Discordance in Global Assessments Between Patient and Estimator in Patients with Newly Diagnosed Rheumatoid Arthritis: Associations with Progressive Joint Destruction and Functional Impairment

Yuko Kaneko, Masataka Kuwana, Harumi Kondo, and Tsutomu Takeuchi

ABSTRACT. ***Objective.*** Factors relevant to the discordance between the patient global assessment (PGA) and estimator global assessment (EGA) in patients newly diagnosed with rheumatoid arthritis (RA) were examined.

Methods. Seventy-five consecutive newly diagnosed patients with RA were prospectively enrolled. We used 3 models in which discordance between PGA and EGA at 12 months was set at 5 mm, 10 mm, or 20 mm. We adopted 10 mm as representative and examined time course changes in clinical variables over 12 months.

Results. No significant difference was found between the concordance and the higher PGA groups regarding baseline characteristics and treatment. At 12 months, EGA, swollen joint count, and inflammatory marker values were not different, but pain visual analog scale and tender joint count were significantly higher in the higher PGA group, and the Health Assessment Questionnaire improved less. In the 10 mm and 20 mm models, the structural remission rate was significantly lower in the higher PGA group and the rapid radiological progression rate significantly higher. The discrepancy was already significant at 3 months.

Conclusion. In newly diagnosed RA, PGA at 12 months may be more sensitive for indicating progressive joint destruction and functional impairment when compared with EGA, and there is a discrepancy directed toward a worse assessment by patients. (J Rheumatol First Release May 1 2014; doi:10.3899/jrheum.131468)

Key Indexing Terms:
RHEUMATOID ARTHRITIS
ESTIMATOR GLOBAL ASSESSMENT
PATIENT GLOBAL ASSESSMENT
DISCORDANCE

The management of rheumatoid arthritis (RA) involves multiple processes, including discussion and agreement between patients and their physicians. A patient's condition is generally expressed using patient's global assessment (PGA) and the physician's evaluation by estimator global assessment (EGA). The PGA does not necessarily agree with the EGA[1,2,3,4]. The discrepancy between PGA and EGA has been reported to be 24–76%, varying according to the definition of the discrepancy and often directed toward a better assessment by physicians than by patients. Nicolau, *et al*[1] reported that patients with a greater PGA discrepancy presented with higher pain scores and tender joint count (TJC). Barton, *et al*[2] reported that depressive symptoms are associated with greater PGA discordance. Studenic, *et al*[3] described the pain score as the most significant determinant of greater PGA discordance, and Khan, *et al*[4] reported that pain is the most important determinant of the PGA. Although these reports suggest that pain is the most influential factor for elevated PGA, the results were derived from cohorts including patients with long disease duration. Joint tenderness is an important feature of disease activity, but pain is also caused by established joint damage without active inflammation, which physicians may not be willing to take into account in disease activity.

Therefore, we focused on newly diagnosed patients with little joint destruction and examined factors relevant to discordance between the PGA and EGA 12 months after diagnosis.

MATERIALS AND METHODS

Patients. This study was conducted with part of the SAKURA cohort of consecutive patients who were newly diagnosed with RA at Keio

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

Supported in part by Grants-in-Aid for Scientific Research from the Ministry of Education, Culture, Sports, Science and Technology of Japan (23701120). Also partly funded by Abbott Japan Co. Ltd., Asahi Kasei Pharma Co., Astellas Pharma Inc., Chugai Pharmaceutical Co. Ltd., Eizai Co. Ltd., Mitsubishi Tanabe Pharma Co., Santen Pharmaceutical Co. Ltd., and Wyeth.

Y. Kaneko, Instructor; M. Kuwana, Associate Professor; H. Kondo, Rheumatology Research Nurse; T. Takeuchi, Professor.

Address correspondence to Y. Kaneko, Division of Rheumatology, Department of Internal Medicine, Keio University School of Medicine, 35 Shinanomachi, Shinjuku-ku, Tokyo, Japan. E-mail: ykaneko@z6.keio.jp

Accepted for publication February 18, 2014.

