6. 患者と医療者：何を共有し，何を目指すのか？

患者と医療者が共有するものは何か？　ここでは，その候補として，情報，次に責任，そしてコミュニケーションのプロセスの3点を挙げる．

第一には，治療の必要性や益・不利益（リスク）に関する可能な限り正確な数字に基づくエビデンスの情報である．その治療を行わない場合や，他の治療法を行う場合の益・不利益に関して利用可能な情報があれば共有し，それらを比較できることが望ましい．既存のエビデンスを集約する役割を担う診療ガイドラインについては，適切な作成方法が今以上に普及することが強く望まれる．さらに，その情報をどのような相手に，どのように提示するのが意思決定・行動を促進するか，コミュニケーションとリテラシーの両面から検討を進めるべき課題となろう．その上で，医療者の考えや経験，医学的に望ましいと考える治療方針，患者の価値観・好み，ヘルスリテラシー，必要に応じて家族・仕事との関係など社会経済的な状況の情報共有が必要となる．

第2は患者自身と医療者の責任の共有である．これまでの患者は，医療におけるさまざまな選択に際して，必ずしも自律的な意思決定ができなかったが，共有決定の普及と共に，そのような場面に出会うことが多くなるであろう．患者の自己決定の拡大は，社会から好意的に受け止められるが，同時に患者の抱える葛藤や責任は重くなることも予想される．しかし最終決定を患者が行ったとしても，医療者は，その全責任を患者にあずけることはできない．一つの意思決定に患者と医療者が共に関わり，その責任を分かち合うことは，共有決定の大切な要件となるであろう．

第3として挙げたコミュニケーションは，双方向性・相互作用があり，動的（dynamic），すなわち時間と共に変化するプロセスという特性を持つ．このようなコミュニケーションに際して医療者は患者に対し，価値観の尊重，葛藤への共感，必要な時間を待ち，リスクの認知と自分の価値観を擦り合わせていく過程の支援などが求められるであろう．

医療に対する関心の増大，社会における情報基盤の充実と共に，患者と医療者の関係の変化も加速されていく．EBMが臨床医のための方法論を越えて，患者，そして社会のヘルスリテラシーの向上に役立つことはEBMの目指すところに照らせば，その本来の意義の一つと言えよう．そしてEBMや診療ガイドラインが患者と医療者のコミュニケーションの基点となり，両者が協力して方向性を探り，共に治療に取り組むことを通して，患者そして家族の方々のQOLがより良いものとなっていくことが願われる．

（貴重なご助言を賜りました杉森裕樹先生（大東文化大学教授）に紙面をお借りして御礼申し上げます．）

著者のCOI（conflicts of interest）開示：中山健夫；研究費・助成金（テラ）

参考文献

1) Straus SE, et al : Evidence-Based Medicine : How to Practice and Teach it, 4th ed, Churchill Livingstone, 2010.
2) 杉森裕樹，中山健夫編：からだの科学：IT時代のヘルスリテラシー．2006.
3) ラングTA：トム・ラングの医学論文「執筆・出版・発表」実践ガイド．宮崎貴久子，中山健夫監訳．シナジー，2012.
4) 中山健夫：健康・医療の情報を読み解く：健康情報学への招待．丸善出版，2008.
5) ノートハウスPG，ノートハウスRL：ヘルス・コミュニケーション：これからの医療者の必須技術（改訂版［原著第3版］）．萩原明人訳．九州大学出版会，2010.

［参考］日本消化器外科学会・動画による市民向け講座「医療の不確実性」（中山健夫）http://www.jsgs.or.jp/modules/mvel/index.php?content_id=1

担当者のコメント

今回は中山先生よりヘルスリテラシーの意味，タイプ分けから始まり，ヘルスリテラシーと医療の質，患者安全との関連の明確な説明を頂いた．さらに先生は薬剤，処置，手術に次ぐ第4の医療技術としての「医療者と患者をつなぐコミュニケーション」の重要性を強調された．そして診療ガイドラインを「患者と医療者の情報共有の基点であり，コミュニケーションの有用なツール」と位置づけられ，不確定でリスクを伴う医療についての情報を含む種々の情報の共有や最終決定についての責任の共有，そしてお互いのコミュニケーションプロセスの共有の3点が課題であると指摘されている．標準化されたエビデンスをどう個別化して適用していくか，供給側・受ける側ともに担っていく医療の提供はプロの仕事の大変やりがいのある部分である．

（シリーズ担当　立教大学　大生定義）

Journal of Evaluation in Clinical Practice
International Journal of Public Health Policy and Health Services Research

Journal of Evaluation in Clinical Practice ISSN 1365-2753

Opinion of Japanese rheumatology physicians on methods of assessing the quality of rheumatoid arthritis care

Takahiro Higashi MD PhD,[1] Shunichi Fukuhara MD MSc DMSc[2] and Takeo Nakayama MD MPH PhD[3]

[1]Associate Professor, Department of Public Health/Health Policy, Graduate School of Medicine, The University of Tokyo, Tokyo, Japan
[2]Professor, Department of Epidemiology and Healthcare Research, Kyoto University School of Public Health, Kyoto, Japan
[3]Professor, Department of Health Informatics, Kyoto University School of Public Health, Kyoto, Japan

Keywords
physician opinion, quality of care, rheumatoid arthritis

Correspondence
Dr Takahiro Higashi
Department of Public Health/Health Policy
Graduate School of Medicine
The University of Tokyo
7-3-1 Hongo
Bunkyo-ku
Tokyo 113-0033
Japan
E-mail: higashi@m.u-tokyo.ac.jp

This study was supported in part by a grant-in-aid (health technology assessment) from the Ministry of Health, Labor and Welfare, Japan.

