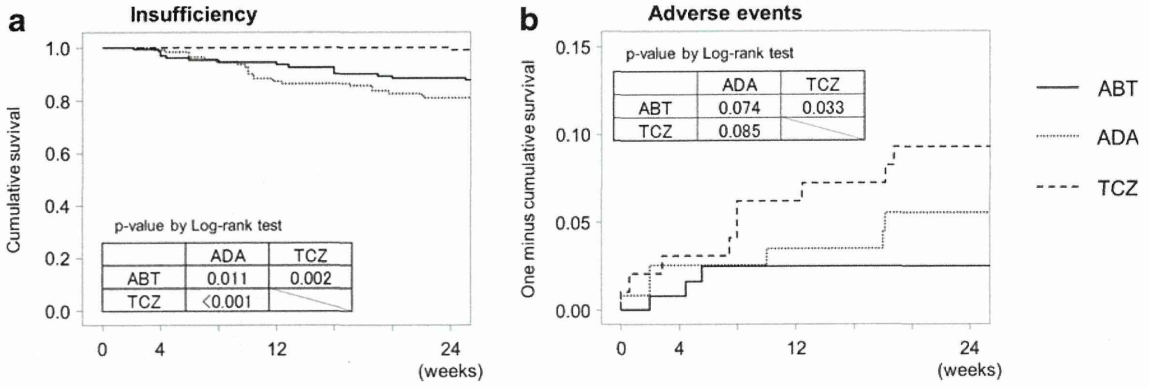

Fig. 4 Kaplan–Meier curves for time to discontinuation for each biologic. Withdrawal was due to **a** insufficient clinical efficacy (insufficiency) and **b** adverse events. Retention rates were compared using the log-rank test among groups. *ABT* abatacept, *ADA* adalimumab, *TCZ* tocilizumab

efficacy, or future outcomes in patients with comorbidities. The value of such registries in accumulating and evaluating relevant data cannot be underestimated.

In this study, differences in the DAS28-CRP score between patients treated with abatacept in the ≤MDA and HDA groups were consistent throughout the study period and remained significant at 24 weeks. The proportion of patients who achieved LDA or remission at 24 weeks was significantly lower in the HDA group. Multivariate regression analysis demonstrated that HDA at baseline was an independent negative predictor for achieving LDA and remission. Abatacept treatment in patients with HDA appeared to yield poor clinical results. However, similar results have been reported in previous studies related to TNF inhibitors and tocilizumab [1–5, 18]. Thus, inferior clinical efficacy in HDA patients is not abatacept specific, but is likely due to common features of DMARDs. The proportion of patients who achieved a moderate or good EULAR response was higher in the HDA group at 24 weeks. There was a sharp downward trend in the HDA group between 12 and 24 weeks, whereas the trend was gradual in the ≤MDA group after 4 weeks. A longer period is necessary to evaluate whether disease activity in the HDA group can eventually correspond to activity in the ≤MDA group.

Clinical efficacy in patients with HDA was similar between abatacept, adalimumab, and tocilizumab. This is the first study to demonstrate the clinical efficacy of three different classes of biologics in RA patients with HDA in clinical practice from the TBCR. Given that neither adalimumab nor tocilizumab were independent factors for achieving LDA or remission compared with abatacept, we suggest that there are no significant differences between the three biologics regarding clinical efficacy for HDA RA. However, several differences were observed. Tocilizumab treatment resulted in a higher proportion of patients who achieved a moderate EULAR response at 24 weeks and was an independent factor for a moderate EULAR response at 24 weeks compared to abatacept. Cytokine-blocking biologics, specifically tocilizumab, led to normal acute phase reactants (e.g. CRP or ESR) in almost all patients. While this constitutes a positive treatment effect, improvement in CRP might lead to an overestimation of the EULAR response rate based on DAS28-CRP [19]. Abatacept had an average discontinuation rate due to insufficient clinical efficacy. Adalimumab had the highest discontinuation rate due to insufficiency despite a higher proportion of biologic-naïve patients and concomitant MTX use compared to abatacept and tocilizumab, which could be due to relatively low MTX doses in Japan compared to doses used in European countries and the USA. It will be necessary to study patients treated with higher doses of MTX in the future. Tocilizumab had the lowest discontinuation rate due to insufficiency despite having the lowest proportion of biologic-naïve patients and concomitant MTX use. This could be partially explained by a higher rate of achieving a EULAR response, which generally encourages physicians to continue treatment even if clinical efficacy appears to be inadequate. It will be necessary to study whether low discontinuation rates can be maintained for longer periods of time. In contrast, tocilizumab demonstrated the highest discontinuation rate due to adverse events compared to abatacept. Abatacept satisfactorily balances clinical efficacy and safety in RA patients with HDA.

'Biologic-naïve' was an independent factor for achieving LDA or EULAR responses at 24 weeks in patients treated with abatacept. Similar to other classes of biologics, abatacept likely demonstrates optimal efficacy in biologic-naïve patients. Several reports have indicated that adalimumab or tocilizumab demonstrate higher efficacy in biologic-naïve patients compared to patients with a history of prior biologic use [5, 20–26]. Advanced functional impairment has also been reported as a negative factor regarding clinical efficacy of adalimumab and tocilizumab [1, 18, 27, 28]. 'Better physical function' in all patients treated with abatacept was an independent factor for achieving LDA. In patients with HDA at baseline using abatacept, adalimumab, or tocilizumab, 'biologic-naïve' or 'better physical function' were independent factors for achieving LDA or remission rather than the specific agent used. Thus, baseline characteristics are more critical

than treatment agents for predicting favourable clinical efficacy in RA patients with HDA.

This study has several limitations. It was observational and not randomised, and treatments were likely influenced by patient characteristics and other factors such as preference of administration routes. Although concomitant MTX use was not an independent factor for achieving LDA, remission, or a moderate EULAR response in all patients treated with abatacept and patients with HDA treated with abatacept, adalimumab, or tocilizumab, the mean MTX dose was relatively low in this study. Future studies with higher MTX doses are necessary to conclude whether MTX has a synergistic effect. In addition, radiographic data were not available. Due to the importance of joint protective effects in demonstrating clinical efficacy, evaluating radiographic changes in patients treated with abatacept will be necessary in the future.

In conclusion, this study demonstrated the clinical efficacy of abatacept, adalimumab, and tocilizumab in clinical practice. The clinical efficacy in RA patients with HDA was similar between the three classes of biologics. We suggest that abatacept can be used to treat patients with low, moderate, and high disease activity in clinical practice.