University Hospital and had never been treated with either disease-modifying antirheumatic drugs or steroids and prospectively observed since September 2007. The diagnosis of RA was made based on the 1987 American College of Rheumatology (ACR) RA criteria[5] or 1994 Japanese College of Rheumatology (JCR) early RA criteria[6]. Our study was approved by the ethics committee, and all patients provided written consent.

Laboratory data included C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR). Patient pain, PGA, and EGA were measured on a visual analog scale (VAS) ranging from 0 to 100 mm. The questions for the PGA, EGA, and pain were, "How do you estimate your disease activity today?", "How do you estimate the patient's disease activity today?", and "How severe is your pain today?," respectively. A Health Assessment Questionnaire (HAQ) was filled out by each patient. EGA and joint assessment were recorded by 1 of any 5 rheumatologists, all of whom had more than 10 years of experience. Hands and feet radiographs were taken at the time of diagnosis and 12 months later. The radiographs were blinded and read independently by 2 readers (YK and MK) according to van der Heijde/modified total Sharp score (mTSS); the mean values were used in the analysis. The ∅mTSS value was the progression over a year by subtracting the mTSS at baseline from the mTSS at 12 months. Structural remission (sREM) and radiological rapid progression (RRP) were defined as ∅TSS ≤ 0.5/year and ≥ 5/year, respectively.

Analysis of factors relevant to discrepancies between PGA and EGA 12 months after diagnosis. In previous reports, the definition of discordance between the PGA and EGA was 5 to 30 mm[2,3,4,5]. We used 3 models in which the discordance at 12 months was set at 5 mm, 10 mm, or 20 mm. Each model divided the patients into 3 groups: higher PGA, concordance, and higher EGA.

Time course changes in clinical variables. We examined changes in PGA, EGA, pain VAS, 28-joint Disease Activity Score (DAS28), TJC, swollen joint count (SJC), CRP, and HAQ over 12 months and compared them between groups.

Statistical analysis. The means of continuous variables were compared by Student's t test, and proportions were compared by chi-square test. The level of concordance between PGA and EGA was analyzed using Lin's concordance correlation coefficient. The comparisons of time series data were analyzed by 2-way repeated measures of ANOVA using the posthoc Tukey method. All statistical analyses were performed using SPSS version 20.0.

RESULTS

Patients. A total of 75 consecutive patients were newly diagnosed as having RA in the SAKURA cohort between September 2007 and August 2009 and included in this study. Forty-two patients (56%) fulfilled 1987 ACR classification criteria, and 68 patients (91%) fulfilled 2010 ACR/European League Against Rheumatism (EULAR) criteria[7]. Eighty-six percent were female. At the time of diagnosis, the patients had a mean age of 60.9 years, and the mean duration from symptom onset to the time of diagnosis was 9.1 months. Seventy-nine percent were positive for anticyclic citrullinated peptide antibodies, and a mean DAS28 was 4.5.

Comparison of variables between the concordance group and higher PGA group. When the discordance was defined as 5 mm, 10 mm, or 20 mm, the higher PGA group comprised 38 (51%), 34 (45%), and 24 (32%) patients, the concordance group 29 (39%), 38 (51%), and 48 (64%) patients, and the higher EGA group 8 (10%), 3 (4%), and 3 (4%) patients, respectively. The higher EGA group did not have enough patients to analyze; therefore, we compared the higher PGA group and concordance group.

No significant differences were found between the concordance group and the higher PGA group regarding baseline characteristics and treatment at 12 months (Table 1). The EGA, SJC, CRP, and ESR did not differ between the groups in any model at 12 months. However, in all 3 models at 12 months, the pain and TJC were significantly higher in the higher PGA group than in the concordance group, and HAQ improved less. In the 10 mm and 20 mm model, radiological progression as a proportion of sREM and RRP was significantly worse in the higher PGA group and the RRP higher. In addition, in the 20 mm model, SJC was even higher in the higher PGA group.