Accepted for publication: 5 August 2010

doi:10.1111/j.1365-2753.2010.01575.x

Abstract

Objective To examine the opinion of rheumatology physicians in Japan regarding desirable quality assessment methods.
Methods We conducted a cross-sectional self-administered mail survey on a random sample of physicians and surgeons registered with the Japan Rheumatism Foundation. In the survey, respondents were asked to rank seven proposed assessment methods for the quality of rheumatoid arthritis care, namely patient satisfaction, risk-adjusted outcomes such as complication incidence and admission rate, guideline compliance, waiting time at clinics, voting by local general practitioners, degree of newspaper and magazine reportage, and volume of patients receiving treatment for rheumatoid arthritis.
Results Among 531 respondents (response rate 48%), the respondents ranked patient satisfaction most favourably (mean rank 1.6), followed by complication/admission rate and number of patients. Guideline adherence was ranked almost the same as voting by local physicians. Waiting time and media reportage were not considered good methods for quality evaluation. Ranking distribution did not differ by working facility or place, volume of patients or years in practice. Multivariate analysis revealed that respondents who care for a large number of rheumatoid arthritis patients (>40 regular patients) were less likely to rank guideline adherence highly (first to third) than those who care for few patients (≤10 regular patients), with an odds ratio of 0.38 ($P < 0.01$) after adjustment for other variables.
Conclusions A majority of Japanese rheumatology physicians consider patient satisfaction the most trustworthy method of assessing the quality of rheumatoid arthritis care. Future research should explore convincing methods of assessing the technical quality of rheumatoid arthritis care.

Introduction

The quality of medical care has gained increasing public attention. Many studies have reported unexplained variations in care across geography [1–4], setting [5] and race [6] in western countries, and gaps between current standards and actual practice [7,8]. This growing concern has fuelled activities to measure and publicly report the quality of medical care for accountability purposes [9,10], and many settings in western countries have gone so far as to adopt payment schemes that reward a high quality of care [11–13]. Concern is growing in Japan also, where professionals have traditionally enjoyed freedom from rigorous quality scrutiny, as exemplified by increases in the number of malpractice litigation cases [14] and in media reporting of quality information, such as the surgical mortality of hospitals based on their own surveys [15,16]. A clear need to systematically measure the quality of care has emerged.

One popular way of measuring quality is to evaluate the process of care in comparison with a set of explicit criteria [7,8,17]. These explicit criteria usually describe standards of care based on clinical evidence and professional consensus, and quality is calculated as the proportion of patients who receive the described care among those eligible for it. These criteria sometimes derive from clinical practice guidelines, which are usually based on clinical evidence and professional consensus. Although the quality of care can also be measured using structural (i.e. staff–patient ratio and presence/absence of high-tech equipment) or outcome (patient survival or re-admission rate) measures, process measures have advantages, such as not requiring the statistical case-mix adjustment necessary in outcome measures and the ability to examine the care provided, for which providers are directly responsible.

Despite the growth of quality measurement in western countries, provider opinions of how quality should be measured are

rarely examined. Providers naturally oppose the idea of 'being measured' and tend to be critical of quality measurement. Simple questioning on whether a certain quality measurement (e.g. process measurement) is appropriate may result in a majority negative response which merely reflects reluctance to be measured. In this regard, a survey of US generalist physicians revealed that 70% of respondents felt that quality is not adequately measured at present, while a majority of the same sample were willing to be paid on quality provided that quality is adequately measured [18]. A qualitative study and an anecdotal story show that the current quality measurement schemes can distort the traditional goodness of the physician–patient encounter [19]. If these critiques shed light on the problems of quality measurement, the need to assure the accountability of health care providers may warrant the consideration of alternative ways of measuring quality. An understanding of physician opinions of how quality should be operationally measured may help identify optimum approaches and facilitate physician cooperation in measuring and improving quality.

Using a survey of attitudes towards the newly revised clinical practice guidelines for rheumatoid arthritis, we investigated current provider opinions of rheumatology physicians defined as physicians whose practice is focused on rheumatic diseases, including rheumatologists, orthopaedic surgeons and some general physicians in Japan regarding which methods are desirable in evaluating the quality of rheumatoid arthritis care. We also analysed the relative degree of acceptance of process-of-care quality measurement among alternative methods of quality assessment.

Methods

Physician survey

We analysed data obtained from a larger survey conducted to evaluate the usefulness of the revised Japanese rheumatoid arthritis clinical practice guidelines [20,21] and rheumatology physicians' general attitudes towards clinical practice guidelines. Details of the survey are reported elsewhere [22]. Briefly, the survey was distributed to a random sample of rheumatology physicians registered with the Japan Rheumatism Foundation. This Foundation is an affiliate of the Japan College of Rheumatology, which plays a central role in supporting research and practice in rheumatology in Japan by funding programmes and disseminating up-to-date information to providers and patients. Eligibility to register with the Foundation is limited to physicians who have been focused on rheumatology practice for at least 5 years and are approved by the review committee based on documentation of cases they have cared for. They are typically but not exclusively rheumatologists and orthopaedic surgeons. The survey was conducted in two waves, the first in December 2002 and the second in March–April 2006. Only the second included questions related to quality of care, and thus the current analysis used this wave only.

Quality of care question item

Among questions about the rheumatoid arthritis guidelines and respondents' practice patterns, the second wave survey included several items that asked about the quality of care in the framework of clinical practice guidelines. The main question asked respondents to rank proposed methods of assessing the quality of institution-provided rheumatoid arthritis care, namely patient satisfaction, risk-adjusted outcomes such as complication incidence and admission rate, guideline compliance, waiting time at clinics, voting by local general practitioners, degree of reportage by newspapers and magazines, and the volume of patients receiving treatment for rheumatoid arthritis. Tied rankings were not explicitly permitted but were treated as such if selected. Because this question of quality assessment was the focus of the present analysis, only respondents who answered this item were entered in the analyses.