Acknowledgments We thank Dr. Toshihisa Kanamono (Department of Orthopedic Surgery, Nagano Red Cross Hospital, Nagano, Japan), Dr. Yukiyoshi Oh-ishi (Department of Rheumatology, Toyohashi Municipal Hospital, Toyohashi, Japan), Dr. Yoshito Etoh (Department of Orthopedic Surgery, Higashi Nagoya National Hospital, Nagoya, Japan), and Dr. Masahiro Kobayakawa (Department of Orthopedic Surgery, Fukuroi Municipal Hospital, Fukuroi, Japan) for their kind suggestions.

Conflicts of interest N. Ishiguro, T. Kojima, Y. Hirano, and A. Kaneko have received speaking fees (less than $5,000) from Abbott Japan Co. Ltd., Eisai Co. Ltd., Mitsubishi Tanabe Pharma Corporation, Pfizer Co. Ltd, Chugai Pharmaceutical Co. Ltd., and Bristol-Myers Squibb Co. Ltd. The other authors declare no conflicts of interest.

References

1. Hyrich KL, Watson KD, Silman AJ, Symmons DP, British Society for Rheumatology Biologics R (2006) Predictors of response to anti-TNF-alpha therapy among patients with rheumatoid arthritis: results from the British society for rheumatology biologics register. Rheumatology 45(12):1558–1565. doi:10.1093/rheumatology/kel149
2. van der Heijde D, Klareskog L, Landewe R, Bruyn GA, Cantagrel A, Durez P, Herrero-Beaumont G, Molad Y, Codreanu C, Valentini G, Zahora R, Pedersen R, MacPeek D, Wajdula J, Fatenejad S (2007) Disease remission and sustained halting of radiographic progression with combination etanercept and methotrexate in patients with rheumatoid arthritis. Arthritis Rheum 56(12):3928–3939. doi:10.1002/art.23141
3. Iwamoto N, Kawakami A, Fujikawa K, Aramaki T, Kawashiri SY, Tamai M, Arima K, Ichinose K, Kamachi M, Yamasaki S, Nakamura H, Nakashima M, Mizokami A, Goto A, Fukuda T, Matsuoka N, Ueki Y, Tsukada T, Migita K, Shoumura F, Kawabe Y, Shibatomi K, Mine M, Ida H, Origuchi T, Aoyagi K, Eguchi K (2009) Prediction of DAS28-ESR remission at 6 months by baseline variables in patients with rheumatoid arthritis treated with etanercept in Japanese population. Mod Rheumatol Jpn Rheum Assoc 19(5):488–492
4. Tanaka Y, Takeuchi T, Inoue E, Saito K, Sekiguchi N, Sato E, Nawata M, Kameda H, Iwata S, Amano K, Yamanaka H (2008) Retrospective clinical study on the notable efficacy and related factors of infliximab therapy in a rheumatoid arthritis management group in Japan: one-year clinical outcomes (RECONFIRM-2). Mod Rheumatol Jpn Rheum Assoc 18(2):146–152. doi:10.1007/s10165-008-0026-3
5. Burmester GR, Feist E, Kellner H, Braun J, Iking-Konert C, Rubbert-Roth A (2011) Effectiveness and safety of the interleukin 6-receptor antagonist tocilizumab after 4 and 24 weeks in patients with active rheumatoid arthritis: the first phase IIIb real-life study (TAMARA). Ann Rheum Dis 70(5):755–759. doi:10.1136/ard.2010.139725
6. Kremer JM, Genant HK, Moreland LW, Russell AS, Emery P, Abud-Mendoza C, Szechinski J, Li T, Ge Z, Becker JC, Westhovens R (2006) Effects of abatacept in patients with methotrexate-resistant active rheumatoid arthritis: a randomized trial. Ann Intern Med 144(12):865–876
7. Kremer JM, Russell AS, Emery P, Abud-Mendoza C, Szechinski J, Westhovens R, Li T, Zhou X, Becker JC, Aranda R, Peterfy C, Genant HK (2011) Long-term safety, efficacy and inhibition of radiographic progression with abatacept treatment in patients with rheumatoid arthritis and an inadequate response to methotrexate: 3-year results from the AIM trial. Ann Rheum Dis 70(10):1826–1830. doi:10.1136/ard.2010.139345
8. Schiff M, Keiserman M, Codding C, Songcharoen S, Berman A, Nayiager S, Saldate C, Li T, Aranda R, Becker JC, Lin C, Cornet PL, Dougados M (2008) Efficacy and safety of abatacept or infliximab vs placebo in ATTEST: a phase III, multi-centre, randomised, double-blind, placebo-controlled study in patients with rheumatoid arthritis and an inadequate response to methotrexate. Ann Rheum Dis 67(8):1096–1103. doi:10.1136/ard.2007.080002
9. Schiff M, Pritchard C, Huffstutter JE, Rodriguez-Valverde V, Durez P, Zhou X, Li T, Bahrt K, Kelly S, Le Bars M, Genovese MC (2009) The 6-month safety and efficacy of abatacept in patients with rheumatoid arthritis who underwent a washout after anti-tumour necrosis factor therapy or were directly switched to abatacept: the ARRIVE trial. Ann Rheum Dis 68(11):1708–1714. doi:10.1136/ard.2008.099218
10. Westhovens R, Robles M, Ximenes AC, Nayiager S, Wollenhaupt J, Durez P, Gomez-Reino J, Grassi W, Haraoui B, Shergy W, Park SH, Genant H, Peterfy C, Becker JC, Covucci A, Helfrick R, Bathon J (2009) Clinical efficacy and safety of abatacept in methotrexate-naive patients with early rheumatoid arthritis and poor prognostic factors. Ann Rheum Dis 68(12):1870–1877. doi:10.1136/ard.2008.101121
11. Leffers HC, Ostergaard M, Glintborg B, Krogh NS, Foged H, Tarp U, Lorenzen T, Hansen A, Hansen MS, Jacobsen MS, Dreyer L, Hetland ML (2011) All departments of rheumatology in D (2011) efficacy of abatacept and tocilizumab in patients with rheumatoid arthritis treated in clinical practice: results from the nationwide Danish DANBIO registry. Ann Rheum Dis 70(7):1216–1222. doi:10.1136/ard.2010.140129
12. Takahashi N, Kojima T, Terabe K, Kaneko A, Kida D, Hirano Y, Fujibayashi T, Yabe Y, Takagi H, Oguchi T, Miyake H, Kato T, Fukaya N, Ishikawa H, Hayashi M, Tsuboi S, Kato D, Funahashi K, Matsubara H, Hattori Y, Hanabayashi M, Hirabara S, Yoshioka Y, Ishiguro N (2012) Clinical efficacy of abatacept in Japanese rheumatoid arthritis patients. Mod Rheumatol Jpn Rheum Assoc. doi:10.1007/s10165-012-0760-4