Probability plot of yearly radiographic progression with 10 mm discordance. Because a radiological progression and the lesser improvement in HAQ were picked up by defining discordance as 10 and 20 mm, we adopted 10 mm as representative. The probability plot of ΔTSS for 10 mm is shown in Figure 1.

Time course changes in the level of concordance between EGA and PGA and disease activity-related variables. The changes in PGA and EGA over 12 months are presented in Appendix 1. The levels of concordance shown by Lin's concordance correlation coefficient were 0.55, 0.36, 0.37, 0.36, and 0.37 at baseline, 3, 6, 9, and 12 months, respectively. Time course changes in disease activity variables were examined at a discordance of 10 mm (Figure 2). In the concordance group, EGA and PGA decreased in parallel, as well as TJC, SJC, CRP, and HAQ. In the higher PGA group, the PGA did not change over 12 months, but the EGA decreased. The discrepancy between the PGA and EGA was significant at 3 months.

DISCUSSION

Our study shows that about half of newly diagnosed patients with RA exhibit discordance between PGA and EGA 12 months after diagnosis, and the PGA at 12 months might be more sensitive for detecting progressive joint destruction and less improvement of functional impairment when compared with EGA, and there is a discrepancy toward a worse assessment by patients.

There is a growing interest in the use of patient-reported outcomes in RA[8,9]. However, disagreement exists between patients and their physicians, often with PGA showing worse than EGA[1,2,3,4]. We examined patients' clinical characteristics using 3 different definitions and found that, even when defining discordance as 5 mm, a worse PGA reflected more TJC and worse pain. When the discordance was defined as 10 mm, the difference in sREM and RRP rates became significant. These results show that, while we could describe 5 mm as discordance between patients and their physicians, the appropriate definition of discordance

Table 1. Baseline and 12-month characteristics of concordance and higher PGA groups in the 3 models. Data are expressed as mean (SD) unless otherwise indicated. The numbers for current treatments include combination therapy use.