Statistical analysis

To obtain a summarized group opinion, we report the modal rank and mean rank for each candidate quality assessment method. After ranking methods by mean rank, we then tested statistical differences in mean ranks between adjacently ranked methods (i.e. first versus second rank, second versus third rank, etc.) using the *t*-test.

Focusing on process measures as represented by guideline adherence, we further examined the relationship of respondent characteristics with the high ranking (i.e. first to third ranking among the proposed measures) of 'guideline adherence' as the quality measure. First, we described the proportion of respondents who ranked guideline adherence highly by stratifying physician characteristics, and then compared proportions using the chi-squared test. Second, we used a multivariable logistic regression to examine the independent association of these factors with the high ranking of guideline adherence. The examined factors included respondent gender, years in practice (<20 years/21–40 years/>41 years), specialty (surgeon/internists), patient volume (~10/11–20/21–30/31–40/≥41 patients for whom the respondents care regularly), type of practice setting (office practice/non-university hospital/university hospital), practice location (eastern/western Japan) and area type (metropolitan/urban/rural). Non-respondents to each item were excluded from the bivariate and multivariate analyses. An alpha level of 0.05 was used to decide statistical significance. The study protocol was approved by the Institutional Review Board of Kyoto University Graduate School of Medicine and Public Health.

Results

Among 1111 physicians surveyed in the second wave, 531 (48%) responded to the question about quality assessment and were entered into the analysis. Respondent characteristics are presented in Table 1; average age was 54 years (range 37–91), with 28 years in practice (12–64), and 5% were female.

Figure 1 shows the distribution of assigned rankings for each quality assessment method. Patient satisfaction was most favourably ranked, with a mean rank of 1.6, followed by complication rate (mean rank 2.7) and number of patients (mean rank 3.3). Guideline adherence was ranked mostly in the middle with a mode ranking of 4 (mean 4.0), which was about the same as that for voting by local physicians (mean rank 4.2). Assessment by waiting time and reportage in newspapers and magazines were considered

Table 1 Subject characteristics ($n = 531$) and percentages of respondents ranking 'guideline adherence' highly as a desirable quality measure

	n (%)	High rank for 'guideline adherence'	
Gender			$P = 0.90$
Female	27 (5)	33%	
Male	498 (95)	35%	
Years in practice			$P = 0.41$
<20	207 (39)	32%	
21–40	265 (50)	35%	
≥41	53 (10)	42%	
Specialty			$P = 0.68$
Surgeons	358 (70)	34%	
Internists/others	163 (30)	36%	
Number of rheumatoid arthritis patients (%)*			$P = 0.07$
≤10	104 (20)	41%	
11–20	100 (19)	34%	
21–30	82 (16)	40%	
31–40	54 (10)	37%	
≥41	184 (35)	27%	
Practice settings			$P = 0.34$
University hospital	62 (12)	29%	
Non-university hospital	205 (39)	33%	
Physician office	249 (47)	36%	
Other	11 (2)	55%	
Area type			$P = 0.66$
Metropolitan	149 (28)	34%	
Urban	318 (60)	33%	
Rural	61 (12)	39%	
Practice location			$P = 0.15$
Eastern Japan	218 (41)	37%	
Western Japan	313 (59)	31%	

*Does not add up to 100% because of rounding.
The following non-responding subjects were excluded: 6 subjects for gender and years in practice, 10 subjects for specialty, 4 subjects for practice setting, 7 subjects for number of rheumatoid arthritis patients and 3 subjects for area type.

unfavourable methods of assessment (mean rank of 6 and 6.1, respectively). The differences in mean rank between adjacently ranked methods were significantly different except for that between guideline adherence and voting by local physicians ($P = 0.14$) and between waiting time and reportage in the media ($P = 0.76$). This general ranking trend did not change on stratified analysis by working facility, place of practice, volume of patients or years in practice.

The exploration of factors related to the high ranking of guideline adherence in the unadjusted analysis is presented in the right columns of Table 1. None of the factors examined was associated with the high ranking of guideline adherence as a desirable quality measure. An exception was the number of rheumatoid arthritis patients for whom the respondent cares, which showed the non-significant trend that high-volume respondents with ≥41 regular patients were less likely to rank guideline adherence highly (overall $P = 0.07$). After adjustment for these factors using the logistic regression analysis, this group appeared significantly less likely to rank guideline adherence highly (odds ratio = 0.38 compared to the low-volume group with ≤10 regular patients, $P < 0.01$; Table 2). The Hosmer–Lemeshow test revealed that the model had a reasonable fit, with a P-value of 0.88.

Discussion

Our survey revealed a number of interesting points about Japanese rheumatology physicians' opinions on how the quality of care should be assessed. First, patient satisfaction is considered the best method of quality assessment, with this option ranked higher than other methods which target the technical aspects of care. The preference for this interpersonal quality over technical quality may indicate that the assessment of technical care is not considered to capture the 'true' technical quality of care. Alternatively, respondents may be reluctant to subject their practice to the physical and psychological intrusion of technical assessment.