13. Kojima T, Kaneko A, Hirano Y, Ishikawa H, Miyake H, Oguchi T, Takagi H, Yabe Y, Kato T, Ito T, Terabe K, Fukaya N, Kanayama Y, Shioura T, Funahashi K, Hayashi M, Kato D, Matsubara H, Fujibayashi T, Kojima M, Ishiguro N, TBC (2011) Study protocol of a multicenter registry of patients with rheumatoid arthritis starting biologic therapy in Japan: tsurumai biologics communication registry (TBCR) study. Mod Rheumatol Jpn Rheum Assoc. doi:10.1007/s10165-011-0518-4
14. Matsui T, Kuga Y, Kaneko A, Nishino J, Eto Y, Chiba N, Yasuda M, Saisho K, Shimada K, Tohma S (2007) Disease activity score 28 (DAS28) using C-reactive protein underestimates disease activity and overestimates EULAR response criteria compared with DAS28 using erythrocyte sedimentation rate in a large observational cohort of rheumatoid arthritis patients in Japan. Ann Rheum Dis 66(9):1221–1226. doi:10.1136/ard.2006.063834
15. van Gestel A, van Riel P (1996) American college of rheumatology preliminary definition of improvement in rheumatoid arthritis: comment on the article by Felson et al. Arthritis Rheum 39(3):535–537
16. Weinblatt ME, Schiff M, Valente R, van der Heijde D, Citera G, Zhao C, Maldonado M, Fleischmann R (2012) Head-to-head comparison of subcutaneous abatacept versus adalimumab for rheumatoid arthritis. Arthritis Rheum. doi:10.1002/art.37711
17. Gabay C, Emery P, van Vollenhoven R, Dikranian A, Alten R, Klearman M, Musselman D, Agarwal S, Green J, Kavanaugh A (2012) Tocilizumab (TCZ) Monotherapy is superior to adalimumab (ADA) Monotherapy in reducing disease activity in patients with rheumatoid arthritis (RA): 24-week data from the phase 4 ADACTA trial. Ann Rheum Dis 71(Suppl 3):152
18. Kristensen LE, Kapetanovic MC, Gulfe A, Soderlin M, Saxne T, Geborek P (2008) Predictors of response to anti-TNF therapy according to ACR and EULAR criteria in patients with established RA: results from the south Swedish arthritis treatment group register. Rheumatology 47(4):495–499. doi:10.1093/rheumatology/ken002
19. Smolen JS, Aletaha D (2011) Interleukin-6 receptor inhibition with tocilizumab and attainment of disease remission in rheumatoid arthritis: the role of acute-phase reactants. Arthritis Rheum 63(1):43–52. doi:10.1002/art.27740
20. Takeuchi T, Tanaka Y, Kaneko Y, Tanaka E, Hirata S, Kurasawa T, Kubo S, Saito K, Shidara K, Kimura N, Nagasawa H, Kameda H, Amano K, Yamanaka H (2012) Effectiveness and safety of adalimumab in Japanese patients with rheumatoid arthritis: retrospective analyses of data collected during the first year of adalimumab treatment in routine clinical practice (HARMONY study). Mod Rheumatol Jpn Rheum Association 22(3):327–338. doi:10.1007/s10165-011-0516-6
21. Bombardieri S, Ruiz AA, Fardellone P, Geusens P, McKenna F, Unnebrink K, Oezer U, Kary S, Kupper H, Burmester GR, Research in Active Rheumatoid Arthritis Study G (2007) Effectiveness of adalimumab for rheumatoid arthritis in patients with a history of TNF-antagonist therapy in clinical practice. Rheumatology 46(7):1191–1199. doi:10.1093/rheumatology/kem091
22. Kaneko A, Hirano Y, Fujibayashi T, Hattori Y, Terabe K, Kojima T, Ishiguro N (2012) 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 Jpn Rheum Assoc. doi:10.1007/s10165-012-0705-y
23. Yamanaka H, Tanaka Y, Inoue E, Hoshi D, Momohara S, Hanami K, Yunoue N, Saito K, Amano K, Kameda H, Takeuchi T (2011) Efficacy and tolerability of tocilizumab in rheumatoid arthritis patients seen in daily clinical practice in Japan: results from a retrospective study (REACTION study). Mod Rheumatol Jpn Rheum Assoc 21(2):122–133. doi:10.1007/s10165-010-0366-7
24. Yabe Y, Kojima T, Kaneko A, Asai N, Kobayakawa T, Ishiguro N (2012) A review of tocilizumab treatment in 122 rheumatoid arthritis patients included in the tsurumai biologics communication registry (TBCR) study. Mod Rheumatol Jpn Rheum Assoc. doi:10.1007/s10165-012-0648-3
25. Nakashima Y, Kondo M, Harada H, Horiuchi T, Ishinishi T, Jojima H, Kuroda K, Miyahara H, Nagamine R, Nakashima H, Otsuka T, Saikawa I, Shono E, Suematsu E, Tsuru T, Wada K, Iwamoto Y (2010) Clinical evaluation of tocilizumab for patients with active rheumatoid arthritis refractory to anti-TNF biologics: tocilizumab in combination with methotrexate. Mod Rheumatol Jpn Rheum Assoc 20(4):343–352. doi:10.1007/s10165-010-0290-x
26. Bykerk VP, Ostor AJ, Alvaro-Gracia J, Pavelka K, Ivorra JA, Graninger W, Bensen W, Nurmohamed MT, Krause A, Bernasconi C, Stancati A, Sibilia J (2012) Tocilizumab in patients with active rheumatoid arthritis and inadequate responses to DMARDs and/or TNF inhibitors: a large, open-label study close to clinical practice. Ann Rheum Dis 71(12):1950–1954. doi:10.1136/annrheumdis-2011-201087
27. Mancarella L, Bobbio-Pallavicini F, Ceccarelli F, Falappone PC, Ferrante A, Malesci D, Massara A, Nacci F, Secchi ME, Manganelli S, Salaffi F, Bambara ML, Bombardieri S, Cutolo M, Ferri C, Galeazzi M, Gerli R, Giacomelli R, Grassi W, Lapadula G, Cerinic MM, Montecucco C, Trotta F, Triolo G, Valentini G, Valesini G, Ferraccioli GF, group G (2007) Good clinical response, remission, and predictors of remission in rheumatoid arthritis patients treated with tumor necrosis factor-alpha blockers: the GISEA study. J Rheumatol 34(8):1670–1673
28. Takeuchi T, Tanaka Y, Amano K, Hoshi D, Nawata M, Nagasawa H, Sato E, Saito K, Kaneko Y, Fukuyo S, Kurasawa T, Hanami K, Kameda H, Yamanaka H (2011) Clinical, radiographic and functional effectiveness of tocilizumab for rheumatoid arthritis patients–REACTION 52-week study. Rheumatology 50(10):1908–1915. doi:10.1093/rheumatology/ker221

Arthritis Care & Research
Vol. 66, No. 5, May 2014, pp 679–686
DOI 10.1002/acr.22203