Discordance Model	5 mm			10 mm			20 mm		
	Concordance, n = 29	PGA Higher, n = 38	p	Concordance, n = 38	PGA Higher, n = 34	p	Concordance, n = 48	PGA Higher, n = 24	p
At baseline									
Age, yrs	62.5 (13.3)	57.1 (14.5)	0.12	62.6 (12.5)	57.2 (15.1)	0.10	61.9 (13.6)	56.4 (14.3)	0.13
Duration, mos	9.4 (14.5)	10.2 (20.6)	0.85	9.9 (22.2)	7.7 (9.9)	0.38	9.5 (20.0)	9.5 (11.3)	1.00
Smoking, n (%)	5 (24)	14 (37)	0.38	9 (24)	10 (35)	0.57	14 (29)	7 (29)	1.00
SE, n (%)	19 (66)	24 (63)	0.90	24 (63)	22 (65)	0.93	32 (67)	14 (58)	0.64
Anti-CCP, n (%)	18 (64)	21 (55)	0.40	25 (66)	18 (52)	0.16	30 (61)	13 (56)	0.61
DAS28	4.3 (1.2)	4.6 (1.1)	0.32	4.4 (1.1)	4.7 (1.1)	0.23	4.4 (1.2)	4.6 (1.0)	0.64
SDAI	15.3 (10.1)	16.9 (10.6)	0.54	16.2 (10.3)	17.2 (10.9)	0.68	17.0 (11.4)	16.0 (8.9)	0.66
CDAI	13.3 (8.7)	15.0 (9.2)	0.45	14.4 (9.3)	15.2 (9.5)	0.73	15.1 (10.0)	14.2 (7.8)	0.67
SJC	3.2 (2.8)	3.8 (3.7)	0.43	4.0 (3.5)	3.8 (3.7)	0.9	4.1 (3.9)	3.5 (3.0)	0.50
TJC	2.6 (2.9)	3.1 (3.4)	0.56	3.2 (3.2)	3.2 (3.5)	1.0	3.3 (3.7)	2.9 (3.1)	0.58
PGA, mm	42.6 (33.4)	42.9 (24.2)	0.97	40.7 (31.4)	43.6 (23.4)	0.67	42.4 (30.4)	41.5 (22.0)	0.89
Pain VAS, mm	42.8 (33.3)	43.7 (24.5)	0.90	41.3 (31.9)	44.7 (24.5)	0.61	44.0 (30.0)	40.8 (25.6)	0.65
EGA, mm	32.4 (24.1)	37.9 (21.3)	0.33	32.4 (23.7)	38.2 (20.8)	0.27	34.5 (24.4)	36.3 (18.0)	0.73
CRP, mg/dl	2.0 (2.9)	1.9 (2.1)	0.90	1.8 (2.6)	2.1 (2.2)	0.63	2.0 (2.7)	1.8 (2.0)	0.78
ESR, mm/h	56.7 (36.4)	60.6 (34.0)	0.65	51.4 (34.5)	61.5 (33.7)	0.11	54.2 (34.3)	64.3 (34.8)	0.25
HAQ	0.63 (0.75)	0.84 (0.70)	0.23	0.66 (0.75)	0.84 (0.63)	0.29	0.77 (0.80)	0.69 (0.49)	0.60
TSS	6.6 (7.0)	9.6 (20.5)	0.36	6.3 (7.0)	9.9 (21.4)	0.34	5.4 (6.5)	13.2 (24.9)	0.15
At 12 mos									
DAS28	2.3 (0.8)	3.0 (1.1)	*< 0.01*	2.3 (0.79)	3.1 (1.1)	*< 0.01*	2.3 (0.8)	3.3 (1.0)	*< 0.01*
SDAI	2.8 (5.1)	7.1 (5.1)	*< 0.01*	3.0 (4.6)	7.5 (5.2)	*< 0.01*	3.3 (4.5)	3.3 (4.5)	*< 0.01*
CDAI	2.7 (5.0)	6.8 (5.0)	*< 0.01*	2.85 (4.5)	7.3 (5.1)	*< 0.01*	3.1 (4.4)	8.5 (4.9)	*< 0.01*
SJC	0.8 (2.0)	1.3 (1.8)	0.30	0.8 (1.8)	1.3 (1.9)	0.16	0.7 (1.6)	1.8 (2.0)	*0.04*
TJC	0.2 (0.6)	1.0 (1.8)	*0.01*	0.3 (0.8)	1.0 (1.8)	*0.04*	0.3 (0.8)	1.3 (2.0)	*0.04*
PGA, mm	8.7 (17.0)	37.1 (21.0)	*< 0.01*	8.8 (15.2)	40.1 (20.2)	*< 0.01*	12.1 (16.5)	46.6 (18.9)	*< 0.01*
Pain VAS, mm	8.7 (16.3)	30.0 (23.2)	*< 0.01*	8.5 (14.5)	32.2 (23.6)	*< 0.01*	11.0 (17.1)	37.0 (22.3)	*< 0.01*
EGA, mm	8.2 (17.3)	8.3 (10.0)	0.98	8.7 (15.8)	8.8 (10.4)	0.98	8.7 (15.2)	8.8 (9.0)	0.96
CRP, mg/dl	0.1 (0.2)	0.3 (0.3)	0.06	0.2 (0.2)	0.3 (0.3)	0.16	0.2 (0.2)	0.3 (0.4)	0.23
ESR, mm/h	21.6 (18.7)	24.7 (22.2)	0.54	20.7 (17.5)	26.1 (22.9)	0.28	21.2 (18.7)	27.3 (23.0)	0.27
HAQ	0.26 (0.56)	0.58 (0.46)	*0.01*	0.25 (0.50)	0.61 (0.46)	*< 0.01*	0.29 (0.50)	0.67 (0.45)	*< 0.01*
∅TSS, n (%)	2.4 (6.7)	5.1 (9.2)	0.17	2.4 (6.3)	7.9 (12.8)	0.05	2.6 (6.0)	8.2 (14.8)	0.09
≤ 0.5 (sREM)	17 (59)	15 (39)		24 (63)	12 (35)		29 (60)	7 (29)	
0.5 to 5	7 (25)	10 (27)	0.22	8 (21)	9 (27)	*0.04*	10 (21)	7 (29)	*0.03*
≥ 5 (RRP)	5 (17)	13 (34)		6 (16)	13 (38)		9 (19)	10 (42)	
Current tx, n (%)									
MTX	17 (59)	24 (63)	0.90	24 (63)	21 (62)	0.90	31 (65)	14 (58)	0.80
Steroid	2 (7)	3 (8)	0.88	3 (8)	3 (9)	0.89	3 (6)	3 (13)	0.65
Biologic	5 (17)	10 (26)	0.56	6 (16)	9 (26)	0.41	10 (21)	5 (21)	1.00
Others	14 (48)	16 (42)	0.80	17 (45)	15 (44)	0.96	20 (42)	12 (50)	0.68