Among the assessment methods targeting the technical aspect of care, the outcome measure of complication/admission rate was preferred over the process measure of guideline adherence. This finding stands in stark contrast to extensive use of process measures in western countries [4,7–9,11]. Because no nationwide quality assessment system for either outcome or process is implemented in Japan, the idea of using guidelines to assess quality may be difficult for the respondents to imagine. Furthermore, process measures used in practice are usually modified from the guideline recommendations themselves so that they can serve a measurement

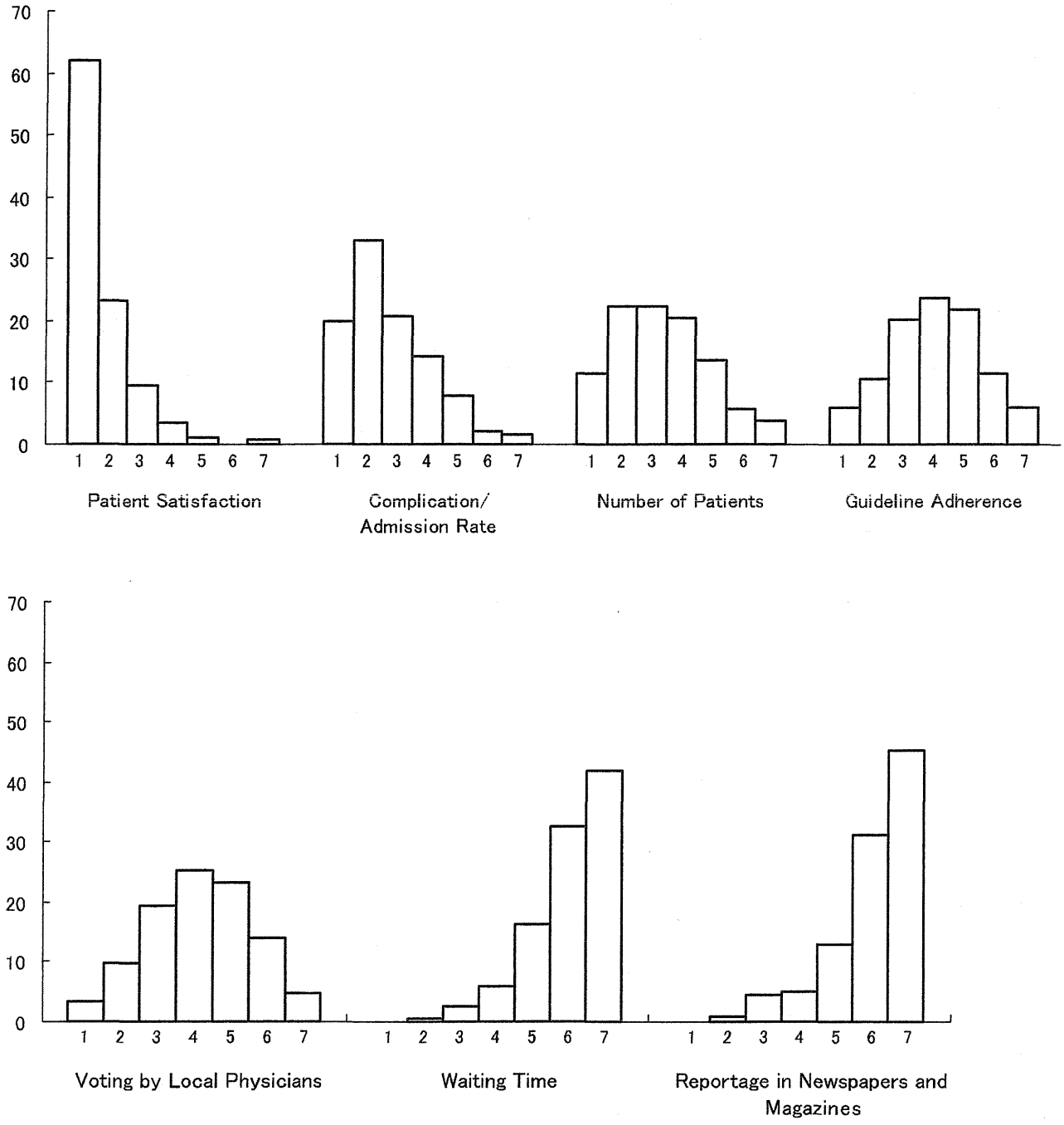

Figure 1 Ranking distribution of quality assessment methods for rheumatoid arthritis care.

purpose. Unfortunately, we suspect that the respondents had little experience or knowledge of process quality-of-care measurement, and concede that use of the term 'guideline adherence' to mean process measures in the questionnaire may have lacked precision. In any case, if guideline recommendations are to be used as quality indicators after pertinent modification, additional effort to convince physicians appears necessary, such as the convening of an expert panel specifically commissioned to examine the validity of each recommendation as a quality indicator.

A second interesting point is that 'number of patients' was considered preferable to guideline adherence as a quality assessment. Although the volume–outcome or volume–quality relationship has been extensively studied in surgical and medical conditions [23], we are unaware of any study showing that

Table 2 Respondent factors in relation to a higher (first to third) ranking of guideline adherence as the quality measure

		Odds ratio (95% CI)	*P*-value*
Sex	Female (vs male)	0.78 (0.33–1.99)	0.60
Years in practice	(vs <20)		0.18
	21–40	1.25 (0.82–1.89)	
	≥41	1.85 (0.95–3.60)	
Specialty	Surgeons (vs others)	0.72 (0.45–1.13)	0.16
Working facility	(vs university hospital)		0.40
	Non-university hospital	0.87 (0.44–1.71)	
	Physician office	0.97 (0.49–1.92)	
	Other	3.25 (0.64–16.45)	
Number of rheumatoid arthritis patients	(vs ≤10)		0.01
	11–20	0.61 (0.34–1.11)	
	21–30	0.80 (0.43–1.47)	
	31–40	0.60 (0.29–1.22)	
	≥41	0.38 (0.22–0.67)	
Area (%)	(vs metropolitan)		0.68
	Urban	0.97 (0.62–1.51)	
	Rural	1.27 (0.64–2.50)	
Practice location	Eastern Japan (vs western)	0.71 (0.47–1.07)	0.10

*Overall *P*-values for categories.

larger-volume providers of rheumatoid arthritis care produce better outcomes. Because the strength of the volume–outcome relationship varies across surgery types [24], future research should test the opinion of rheumatology physicians, as identified in this survey, that volume is a good proxy of quality of care, which leads to better rheumatic care outcomes, or is at least a better proxy than explicit guideline adherence.