ORIGINAL ARTICLE

Alexithymia, Depression, Inflammation, and Pain in Patients With Rheumatoid Arthritis

MASAYO KOJIMA,[1] TOSHIHISA KOJIMA,[2] SADAO SUZUKI,[1] NOBUNORI TAKAHASHI,[3] KOJI FUNAHASHI,[3] DAIZO KATO,[3] MASAHIRO HANABAYASHI,[3] SHINYA HIRABARA,[3] SHUJI ASAI,[3] AND NAOKI ISHIGURO[2]

Objective. **We previously reported that depression and inflammation have independent effects on pain severity in patients with rheumatoid arthritis (RA). Alexithymia is a personality trait characterized by deficits in cognitive processing and regulation of emotions. A broad association between alexithymia and various health problems has been suggested, including depression, inflammation, and pain. The objective of this study was to examine the independent influence of alexithymia on pain perception and its relationship to depression and inflammation.**

Methods. **We evaluated 213 RA outpatients who completed self-administered questionnaires, including the Beck Depression Inventory-II (BDI-II) to measure depression severity, the 20-item Toronto Alexithymia Scale (TAS-20) to measure degree of alexithymia, and a visual analog scale to quantify perceived pain. Serum C-reactive protein (CRP) levels were measured to quantify inflammation severity.**

Results. **An initial significant positive association between the TAS-20 score and pain severity ($P = 0.01$) lost significance after controlling for BDI-II score and CRP level using regression analysis. An interaction was observed among alexithymia, depression, and inflammation with regard to perceived pain. Among those without alexithymia, pain severity increased linearly with the CRP tertile levels regardless of the presence of depression ($P < 0.001$ for trend). No linear association between pain severity and CRP level was observed among those with alexithymia. Moreover, depressed patients with alexithymia (BDI-II score ≥14 and TAS-20 score ≥61) reported severe pain even at low CRP levels.**

Conclusion. **Alexithymia might have a substantial role in pain perception as well as depression in patients with RA. A biopsychosocial approach is essential to achieve better pain control.**

INTRODUCTION

Rheumatoid arthritis (RA) is a chronic disease in which an autoimmune disorder causes inflammation of the joints and surrounding tissues. Patients with RA experience persistent pain, arising from inflammation. This pain is also known to possess a strong emotional component and is affected by mood and psychosocial factors (1). We previously reported the independent influences of depression severity and inflammation on perceived pain in patients with RA (2). Both the depression score and the serum levels of C-reactive protein (CRP), a biomarker of inflammation, were significantly associated with pain, even after controlling for each other and for clinical covariates by regression analysis.

Supported by the Japan Society for the Promotion of Science (JSPS KAKENHI grant 21590708).

[1]Masayo Kojima, MD, PhD, Sadao Suzuki, MD, PhD: Nagoya City University Graduate School of Medical Sciences, Nagoya, Japan; [2]Toshihisa Kojima, MD, PhD, Naoki Ishiguro, MD, PhD: Nagoya University Hospital and Nagoya University Graduate School of Medical Sciences, Nagoya, Japan; [3]Nobunori Takahashi, MD, PhD, Koji Funahashi, MD, PhD, Daizo Kato, MD, Masahiro Hanabayashi, MD, Shinya Hirabara, MD, PhD, Shuji Asai, MD, PhD: Nagoya University Graduate School of Medical Science, Nagoya, Japan.

Dr. Masayo Kojima has received speaking fees (less than $10,000 each) from AbbVie, Chugai, Dainippon Sumitomo, Mitsubishi Tanabe, and Pfizer. Dr. Toshihisa Kojima has received speaking fees (less than $10,000 each) from Abbott, Bristol-Myers Squibb, Chugai, Eisai, Mitsubishi Tanabe, Pfizer, and Takeda. Dr. Takahashi has received consulting fees, speaking fees, and/or honoraria (less than $10,000 each) from Astellas, Bristol-Myers Squibb, Chugai, Mitsubishi Tanabe, Pfizer, Takeda, and UCB Japan. Dr. Hirabara has received consulting fees, speaking fees, and/or honoraria (less than $10,000) from Bristol-Myers Squibb. Dr. Ishiguro has received speaking fees (less than $10,000 each) from Abbott, Bristol-Myers Squibb, Chugai, Eisai, Mitsubishi Tanabe, Pfizer, and Takeda.

Address correspondence to Masayo Kojima, MD, PhD, Department of Public Health, Nagoya City University Graduate School of Medical Sciences, Kawasumi 1, Mizuho-cho, Mizuho-Ku, Nagoya, Japan, 467-8601. E-mail: masayok@med.nagoya-cu.ac.jp.

Submitted for publication June 3, 2013; accepted in revised form October 8, 2013.

Significance & Innovations

- Alexithymia, which is a personality trait characterized by the inability to identify and describe one's own feelings and a preference for externally oriented thinking rather than introspection, is considered as a risk factor that is broadly associated with various mental and physical health problems.
- This is the first study to evaluate the interrelationships between alexithymia, depression, inflammation, and perceived pain intensity in patients with rheumatoid arthritis (RA).
- Alexithymia might have played a substantial role in pain perception, and when it was coupled with depression, it could separate the perception of pain from the physical effects of inflammation.
- Therefore, to achieve appropriate pain control in all patients with RA, the assessment of alexithymia and use of biopsychosocial approaches would be required, in addition to traditional pharmaceutical interventions.

Alexithymia is defined as a personality construct with difficulties in affective self-regulation (3). It has been proposed to be a cluster of cognitive and affective characteristics that are commonly observed among classic psychosomatic patients for whom therapy has been unsuccessful (4). Individuals with alexithymia tend to experience difficulties in identifying and describing their inner feelings and have a limited imaginary capacity and a preference for externally oriented thinking rather than introspection (3). To date, alexithymia has been reported to have a broad association with various mental and physical problems, including depression (5), inflammation (6–8), and pain (9). Furthermore, alexithymia is suspected to be an important psychosocial factor affecting disease control and health promotion (10–12).

Pain is a personal, subjective experience produced by multiple influences and is composed of sensory, affective, and cognitive dimensions (13). Considering the construct of alexithymia reflecting deficits in cognitive processing and the regulation of emotions, alexithymia may play some role in pain perception. A high prevalence of alexithymia has been observed in patients with chronic pain (9), including those with RA (14,15). Numerous observational and some experimental studies revealed positive associations between alexithymia and pain intensity and sensitivity (16). However, there are some conflicting reports; alexithymia has been suggested to be associated with poor awareness of physical symptoms, such as cardiac pain, resulting in a delay of seeking treatment (17). One possible reason for this inconsistency may be the influence of negative affect. Alexithymia has been reported to be associated with negative affect (5), which is substantially associated with pain (1). Pain and depression often coexist and each increases the gravity of the other, since they share several pathophysiologic pathways, including neuroendocrine and immune activities (18). The independent effect of alexithymia on pain perception has rarely been examined so far. Hosoi et al examined 129 patients with neuromuscular disorders and found that the association between alexithymia and pain intensity is greatly diminished when controlling for baseline negative affect (19). Another shortcoming of previous studies is that most of them evaluated the output of pain without considering the inputs of pain (13). According to recent experimental studies, those with alexithymia may be insensitive to their own physical sensation when the external stimuli are not strong enough (16,20).