P values in italics are considered significant. SE: shared epitope; anti-CCP: anticyclic citrullinated peptide antibody; DAS28: 28-joint Disease Activity Score; SDAI: Simplified Disease Activity Score; CDAI: Clinical Disease Activity Score; TJC: tender joint count; SJC: swollen joint count; PGA: patient global assessment; VAS: visual analog scale; EGA: evaluator global assessment; CRP: C-reactive protein; ESR: erythrocyte sedimentation rate; MMP: matrix metalloproteinase; HAQ: Health Assessment Questionnaire; TSS: van der Heijde/modified total Sharp score; sREM: structural remission (∅TSS ≤ 0.5/yr); RRP: rapid radiographic progression (∅TSS ≥ 5/yr); tx: treatment; MTX: methotrexate.

may be 10 mm, which allowed us to detect differences in the progression of structural damage.

Several reports showed that pain is the most influential factor for elevated PGA[1,2,3,4], and our results are compatible with those studies. Although PGA has been shown to be influenced by noninflammatory factors[10,11], our study shows that PGA at 12 months may be more sensitive than the EGA for indicating progressive joint destruction and functional disorder. Studenic, *et al*[3] reported that in patients with average pain a concordance between EGA and PGA is attained at 10 swollen joints, suggesting that physicians weigh SJC heavily. However, 10 swollen joints appears quite many, and some studies have reported that synovitis can be detected by sensitive modalities in joints without swelling[12]. We consider that EGA need to be more reflective of pain in newly diagnosed patients.

When we looked at the time course changes, the discordance was already significant at 3 months and increased at 6 months. This result is presumably due to decreases in SJC leading physicians toward an improved rating, but it is not