Guideline adherence was ranked almost the same as 'voting by local physicians', which is a popular method used by the media. The Best Hospitals report published by the US News is one of the most famous examples [25]. In Japan also, several books have used physician voting to evaluate hospitals [16,26]. In a sense, guideline adherence can be viewed as an evaluation using explicit technical criteria, while voting by local physicians is a form of implicit review of quality, if appropriately performed. However, implicit review is known to be unreliable in the absence of detailed instruction and pertinent training of the reviewers, and bias due to suboptimal methodology is sometimes unclear.

Exploration of factors associated with the high ranking of guideline adherence revealed that high-volume respondents who care for >40 regular rheumatoid arthritis patients were less likely to rank guideline adherence highly. Because guidelines are sometimes criticized as 'too cookbook' [22], high-volume respondents who theoretically have more chance to care for atypical patients may feel less inclined to use guideline recommendations as quality standards. Other factors examined here were not significantly associated with ranking of guideline adherence.

Our results should be interpreted in view of several limitations. First, the survey was conducted among rheumatology physicians engaged in rheumatoid arthritis care, potentially limiting its generalizability to other conditions or types of physicians. Rheumatoid arthritis care is unique in that physicians need to select the most suitable of a wide range of anti-rheumatic medications (i.e. disease-modifying anti-rheumatic drugs) and biological agents and to fine-tune dosages to avoid adverse effects. This process is not only more complex and prolonged than that for most other common diseases, but also highly individualized, limiting the value of guideline recommendations. Second, the ranking of candidate assessment methods reveals relative preference only. The physicians may have thought that patient satisfaction is merely 'less bad' than even worse methods and ranked it highly on this basis alone. We chose ranking to focus on the difference between candidate methods, and expect that future research will examine absolute preference for these potential methods. Finally, potential differences between respondents and non-respondents may have biased the results. The overall survey was about guidelines, and respondents may have had a more favourable attitude to guidelines than non-respondents. Although guideline adherence was ranked about in the middle, non-respondents might have rated this item even lower.

Despite these limitations, we found that Japanese rheumatology physicians consider that patient satisfaction is the best method for quality assessment, and presently do not fully accept guideline adherence as a standard criterion of quality. Efforts to gain the support of quality monitoring systems focusing on process of care from practising physicians and enable their smooth introduction should focus on ways to construct convincing methods of assessing the technical quality of rheumatoid arthritis care.

References

1. Ess, S., Savidan, A., Frick, H., Rageth, C., Vlastos, G., Lutolf, U. & Thurlimann, B. (2010) Geographic variation in breast cancer care in Switzerland. *Cancer Epidemiology*, 34 (2), 116–121.
2. O'Hare, A. M., Rodriguez, R. A., Hailpern, S. M., Larson, E. B. & Kurella Tamura, M. (2010) Regional variation in health care intensity and treatment practices for end-stage renal disease in older adults. *JAMA*, 304 (2), 180–186.
3. Pilote, L., Califf, R. M., Sapp, S., Miller, D. P., Mark, D. B., Weaver, W. D., Gore, J. M., Armstrong, P. W., Ohman, E. M. & Topol, E. J. (1995) Regional variation across the United States in the management of acute myocardial infarction. GUSTO-1 Investigators. Global Utilization of Streptokinase and Tissue Plasminogen Activator for