The purpose of this study was to examine the independent impact of alexithymia on pain perception among patients with RA. From accumulating evidence, we hypothesized that the association of perceived pain severity is altered by the level of inflammation and by the presence of depression and alexithymia. It is speculated that RA patients with alexithymia may report more severe pain than the level estimated from CRP results when they are depressed because they are unable to modulate their own feelings and tend to amplify bodily sensations due to psychological distress (21). On the other hand, patients with alexithymia may be less responsive to inflammation when they are not depressive because of their external focus of attention (17).

To our knowledge, this is the first study assessing the interrelationships between alexithymia, depression, inflammation, and pain perception. We explored how alexithymia may intervene in the association we had observed in the previous study.

PATIENTS AND METHODS

We conducted a secondary analysis of data from the observational study focusing on the association between the psychosocial factors and clinical evaluations in patients with RA. The study protocol followed has been described in detail in a previous publication (2). The Research Ethics Committee of Nagoya City University Graduate School of Medical Sciences, Japan approved the research protocol.

Subjects. The study subjects were selected from among patients who met the criteria of the American College of Rheumatology (22) and attended the Outpatient Rheumatology Clinic of Nagoya University Hospital (Nagoya, Japan) between March 7 and April 18, 2003. During this period, trained research assistants invited 321 eligible patients to participate in the study after briefly explaining the protocol. Of these 321 patients, 303 provided written informed consent for participation and completed the self-administered questionnaires. Finally, a total of 218 patients, who completed all of the clinical examinations and questionnaire surveys, were included in the current study.

Measures. All of the patients who agreed to participate in the study were asked to complete self-administered questionnaires that reported their sociodemographic characteristics, smoking and drinking habits, year of RA onset, and current perceived pain severity using a visual analog

scale. The details of the questionnaire have been described in a previous study (2). In addition, the questionnaire included a battery of well-validated self-reporting inventories for evaluation of psychosocial factors. Alexithymia was evaluated using the Japanese version (23) of the 20-item Toronto Alexithymia Scale (TAS-20) (24,25), which is the most internationally popular instrument to assess alexithymia (12). Total TAS-20 scores range from 20–100, and a score of ≥61 was suggested for use in alexithymia screening by the original authors (25). Depression severity was assessed using the Japanese version (26) of the Beck Depression Inventory-II (BDI-II) (27). BDI-II scores range from 0–63, and a score of ≥14 indicates the presence of at least mild to moderate symptoms of depression (27,28).

As part of routine clinical examinations, experienced rheumatologists who were unaware of patients' participation in this study assessed the number of swollen and/or tender joints along with the Steinbrocker functional classification (29) and made a global assessment of disease severity for each of their patients. Serum CRP levels were measured using standard methodology (30) on a JCA-BM 2250 autoanalyzer (JEOL) with CRP-Latex (II) X2 SEIKEN reagents from Denka Seiken. Inter- and intraassay variations of the measurements for CRP were <10%.

Blood sampling, clinical assessment, and the self-administered questionnaire were completed on the same day. The time intervals between them were <12 hours (2–4 hours for most patients).

Statistical analysis. Data were analyzed using SPSS for Windows (IBM SPSS statistics 19). All statistical tests were 2-sided. A *P* value of less than 0.05 was considered significant, and a value between 0.05 and 0.1 was considered marginally significant. Each variable was visually inspected to validate the assumption of a normal distribution. The CRP data were natural log–transformed after adding 1 to each value, since these data were skewed and 2 of the subjects had values of 0.

The background characteristics of the patients were initially compared on the basis of the presence of alexithymia using the chi-square test for categorical variables and the *t*-test for continuous variables. A TAS-20 score of 61 was used as the cutoff to define the presence of alexithymia (25). To explore the relationships between variables, Pearson's correlation coefficients were calculated.

Thereafter, linear regression analyses were performed to evaluate the independent association of the TAS-20, the BDI-II, and the log-transformed CRP with perceived pain severity. The dependent variable was pain severity, and each variable was individually entered as an independent variable initially. Subsequently, CRP, TAS-20, and BDI-II scores were entered into the same model in succession. Variables to be entered as potential confounders into the final model were selected from those that exhibited a significant correlation with perceived pain and any of the TAS-20, BDI-II, or CRP scores (31).

To confirm the hypotheses that RA patients with alexithymia perceive more severe pain than expected, based on their level of inflammation and depression, interaction terms between the TAS-20, the BDI-II, and CRP were entered into the regression model. Upper and lower tertiles were used as cutoff points to categorize CRP level into 3 groups. Further, the subjects were divided into 4 groups according to the presence or absence of depression (BDI-II score ≥14) and alexithymia (TAS-20 score ≥61). Regression analysis was conducted separately to estimate the impact of CRP level on pain severity perceived by the groups. Finally, average pain severity by the low, middle, and high levels of CRP by the presence of depression and alexithymia adjusted for covariates was estimated by using analysis of covariance. Upper and lower tertiles were used as cutoff points to categorize CRP into 3 levels.

RESULTS

Background characteristics and the presence of alexithymia. The mean ± SD age of the subjects was 60 ± 12 years and 81.7% were women. In total, 46 patients (21.6%) had alexithymia according to the TAS-20 cutoff score of ≥61. The demographic, laboratory, and psychosocial variables, organized on the basis of the presence of alexithymia, are shown in Table 1. Subjects with alexithymia were more likely to be unmarried, be living alone, have incomplete higher education, and have severe physical disabilities compared with those without alexithymia. Both the pain and BDI-II scores of those with alexithymia were higher compared with those without alexithymia. There were no differences in age, sex, disease duration, or CRP level between those with and without alexithymia.

Interrelationships between variables. Pearson's correlation coefficients between the variables TAS-20 score, BDI-II score, and CRP level, along with the potential covariates physical function, age, living status, and educational level, are listed in Table 2. TAS-20 score revealed statistically significant correlations with BDI-II score, physical function, and years of education. TAS-20 score was not significantly associated with CRP level, whereas BDI-II score was positively associated with CRP level and physical function. In addition, age was significantly correlated only with physical function.

Perceived pain severity was significantly correlated with TAS-20 and BDI-II scores, CRP level, age, the total number of swollen joint counts, physical function, and years of education (data are not shown in the table because equivalent data are shown in Table 3). However, sex was only marginally associated with CRP level ($r = 0.13$, $P = 0.06$) and living status ($r = -0.12$, $P = 0.07$) and was not associated with pain, TAS-20 score, or BDI-II score. Therefore, the combined data of men and women were used for further analysis.