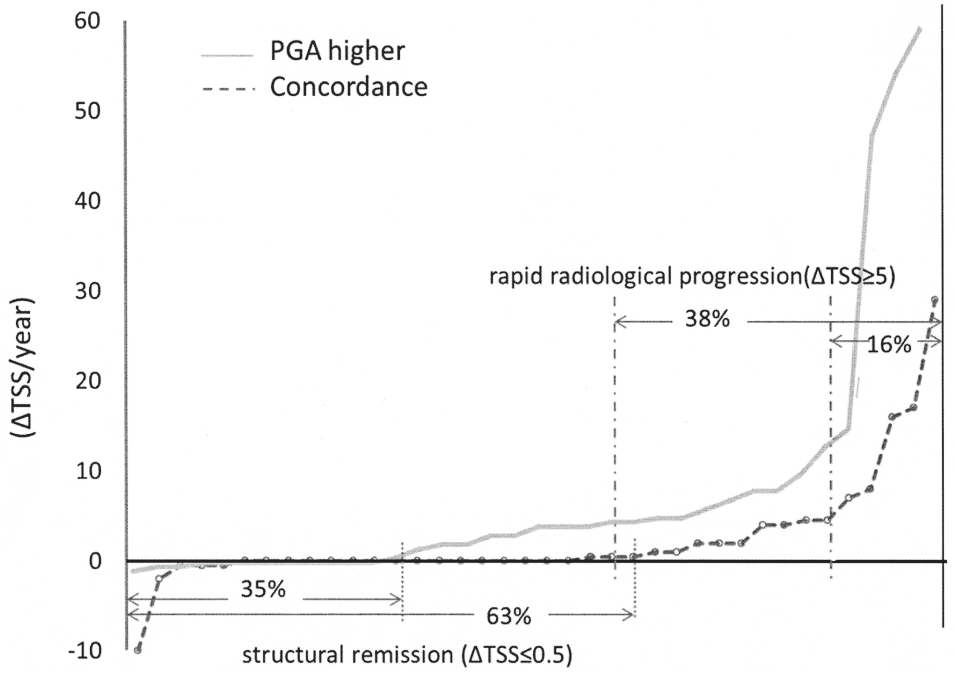

Figure 1. Radiological changes in patients at 12 months expressed by a probability plot with 10 mm discordance. The concordance group is indicated by solid lines, the higher PGA group by dotted lines. The PGA higher group showed worse progression than concordance group. The sREM rate was significantly lower in the higher PGA group and the RRP higher (35 vs 63%, 38 vs 16, respectively). TSS: modified total Sharp score; PGA: patient's global assessment; sREM: structural remission; RRP: rapid radiological progression.

necessarily the same for the perception of patients with persistent pain. Based on our results indicating that a higher level of pain or a modest increase in SJC can be associated with radiological progression, physicians should be more aware of the importance of pain and small changes in SJC in newly diagnosed patients.

Our study has some limitations. It was conducted in a single Japanese center. Because pain is expressed differently among different cultural backgrounds[13], future investigations are encouraged. As a result of the small sample size, very few patients were in the higher EGA group, which forced us to exclude those patients from the analysis. Patients with higher EGA may have different features[4] and need to be investigated. Some characteristics associated with poor prognosis were inclined to be higher in the higher PGA group, including HAQ and mTSS. Although these differences were not statistically significant, it might be partly due to the relatively small number of patients in each group. Moreover, over 12 months, more patients in the higher PGA group started to use biological agents. Hence, the differences in the worse outcomes in HAQ and mTSS may in addition to discordance between PGA and EGA reflect some underlying propensity for worse prognosis. Nonetheless, our findings point to focusing closer attention on the patient's disease experience. We did not examine a Routine Assessment of Patient Index Data 3 (RAPID3) score composed of major patient-reported outcomes: multidimensional HAQ, pain, and patient global estimate. However, our results warrant further research on the importance of patient-reported outcomes. Our patients were diagnosed based on 1987 ACR criteria or 1994 JCR early RA criteria because the SAKURA study was started before 2010 ACR/EULAR classification criteria were announced. However, because more than 90% of our patients fulfilled the new criteria, our results have enough generalizability.

In newly diagnosed patients with RA, PGA at 12 months may be more sensitive for indicating progressive joint destruction and less improvement of functional impairment when compared with EGA, and there is a discrepancy toward a worse assessment by patients.

ACKNOWLEDGMENT

Particular thanks go to Mayumi Ohta for her assistance.