Occluded Coronary Arteries. *The New England Journal of Medicine*, 333 (9), 565–572.
4. Jencks, S. F., Cuerdon, T., Burwen, D. R., Fleming, B., Houck, P. M., Kussmaul, A. E., Nilasena, D. S., Ordin, D. L. & Arday, D. R. (2000) Quality of medical care delivered to Medicare beneficiaries: a profile at state and national levels. *JAMA*, 284 (13), 1670–1676.
5. Riley, G. F., Warren, J. L., Potosky, A. L., Klabunde, C. N., Harlan, L. C. & Osswald, M. B. (2008) Comparison of cancer diagnosis and treatment in Medicare fee-for-service and managed care plans. *Medical Care*, 46 (10), 1108–1115.
6. Kressin, N. R. & Petersen, L. A. (2001) Racial differences in the use of invasive cardiovascular procedures: review of the literature and prescription for future research. *Annals of Internal Medicine*, 135 (5), 352–366.
7. McGlynn, E. A., Asch, S. M., Adams, J., Keesey, J., Hicks, J., DeCristofaro, A. & Kerr, E. A. (2003) The quality of health care delivered to adults in the United States. *The New England Journal of Medicine*, 348 (26), 2635–2645.
8. Wenger, N. S., Solomon, D. H., Roth, C. P., *et al.* (2003) The quality of medical care provided to vulnerable community-dwelling older patients. *Annals of Internal Medicine*, 139 (9), 740–747.
9. The US Department of Health and Human Services (2010) *Medicare hospital compare*. Available at: http://www.hospitalcompare.hhs.gov/ (last accessed 28 December 2010).
10. Cancer Care Ontario (2010) *Cancer systems quality index*. Available at: http://csqi.cancercare.on.ca/ (last accessed 28 December 2010).
11. Doran, T., Fullwood, C., Gravelle, H., Reeves, D., Kontopantelis, E., Hiroeh, U. & Roland, M. (2006) Pay-for-performance programs in family practices in the United Kingdom. *The New England Journal of Medicine*, 355 (4), 375–384.
12. Epstein, A. M., Lee, T. H. & Hamel, M. B. (2004) Paying physicians for high-quality care. *The New England Journal of Medicine*, 350 (4), 406–410.
13. Scott, I. A. (2008) Pay for performance programs in Australia: a need for guiding principles. *Australian Health Review*, 32 (4), 740–749.
14. The Supreme Court of Japan General Administrative Office (2006) *Status of medical malpractice cases processes and average litigation length* (in Japanese). Available at: http://www.courts.go.jp/saikosai/about/iinkai/izikankei/toukei_02.html (last accessed 28 December 2010).
15. NIKKEI_NET (2004) *Survey of operative performance in major hospitals* (in Japanese). Available at: http://health.nikkei.co.jp/hResearch/ (last accessed 15 September 2004).
16. Medical, N. (2004) Japanese Best Hospitals (Zenkoku Yuryou Byoin Ranking – Japanese). Tokyo: Nikkei BP.
17. Seddon, M. E., Marshall, M. N., Campbell, S. M. & Roland, M. O. (2001) Systematic review of studies of quality of clinical care in general practice in the UK, Australia and New Zealand. *Quality in Health Care*, 10 (3), 152–158.
18. Casalino, L. P., Alexander, G. C., Jin, L. & Konetzka, R. T. (2007) General internists' views on pay-for-performance and public reporting of quality scores: a national survey. *Health Affairs (Project Hope)*, 26 (2), 492–499.
19. Casalino, L. P. (1999) The unintended consequences of measuring quality on the quality of medical care. *The New England Journal of Medicine*, 341 (15), 1147–1150.
20. Nakayama, T. & Fukuhara, S. T. K. (2003) Contributions of clinical epidemiologists and medical librarians to developing evidence-based clinical practice guidelines in Japan : a case of the treatment of rheumatoid arthritis. *General Medicine*, 4 (1), 21–28.
21. Working Group on Development of Clinical Practice Guidelines for the Treatment of Rheumatoid Arthritis (Principal Investigator: Takahiro Ochi) (2004) A Manual for the Treatment of Rheumatoid Arthritis (in Japanese). Tokyo: Japan Rheumatism Foundation.
22. Higashi, T., Nakayama, T., Fukuhara, S., *et al.* (2010) Opinions of Japanese rheumatology physicians regarding clinical practice guidelines. *International Journal for Quality in Health Care*, 22 (2), 78–85.
23. Institute of Medicine (2000) Interpreting the Volume-Outcome Relationship in the Context of Health Care Quality: Workshop Summary. Washington, D.C.: National Academies Press.
24. Birkmeyer, J. D., Siewers, A. E., Finlayson, E. V., Stukel, T. A., Lucas, F. L., Batista, I., Welch, H. G. & Wennberg, D. E. (2002) Hospital volume and surgical mortality in the United States. *The New England Journal of Medicine*, 346 (15), 1128–1137.
25. US News & World Report (2006) *Best hospitals*. Available at: http://www.usnews.com/usnews/health/best-hospitals/tophosp.htm (last accessed 28 December 2010).
26. Yoshihara, S. (2008) The Best Doctors and Curing Hospitals (Saikouno Meii Plus Naoru Byoin – Japanese). Tokyo: Kodansha.

日整会誌 (J. Jpn. Orthop. Assoc.) 86：394-400 2012

シンポジウム　RA 生物学的製剤治療の最前線　—寛解を目指して—

生物製剤の登場による手術療法の動向と適応の変化について*

西田圭一郎[1]　中原龍一[2]　橋詰謙三[2]　斎藤太一[2]
金澤智子[2]　小澤正嗣[2]　那須義久[3]　尾﨑敏文[2]

生物学的製剤登場後の 8 年を振り返って

生物学的製剤の導入から 9 年目となり，積極的なメトトレキサート(methotrexate, MTX)の使用とともに，以前より増して関節リウマチ(rheumatoid arthritis, RA)の薬物コントロールが良好になされるようになってきた．生物学的製剤は，特に MTX との併用において，早い臨床効果の発現，短・中期的な関節破壊防止効果のエビデンスを有し[1)-5)]，さらには破壊された関節に対する修復反応も見られるようになって，早期に診断され，関節破壊を来す以前に至適な薬物治療により適切に疾患コントロールが得られれば，手術の回避はもちろん，一部の患者では寛解も夢ではなくなってきた．わが国より約 5 年早く生物学的製剤が導入された欧米において，2002 年の米国リウマチ学会の早期 RA に対する治療ガイドラインでは，薬物治療がいずれも無効の場合に外科的治療が位置づけられており，実際，ノルウェー，デンマーク，フィンランド，スウェーデンのレジストリーからは手術件数の減少，人工関節手術の減少が報告されている[6)-9)]．一方で，生物学的製剤による治療の問題点として，①生物学的製剤不応例や二次無効，②副作用で中止せざるを得ない場合，③経済的問題・合併症のため使用できない場合，④休薬や薬剤変更の間に関節破壊が進行する場合，⑤全身的に効果が認められるが一部の関節で炎症が持続する場合や関節破壊が進行する場合，⑥長期罹病患者ではすでに関節破壊や変形を来してこれが不可逆的になっている場合，などが次々と経験されるようになってきた．こういった背景のもとでは，従来どおり薬物治療に外科的治療やリハビリテーションを適切に組み合わせた治療戦略が必須である．われわれ整形外科医は新しい薬物治療の時代における「寛解とはなにか」を考えるにあたって，整形外科医がリウマチ診療に積極的に参加している本邦での外科的治療の動向と適応の変化を知ることは重要である．

Key words: Rheumatoid arthritis, Biologic DMARD, Orthopaedic surgery, Japanese treat to target (T2T)

*Trend and practice of orthopaedic surgery for rheumatoid arthritis in the era of biologic agents

