84–8.08)	0.09
HAQ-DI	1.125 (0–2.375)	1.125 (0.625–2.875)	0.56
At the increase of dose frequency			
CRP, mg/dl	0.01 (0.01–0.03)	0.01 (0.01–0.04)	0.56
ESR, mm/h	5 (2–23)	7 (2–23)	0.05
CDAI	1 (0–4.0)	1.4 (0–6.5)	0.23
DAS28-ESR	1.15 (0.49–2.53)	1.75 (0.51–2.48)	0.02
Duration from TCZ initiation to prolongation, weeks	72 (16–212)	84 (16–184)	0.41
Duration from TCZ initiation to remission achievement, weeks	12 (4–40)	32 (12–96)	< 0.01
Duration from remission to prolongation, weeks	56 (4–224)	44 (4–132)	0.28

* Median (interquartile range) of PSL/MTX dose; no. previous biologic treatments are calculated from patients who had PSL, MTX, or previous biologic treatment. TCZ: tocilizumab; RA: rheumatoid arthritis; RF: rheumatoid factor; anti-CCP: anticyclic citrullinated peptide antibodies; MTX: methotrexate; PSL: prednisolone; CRP: C-reactive protein; ESR: erythrocyte sedimentation rate; CDAI: Clinical Disease Activity Index; DAS28-ESR: 28-joint Disease Activity Score based on ESR; HAQ-DI: Health Assessment Questionnaire–Disability Index.

CRP level < 2.4 mg/dl at TCZ initiation and a remission achievement within 24 weeks were key to successful dose frequency reduction.

CRP is an acute-phase protein of hepatic origin induced by IL-6 signal stimulation[8]. Although TCZ is capable of reducing CRP significantly, CRP levels were not normalized in most of the patients with RA who showed insufficient response to 4-week TCZ, indicating that IL-6 signal was not adequately suppressed in such patients. Our study has proved that dose frequency increase of TCZ could lead to greater inhibition of IL-6 signal.

Two studies attempting TCZ discontinuation reported the rate for maintaining remission to be < 20%[9,10], indicating dose frequency reduction may be favorable. To our knowledge, our study is the first report describing the utility of TCZ decreasing dose frequency, showing that about 75% of patients could maintain remission with a 5-week interval administration cycle, and further prolongation to a 6- or 7-week interval was available in more than 80% of those who attempted further prolongation. Patients with lower CRP levels at TCZ initiation may be driven by a weaker IL-6 pathway. Also, patients who have responded to TCZ more quickly are candidates for dose frequency reduction.

We should note the limitations of our study. First, ours is a single-center, prospective observational study based on daily clinical practice. Second, discretion in adjusting TCZ interval depended on the attending physicians. We need a further study to determine appropriate criteria to induce dose frequency adjustment. Third, we did not assess the effect on radiographic changes. Fourth, we did not measure serum TCZ levels, IL-6 levels, or anti-TCZ antibody. Although the detection rate of anti-TCZ antibodies is reported to be infrequent[11,12], it should be further evaluated.

Dose frequency increase would provide better control of RA disease activity in some patients, and dose frequency reduction would allow some patients to take less medication, leading to greater safety and lower costs without disease exacerbation.

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ONLINE SUPPLEMENT

Supplementary material accompanies the online version of this article.

REFERENCES

1. McInnes IB, Schett G. The pathogenesis of rheumatoid arthritis. N Engl J Med 2011;365:2205-19.
2. Dougados M, Kissel K, Sheeran T, Tak PP, Conaghan PG, Mola EM, et al. Adding tocilizumab or switching to tocilizumab monotherapy in methotrexate inadequate responders: 24-week symptomatic and structural results of a 2-year randomised controlled strategy trial in rheumatoid arthritis (ACT-RAY). Ann Rheum Dis 2013;72:43-50.
3. Gabay C, Emery P, van Vollenhoven R, Dikranian A, Alten R, Pavelka K, et al. Tocilizumab monotherapy versus adalimumab monotherapy for treatment of rheumatoid arthritis (ADACTA): a randomised, double-blind, controlled phase 4 trial. Lancet 2013;381:1541-50.
4. van Herwaarden N, van der Maas A, Minten MJ, van den Hoogen FH, Kievit W, van Vollenhoven RF, et al. Disease activity guided dose reduction and withdrawal of adalimumab or etanercept compared with usual care in rheumatoid arthritis: open label, randomised controlled, non-inferiority trial. BMJ 2015;350:h1389.
5. Fautrel B, Pham T, Alfaiate T, Gandjbakhch F, Foltz V, Morel J, et al. Step-down strategy of spacing TNF-blocker injections for established rheumatoid arthritis in remission: results of the multicentre non-inferiority randomised open-label controlled trial (STRASS: Spacing of TNF-blocker injections in Rheumatoid ArthritiS Study). Ann Rheum Dis 2016;75:59-67.
6. Smolen JS, Breedveld FC, Schiff MH, Kalden JR, Emery P, Eberl G, et al. A simplified disease activity index for rheumatoid arthritis for use in clinical practice. Rheumatology 2003;42:244-57.
7. Wells G, Becker JC, Teng J, Dougados M, Schiff M, Smolen J, et al. Validation of the 28-joint Disease Activity Score (DAS28) and European League Against Rheumatism response criteria based on C-reactive protein against disease progression in patients with rheumatoid arthritis, and comparison with the DAS28 based on erythrocyte sedimentation rate. Ann Rheum Dis 2009;68:954-60.
8. Castell JV, Gomez-Lechon MJ, David M, Hirano T, Kishimoto T, Heinrich PC. Recombinant human interleukin-6 (IL-6/BSF-2/HSF) regulates the synthesis of acute phase proteins in human hepatocytes. FEBS Lett 1988;232:347-50.
9. Nishimoto N, Amano K, Hirabayashi Y, Horiuchi T, Ishii T, Iwahashi M, et al. Drug free REmission/low disease activity after cessation of tocilizumab (Actemra) Monotherapy (DREAM) study. Mod Rheumatol 2014;24:17-25.
10. Huizinga TW, Conaghan PG, Martin-Mola E, Schett G, Amital H, Xavier RM, et al. Clinical and radiographic outcomes at 2 years and the effect of tocilizumab discontinuation following sustained remission in the second and third year of the ACT-RAY study. Ann Rheum Dis 2015;74:35-43.
11. Dougados M, Kissel K, Conaghan PG, Mola EM, Schett G, Gerli R, et al. Clinical, radiographic and immunogenic effects after 1 year of tocilizumab-based treatment strategies in rheumatoid arthritis: the ACT-RAY study. Ann Rheum Dis 2014;73:803-9.
12. Vincent FB, Morand EF, Murphy K, Mackay F, Mariette X, Marcelli C. Antidrug antibodies (ADAb) to tumour necrosis factor (TNF)-specific neutralising agents in chronic inflammatory diseases: a real issue, a clinical perspective. Ann Rheum Dis 2013;72:165-78.