Independent influence of alexithymia on perceived pain. To investigate the independent influence of alexithymia on perceived pain, a hierarchical regression analysis was conducted. The standardized beta coefficient of each variable is shown in Table 3. When TAS-20 and BDI-II scores were entered into the same model, the association between TAS-20 score and perceived pain severity

Table 1. Demographic, clinical, and psychosocial characteristics of the patients with RA by the presence of alexithymia*

Variables	Total (n = 213) Value	Total (n = 213) Range	Alexithymic, TAS-20 ≥61 (n = 46)	Nonalexithymic, TAS-20 <61 (n = 167)	*P*
Sociodemographic characteristics					
Age, years	60.0 ± 12.0	18–85	61.2 ± 10.6	59.4 ± 12.4	0.35
Women, %	81.7		80.4	82.6	0.73
Married, %	75.8		62.8	79.0	0.03
Living alone, %	10.6		21.7	7.8	0.01
Current smoker, %	14.6		15.2	13.8	0.80
Education >12 years, %	22.0		11.9	24.6	0.02
Total income >$60,000/year, %	23.3		8.7	26.4	0.05
Clinical characteristics					
RA disease duration, years	11.7 ± 10.6	0.2–60.8	13.0 ± 11.0	11.3 ± 10.6	0.40
Functional disability	2.1 ± 0.7	1–4	2.3 ± 0.6	2.0 ± 0.7	0.01
Rheumatologist global severity	35.6 ± 17.5	0–91	37.0 ± 15.3	35.1 ± 18.0	0.50
Total number of tender joints	2.8 ± 3.9	0–27	2.8 ± 3.3	2.7 ± 4.0	0.86
Total number of swollen joints	4.2 ± 5.4	0–40	3.0 ± 3.0	4.4 ± 5.9	0.03
CRP, mg/liter	2.1 ± 2.4	0–13.9	2.2 ± 2.6	2.1 ± 2.3	0.78
Perceived pain	34.6 ± 24.3	0–100	44.2 ± 22.8	32.1 ± 24.4	0.003
Depressive symptoms (BDI-II)	12.9 ± 9.6	0–48	23.0 ± 11.1	10.3 ± 7.0	< 0.001

* Values are the mean ± SD unless indicated otherwise. RA = rheumatoid arthritis; TAS-20 = 20-item Toronto Alexithymia Scale; CRP = C-reactive protein; BDI-II = Beck Depression Inventory-II.

was attenuated and inverted, whereas the impact of BDI-II score on the pain level was unaltered. By further adding CRP level into the model, the association between TAS-20 score and the pain level became insignificant. However, BDI-II score and CRP level were both independently associated with perceived pain severity even after controlling for age, total number of swollen joints, functional disability, and educational level.

Interaction between alexithymia, depression, inflammation, and perceived pain. A marginally significant interaction was confirmed between perceived pain and the variables TAS-20 score, BDI-II score, and CRP level by adding the interaction terms in the trivariable model (P = 0.07). Further, a significant interaction was observed between perceived pain and the variables BDI-II score and CRP level only among those with alexithymia (P = 0.03).

Table 2. Pearson's correlation coefficients between alexithymia, depression, C-reactive protein (CRP) level, and covariates

Variables	Alexithymia*	Depression†	CRP‡	Total no. of swollen joint counts	Functional disability§	Age
Depression†						
r	0.58	1.00				
P	< 0.001					
CRP‡						
r	0.01	0.17	1.00			
P	1.00	0.01				
Total no. of swollen joint counts						
r	−0.08	0.05	0.47	1.00		
P	0.27	0.44	< 0.001			
Functional disability§						
r	0.14	0.29	0.36	0.27	1.00	
P	0.04	< 0.001	< 0.001	< 0.001		
Age						
r	−0.01	0.07	0.08	0.11	0.21	1.00
P	0.85	0.28	0.26	0.12	0.002	
Years of education						
r	−0.23	−0.19	−0.09	−0.02	−0.12	−0.35
P	0.001	0.01	0.19	0.73	0.07	< 0.001

* Measured with the 20-item Toronto Alexithymia Scale.
† Measured with the Beck Depression Inventory-II.
‡ Each CRP value was natural log–transformed after adding 1.
§ Determined according to Steinbrocker functional classification.

Table 3. Linear regression analyses showing the contribution of alexithymia, depression, natural log–transformed C-reactive protein (CRP) level, and covariates to perceived pain severity in rheumatoid arthritis patients

Dependent variables	Univariable model		Bivariable model*		Trivariable model†		Multiadjusted model‡	
	Standardized β	*P*	Standardized β	*P*	Standardized β	*P*	Standardized β	*P*
Alexithymia§	0.17	0.01	−0.13	0.08	−0.07	0.28	−0.08	0.25
Depression¶	0.45	< 0.001	0.53	< 0.001	0.43	< 0.001	0.40	< 0.001
CRP#	0.45	< 0.001			0.38	< 0.001	0.35	< 0.001
Age	0.16	0.02					0.07	0.26
Total no. of swollen joint counts	0.20	0.004					−0.03	0.66
Functional disability**	0.34	< 0.001					0.10	0.12
Education >12 years	−0.18	0.009					−0.06	0.32

* $R^2 = 0.22$, $F[2,210] = 28.7$, $P < 0.001$.
† $R^2 = 0.36$, $F[3,209] = 38.3$, $P < 0.001$.
‡ $R^2 = 0.22$, $F[7,205] = 17.6$, $P < 0.001$.
§ Measured with the 20-item Toronto Alexithymia Scale.
¶ Measured with the Beck Depression Inventory-II.
# Each CRP value was natural log–transformed after adding 1.
** Determined according to Steinbrocker functional classification.

Average pain severity reported by subjects with low, middle, and high CRP levels, arranged according to the presence or absence of depression and alexithymia and adjusted for age and functional disability, is displayed in Figure 1. Among those without alexithymia, perceived pain severity increased linearly with the level of CRP, regardless of the presence of depression. Among nondepressed patients with alexithymia, the high CRP level subgroup revealed higher average pain severity compared with that in the middle and low CRP level subgroups, but no difference was observed between the middle and low CRP level subgroups. Moreover, among depressed patients with alexithymia, pain severity was comparable across all CRP levels.