[1]岡山大学大学院医歯薬学総合研究科人体構成学分野．Keiichiro Nishida: Department of Human Morphology, Okayama University Graduate School of Medicine, Dentistry and Pharmaceutical Sciences.
[2]岡山大学大学院医歯薬学総合研究科整形外科学．Ryuichi Nakahara, Kenzo Hashizume, Taichi Saito, Tomoko Kanazawa, Masatsugu Ozawa, Toshifumi Ozaki: Department of Orthopaedic Surgery, Okayama University Graduate School of Medicine, Dentistry and Pharmaceutical Sciences
[3]倉敷廣済病院整形外科．Yoshihisa Nasu: Department of Orthopaedic Surgery, Kurashiki Kosai Hospital

RA 関連手術の動向

岡山大学病院整形外科および関連病院 1 施設(倉敷廣済病院)で 2004 年 1 月から 2011 年 6 月までに行われた関節リウマチ関連手術 921 件について調査した．同一患者が同一日に複数関節(部位)の手術を受けていた場合は主たる手術手技のみを 1 件としてカウントした．対象は RA 患者 464 例(男性 41 例，女性 423 例)で手術時平均年齢は 61.7 歳，手術時平均罹病期間は 20.0 年であった．生物学的製剤非使用患者の手術は 766 件(手術時平均年齢 63.0 歳，手術時平均罹病期間 20.6 年)，生物学的製剤使用中患者の手術は 155 件(手術時平均年齢 56.2 歳，手術時平均罹病期間 17.1 年)であり，生物学的製剤使用中患者は有意に年齢が低く，罹病期間が短かった(いずれも $p<0.05$, Mann-Whitney U test)．生物学的製剤使用・非使用別の手術時平均年齢を表 1 に，平均罹病期間の年度別推移を表 2 に

表1 2004年～2011年におけるRA関連手術例の年度毎の手術時平均年齢

生物学的製剤使用	2004	2005	2006	2007	2008	2009	2010	2011
あり		56.7	52.4	51.2	54.1	58.8	57.1	61.4
なし	62.3	62.8	63.4	63.5	63.3	61.1	64.3	63.4
総計	62.3	62.5	61.9	61.6	61.5	60.5	61.8	62.6

(歳)

表2 2004年～2011年におけるRA関連手術例の年度毎の手術時平均罹病期間

生物学的製剤使用	2004	2005	2006	2007	2008	2009	2010	2011
あり		126.7	188.5	225.8	162.3	213.5	243.6	183.4
なし	230.4	241.6	268.3	248.7	244.6	247.0	262.1	240.7
総計	230.4	235.8	257.4	245.1	229.3	238.2	255.6	219.5

(月)

表3 2004年～2010年の各年度における手術件数とその背景の推移

	2004	2005	2006	2007	2008	2009	2010
手術件数	127	141	133	111	125	112	121
手術時平均年齢	62.3	62.5	61.9	61.6	61.5	60.5	61.8
平均罹病期間	230.4	235.8	257.4	245.1	229.3	238.2	255.6
上肢	53 (41.7)	42 (29.8)	57 (42.9)	47 (42.3)	51 (40.8)	58 (51.8)	50 (41.3)
下肢	66 (52.0)	89 (63.1)	69 (51.9)	57 (51.3)	68 (54.4)	48 (42.8)	64 (52.3)
脊椎	8 (6.3)	10 (7.1)	7 (5.3)	7 (6.3)	6 (4.8)	6 (5.4)	7 (5.8)

示す．興味深いことに生物学的製剤使用患者での手術時年齢は近年，非使用患者と差がなくなりつつあり，生物学的製剤を適応する患者年齢が高くなりつつあることが推察される．

2011年を除く2004-2010年の1-12月の各年度において，RAに対する整形外科手術件数は年間110-130件前後(平均124.3件)で推移しており，大きな変化はなかった(表3)．各年度の手術総数に占める上肢，下肢，脊椎の手術が占める比率にも変化はなかった．これはYasuiらの独立行政法人国立病院機構のデータベース(NinJa)の解析結果と同様である[10]．全手術を人工関節置換術(肩，肘，膝，股関節)，手部の手術(指人工関節を含む)，足部の手術，関節鏡視下滑膜切除術，絶対的適応の手術(感染，脊椎脊髄障害，外傷)，その他に分類し，年度別動向を図1および表3に示す．人工関節手術については2006年から2008年にかけてやや減少傾向にあったが，手足の手術はかえって増加傾向にあった．この傾向は，われわれの施設を含む他施設共同研究(CORE study)によるRA関連手術の動向に類似していた[11]．さらに生物学的製剤使用・非使用に分けて手術部位・術式別の施行頻度を比較検討すると，生物学的製剤使用患者においては非使用患者に比して，人工関節置換術は少なく，手足の手術，関節鏡視下滑膜切除術は多く，絶対的適応の手術に差がない傾向がみられた(表4)．