REFERENCES

1. Nicolau G, Yogui MM, Vallochi TL, Gianini RJ, Laurindo IM, Novaes GS. Sources of discrepancy in patient and physician global assessments of rheumatoid arthritis disease activity. J Rheumatol 2004;31:1293–6.
2. Barton JL, Imboden J, Graph J, Glidden D, Yelin EH, Schillinger D. Patient-physician discordance in assessments of global disease severity in rheumatoid arthritis. Arthritis Care Res 2010;62:857-64.
3. Studenic P, Radner H, Smolen J, Aletaha D. Discrepancies between patients and physicians in the perception of rheumatoid arthritis disease activity. Arthritis Rheum 2012;64:2814-23.
4. Khan NA, Spencer HJ, Abda E, Aggarwal A, Alten R, Ancuta C, et

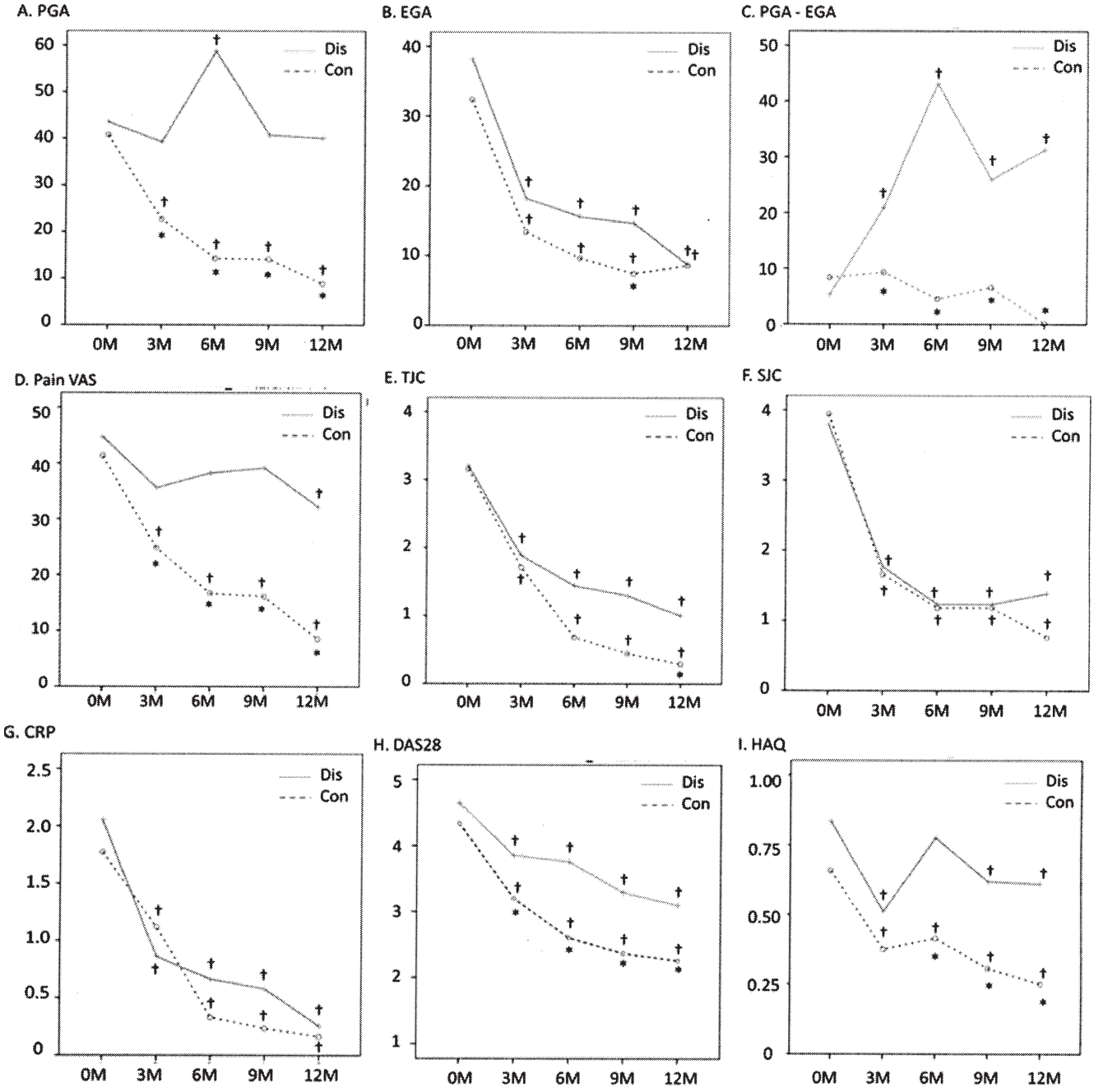

Figure 2. Changes in variables pertinent to disease activity over 12 months. A. Patient's global assessment (PGA). B. Evaluator global assessment (EGA). C. PGA-EGA. D. Pain visual analog scale (VAS). E. Tender joint count (TJC). F. Swollen joint count (SJC). G. C-reactive protein (CRP). H. 28-joint Disease Activity Score (DAS28). I. Health Assessment Questionnaire (HAQ). A discordance between the PGA and the EGA at 12 months was defined as 10 mm. The concordance group is indicated by solid lines, the higher PGA group by dotted lines. * $p < 0.05$ compared to the corresponding time point; † $p < 0.05$ compared to basal values.

al. Determinants of discordance in patients' and physicians' rating of rheumatoid arthritis disease activity. Arthritis Care Res 2012;64:206–14.
5. Arnett FC, Edworthy SM, Bloch DA, McShane DJ, Fries JF, Cooper NS, et al. The American Rheumatism Association 1987 revised criteria for the classification of rheumatoid arthritis. Arthritis Rheum 1988;31:315-24.
6. Yamamoto S, Kashiwazaki S, Nobunaga T. Study on Japan Rheumatism Association diagnostic criteria for early rheumatoid arthritis. 1. Application of the American Rheumatism Association diagnostic criteria to Japanese patients with early rheumatoid arthritis. In Japanese. Ryumachi 1994;34:1013-8.