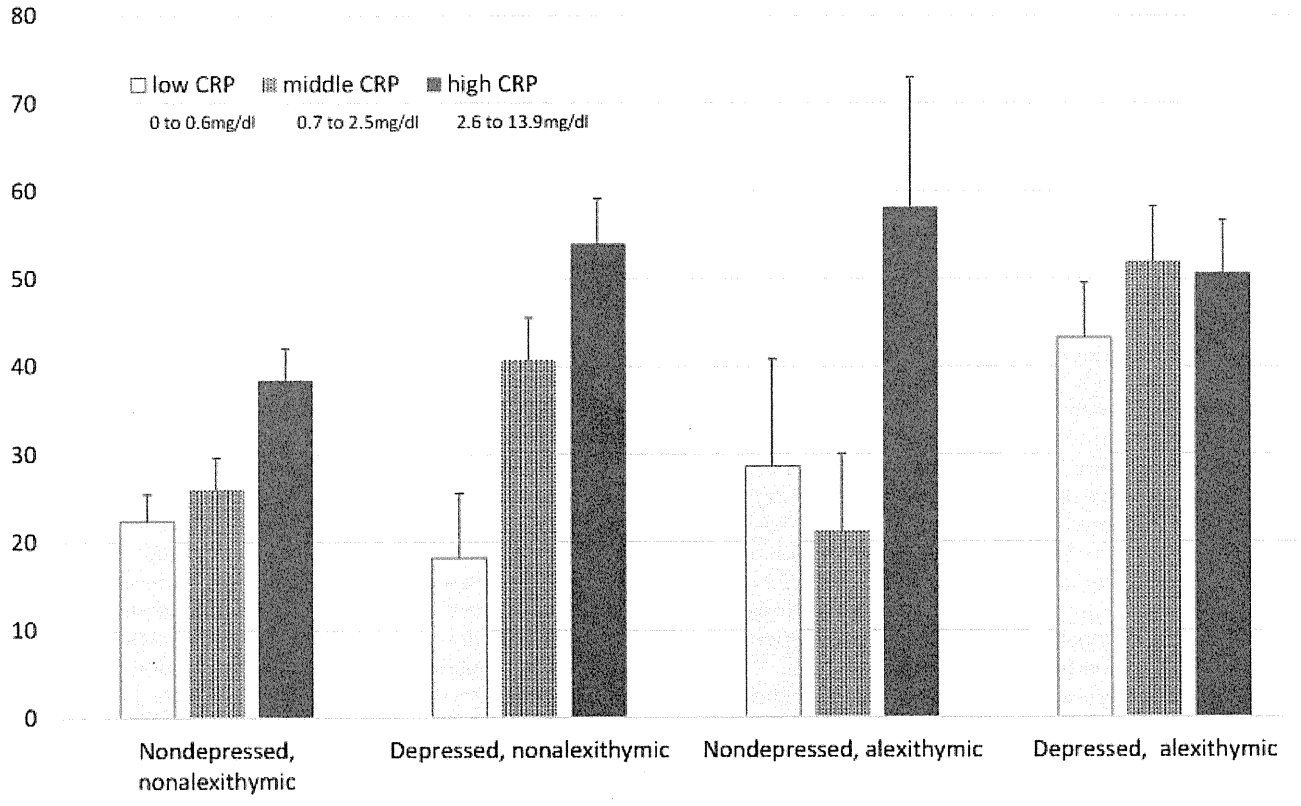

Figure 1. Average pain severity reported by subjects with low, middle, and high C-reactive protein (CRP) levels, arranged according to the presence or absence of depression (Beck Depression Inventory-II score ≥14 or <14) and alexithymia (20-item Toronto Alexithymia Scale score ≥61 or <61), adjusted for age and functional disability. Upper and lower tertiles were used as cutoff points to categorize CRP into 3 levels (0–0.6, 0.7–2.5, and 2.6–13.9 mg/dl).

Table 4. Effect of CRP level on perceived pain severity (increase of 1 mg/dl) by the presence of depression and alexithymia*

	N	Unadjusted		Adjusted	
		β ± SE	P	β ± SE	P
Nonalexithymic, nondepressed (TAS-20 <61, BDI-II <14)	120	14.5 ± 2.9	< 0.001	12.6 ± 3.5	0.001
Nonalexithymic, depressed (TAS-20 <61, BDI-II ≥14)	47	24.0 ± 4.8	< 0.001	23.3 ± 5.8	< 0.001
Alexithymic, nondepressed (TAS-20 ≥61, BDI-II <14)	12	18.9 ± 7.7	0.04	18.3 ± 10.0	0.13
Alexithymic, depressed (TAS-20 ≥61, BDI-II ≥14)	34	7.0 ± 5.5	0.21	2.7 ± 7.0	0.70

* Adjusted for age, total number of swollen joint counts, functional disability, and educational level. CRP = C-reactive protein; TAS-20 = 20-item Toronto Alexithymia Scale; BDI-II = Beck Depression Inventory-II.

The estimated impacts of CRP level on perceived pain arranged by the presence or absence of depression and alexithymia are shown in Table 4. CRP level was significantly associated with perceived pain severity among those without alexithymia, irrespective of the presence of depression, even after controlling for age, total number of swollen joint counts, functional disability, and educational level. Moreover, among nondepressed patients with alexithymia, the linear association between CRP level and pain severity became insignificant after adjusting for covariates. However, no association was observed between CRP level and pain severity among the group of depressed patients with alexithymia.

DISCUSSION

In a previous study, we reported that perceived pain increased independently in proportion with CRP and depression levels (2). In the present study, we provide additional information regarding these associations. Considering that pain is an unpleasant experience with sensory, affective, and cognitive dimensions (13), it is not surprising that alexithymia, a disorder of affect regulation with a cluster of cognitive and affective characteristics, is substantially associated with pain perception.

We confirmed that RA patients with alexithymia report more severe pain than expected because of inflammation. According to the present results, the severity of perceived pain increased independently in a linear fashion with increased CRP levels and with depression only among those without alexithymia. In contrast, among patients with alexithymia, the association between CRP level and depression was more complicated and differed with respect to the presence of depressive symptoms. If they were depressed, patients with alexithymia tended to report severe pain regardless of the inflammation level. Conversely, nondepressed patients with alexithymia did not report severe pain when they had mild to moderate inflammation. Nondepressed patients with alexithymia reported severe pain only when their CRP levels were high.

Two different types of persistent pain are known to exist: nociceptive (inflammatory) pain and neuropathic pain (32). Nociceptive pain is triggered by inflammation, which stimulates nociceptive receptors at the periphery of the nervous system (33). Therefore, it is natural that perceived pain severity increases linearly with CRP level, reflecting the stimulation of nociceptive pain receptors. The present study indicates the possibility that patients with alexithymia are sensitive to neuropathic pain, but not to nociceptive pain. Thus far, the association between alexithymia and nociceptive pain has never been directly discussed. Considering the characteristics of alexithymia, which include difficulty in distinguishing between emotional feelings and physical states (5), it is understandable that patients with alexithymia may be insensitive to mild to moderate physical stimulation originating from their inner body when they are not under emotional stress. A recent experimental study supports our speculation. Herbert et al examined 155 healthy students who had no or only minimal depressive symptoms (mean ± SD BDI-II score 3.52 ± 3.11) and found that the total TAS-20 score was inversely associated with interoceptive awareness, which was measured by the ability to count one's heartbeat (20). Future studies should confirm the interaction between emotional distress and the strength of internal or external stimuli on symptom perception in patients with alexithymia. The findings of such a study may partly explain unhealthy behaviors, including the delay in health care utilization, low compliance, or other behaviors that can lead to poor health outcomes, including early death, that have been consistently observed in the population with alexithymia (11).

Previous studies have repeatedly suggested the necessity of detecting and managing depression in patients attending rheumatology clinics (34–37). The present results clearly suggest the importance of considering the presence and influences of alexithymia when designing an effective approach to reduce pain in RA. According to our observation, if patients have high CRP levels, treatment focusing on inflammation should be prioritized regardless of the levels of alexithymia and depression. With regard to the patients with low to middle levels of CRP, the patients' alexithymic tendency should be considered when designing the pain control strategy. Patients without alexithymia reported increased pain in response to increasing levels of CRP or depression; therefore, antiinflammatory therapy will be effective for them, but a psychosocial approach should be considered as well, since the more depressed the patients are, the more pain they perceive. Further, with regard to patients with alexithymia, the effects of antiinflammatory therapy seem to be limited, and some psychosocial interventions must be necessary.

How should we approach patients with alexithymia? Treating depression using medication and/or psychotherapy has been reported to be difficult among patients with alexithymia (38–41), and methods to reduce alexithymia

have not been established yet (42). Theoretically, supportive psychiatric treatments are recommended for patients with primary alexithymia, whereas modified psychodynamic therapies are considered well suited for those who develop secondary alexithymia as a reaction to stressful situations (43). Two randomized controlled studies demonstrated the effectiveness of 4 months of weekly group psychotherapy, including relaxation and role playing, for patients with coronary heart disease (44) and 5 months of weekly supportive individual psychotherapy for general psychiatric outpatients to reduce alexithymia levels (45). We need a greater accumulation of evidence to identify how to increase the effectiveness of alexithymia treatment. Cognitive–behavioral therapy (CBT) has been an established treatment option for the management of chronic pain (46). A course of therapy that begins with primary individual supportive therapy and continues following a more interpretive approach, focusing on the modification of alexithymic characteristics (45) combined with a CBT program to reduce pain, would be worth trying for patients with severe alexithymia.

A recent systematic review confirmed that psychological interventions in patients with RA had a small but significant beneficial effect (47). According to their comparative analyses, intervention techniques using the self-regulation theory (goal setting, planning, self-monitoring, feedback, and relapse prevention) were more effective in reducing depressive symptoms and anxiety. For individuals with alexithymia, such practical and behavioral approaches seem appropriate; however, the self-monitoring process might need to be modified. Rheumatologists' attention to the psychological problems of each patient and their collaboration with behavioral medicine specialists and expert clinical psychologists are essential to achieve appropriate treatment options (34).

Despite the relatively consistent findings of previous studies demonstrating a positive correlation between alexithymia and CRP level (6–8), we failed to confirm this correlation. Individuals with alexithymia, who are thought to be vulnerable to stressful situations and might have a weakened antiinflammatory buffer capacity, might also tend to have high CRP levels (8). One possible reason for the discrepancy might be the differences in patient characteristics. The subjects of the current study were all patients with RA who experienced chronic inflammation, whereas the previous study subjects were either physically healthy adults (6,7) or subjects randomized from the general population (8). In addition, significant racial/ethnic differences in the distribution of CRP have been known to exist as well (48). Future studies should confirm the differences related to the background of the study population.

There were some limitations to this study. First, we designed this study based on theories derived mainly from observational studies (3,5,9,12,17). Although we believe there were important clinical implications in our study, many issues have yet to be clarified. Recent advances in brain imaging have revealed the uniqueness of alexithymia in the neural response to internal and external stimuli (49), suggesting its possibility in utilizing a biopsychosocial approach in clinical practice (10). Second, the results of this study were based on data measured at a single time point; therefore, we could not assess the direction of the association, and any measurement error may have influenced the findings. Third, our subjects were selected from a group of patients with RA visiting the rheumatology clinic at our university. Although there were no significant differences in the background characteristics of RA patients who did and did not participate in the study, the sample may have differed from the RA patient population as a whole. Finally, we used self-reported measures to evaluate pain and psychological variables. Although the TAS-20 is the most common tool to measure alexithymia internationally, and self-report measures are more acceptable in the clinical setting (34), the use of observer-rated measures has been recommended (25). Future studies should be conducted chronologically along with subjective and objective measures of psychological factors associated with alexithymia.

In conclusion, although there are various interpretive limitations, alexithymia may play a substantial role in pain perception as well as depression. Assessment of alexithymia and the use of biopsychosocial approaches are essential in achieving better pain control in patients with RA.

ACKNOWLEDGMENTS

The authors would like to thank Drs. Takeshi Oguchi, Michinari Oba, Hiroyuki Tsuchiya, Fumiaki Sugiura, and Yasuhide Kanayama and Ms Nobuko Yoshida for their contribution to acquisition of data.

AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be published. Dr. Masayo Kojima had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
Study conception and design. Masayo Kojima, Toshihisa Kojima, Ishiguro.
Acquisition of data. Masayo Kojima, Toshihisa Kojima, Funahashi, Kato, Hanabayashi, Asai, Ishiguro.
Analysis and interpretation of data. Masayo Kojima, Toshihisa Kojima, Suzuki, Takahashi, Hirabara, Ishiguro.

REFERENCES

1. Neugebauer V, Li W, Bird GC, Han JS. The amygdala and persistent pain. Neuroscientist 2004;10:221–34.
2. Kojima M, Kojima T, Suzuki S, Oguchi T, Oba M, Tsuchiya H, et al. Depression, inflammation, and pain in patients with rheumatoid arthritis. Arthritis Rheum 2009;61:1018–24.
3. Taylor GJ. Disorders of affect regulation: alexithymia in medical and psychiatric illness. Cambridge: Cambridge University Press; 2004.
4. Sifneos PE. The prevalence of 'alexithymic' characteristics in psychosomatic patients. Psychother Psychosom 1973;22:255–62.
5. Taylor GJ, Bagby RM. New trends in alexithymia research. Psychother Psychosom 2004;73:68–77.
6. Corcos M, Guilbaud O, Paterniti S, Curt F, Hjalmarsson L, Moussa M, et al. Correlation between serum levels of interleukin-4 and alexithymia scores in healthy female subjects: preliminary findings. Psychoneuroendocrinology 2004;29:686–91.
7. De Berardis D, Serroni N, Campanella D, Carano A, Gambi F,