7. Aletaha D, Neogi T, Silman AJ, Funovits J, Felson DT, Bingham CO 3rd, et al. 2010 rheumatoid arthritis classification criteria: an American College of Rheumatology/European League Against Rheumatism collaborative initiative. Ann Rheum Dis

2010;69:1589-95.
8. van Tuyl LH, Boers M. Patient's global assessment of disease activity: what are we measuring? Arthritis Rheum 2012;64:2811-3.
9. Felson DT, Smolen JS, Wells G, Zhang B, van Tuyl LH, Funovits J, et al. American College of Rheumatology/European League Against Rheumatism provisional definition of remission in rheumatoid arthritis for clinical trials. Arthritis Rheum 2011;63:573–86.
10. Masri KR, Shaver TS, Shahouri SH, Wang S, Anderson JD, Busch RE, et al. Validity and reliability problems with patient global as a component of the ACR/EULAR remission criteria as used in clinical practice. J Rheumatol 2012;39:1139-45.
11. Vermeer M, Kuper HH, van der Bijl AH, Baan H, Posthumus MD, Brus HL, et al. The provisional ACR/EULAR definition of remission in RA: a comment on the patient global assessment criterion. Rheumatology 2012;51:1076-80.
12. 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. 2005;52:27-35.
13. Anderson KO, Green CR, Payne R. Racial and ethnic disparities in pain: causes and consequences of unequal care. J Pain 2009;10:1187–204.

APPENDIX 1. The changes in PGA and EGA over 12 months were analyzed using Bland-Altman plots. The difference between PGA and EGA was assigned as the vertical value, and the mean of the PGA and EGA as the horizontal value, and t. Of 3 horizontal lines, the center one presented the mean value of the difference between the two, the upper was the mean plus 2 SD, and the lower the mean minus 2 SD. PGA: patient's global assessment; EGA: evaluator global assessment.