生物学的製剤使用下での手術

2004年1月から2011年6月までの生物学的製剤投与下での整形外科手術89例155件について，使用中の生物学的製剤ごとの年度別手術件数を表5に，手術

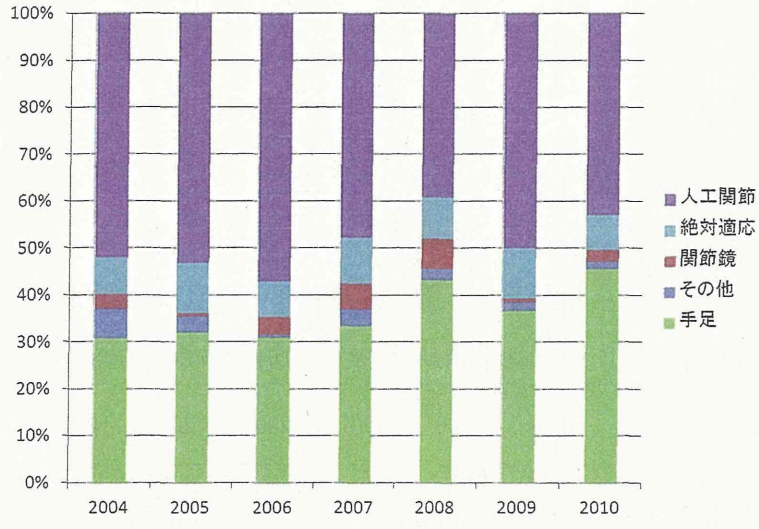

図 1　RA 関連手術の年度別動向．全 RA 関連手術を人工関節置換術(肩，肘，膝，股関節)，手部の手術(指人工関節を含む)，足部の手術，関節鏡視下滑膜切除術，絶対的適応の手術(感染，脊椎脊髄障害，外傷)，その他に分類し，2004 年 1 月から 2010 年 12 月までの各年度におけるそれぞれの比率を示した．

表 4　生物学的製剤使用の有無での手術内容

手術分類	生物学的製剤あり	生物学的製剤なし	合計
人工関節置換術	51 (32.9%)	319 (41.6%)	370
TEA	8	98	106
THA	15	63	78
TKA	26	153	179
TSA	2	5	7
手部	44 (28.4%)	188 (24.5%)	232
指人工関節	15	64	79
手関節(腱断裂を含む)	9	76	85
手指形成術	20	48	68
足部	36 (23.2%)	142 (18.5%)	178
前足部形成術	31	120	151
足関節・中後足部	5	22	27
鏡視下滑膜切除術	11 (7.1%)	19 (2.5%)	30
脊椎	4 (2.6%)	50 (6.5%)	54
外傷	2 (1.3%)	3 (0.4%)	5
感染	4 (2.6%)	21 (2.7%)	25
その他	3	29	33
合計	155	766	921

数，手術時平均年齢，平均罹病期間を表 6 に示す．使用していた生物学的製剤はインフリキシマブ 28 例 42 件，エタネルセプト 38 例 79 件，アダリムマブ 9 例 14 件，トシリズマブ 11 例 17 件，アバタセプト 3 例 3 件であり，本邦での導入が早いインフリキシマブ，エタネルセプト使用中手術の手術件数が多い結果となっている．一方で 2008 年に導入されたアダリムマブおよびトシリズマブ，2010 年に導入されたアバタセプトの手術時平均年齢は前 2 者に比して高くなっており，比較的高齢者にも生物学的製剤が導入されるように変

表 5 使用中の生物学的製剤別の手術件数の推移

	本邦での認可(年)	2004	2005	2006	2007	2008	2009	2010	2011*	計
インフリキシマブ	2003	0		3	4	8	14	10	3	42
エタネルセプト	2005	0	4	15	13	15	10	18	4	79
アダリムマブ	2008	0	2**	0	0	1	1	6	4	14
トシリズマブ	2008	0	1**	0	0	0	4	7	5	17
アバタセプト	2010	0	0	0	0	0	0	0	3	3
総計		0	7	18	17	24	29	41	19	155
総手術数に対する割合(%)		0	5.0	13.5	15.3	19.2	25.9	33.9	35.8	16.8

*2011 年 1 月- 6 月の 6 カ月間のデータ
**治験中の手術

表 6 使用中の生物学的製剤別の総手術件数と患者背景

	手術数	症例数	年齢平均	SD	平均罹病期間(月)	SD
インフリキシマブ	42	28	55.7	12.0	190.8	94.8
エタネルセプト	79	38	54.2	13.0	220.1	131.8
アダリムマブ	14	9	62.6	11.0	149.4	115.7
トシリズマブ	17	11	59.3	13.8	215.2	146.3
アバタセプト	3	3	67.0	19.1	216.0	0.0
総計	155	89	56.2	13.1	204.9	124.4

化してきた可能性がある．また，NinJa の解析結果からも，年間の RA 関連手術のうち生物学的製剤投与中の患者の割合は毎年漸増しており，2007 年は 9.7%であったことが報告されている[10]．われわれの検討結果も同様であり，2009 年度は 25.9%と約 4 人に 1 人，2010 年度は 33.9%と約 3 人に 1 人が生物学的製剤使用中であった．本邦における生物学的製剤の普及率が上昇してきたこともあるが，最近はこれを明らかに上回っており，治療に積極的な RA 患者における生物学的製剤の使用率が高くなってきていると解釈することもできる．

手術分類別の患者背景

われわれはいずれの手術においても，従来からの整形外科的治療介入の適応を変更していない．しかし，生物学的製剤使用中の患者では，以前のように関節破壊が非常に高度となってから手術を希望するのではなく，むしろ関節の不可逆的変化が，日常生活動作や美容的な障害となった時点での手術が増加しており，より軽症化している．これは，生物学的製剤を使用する患者が tight control 下にあること，高い有効性によって全身の多関節症状が緩和して愁訴がしぼられ，より高い ADL(activities of daily living)を要求するようになったことなどが考えられる．手術分類別に各患者群における RA 罹病期間と術前 CRP 値との分布を調査し，それぞれの患者背景から推察できる生物学的製剤使用下での手術の意義と適応について考察した(図 2)．

1) 滑膜切除術

Kanbe らはインフリキシマブ使用中に行った鏡視下滑膜切除術の効果を術後 6 週および 50 週で検討し，血清 CRP，DAS28 による総合的疾患活動性指標の改善をみたことを報告している．滑膜切除術は炎症性サイトカインを産生する滑膜組織を減少させることによって，当該関節における生物学的製剤の効果を改善させる可能性がある．しかし，滑膜切除術の良好な短期成績は以前から認識されており，長期的には関節破

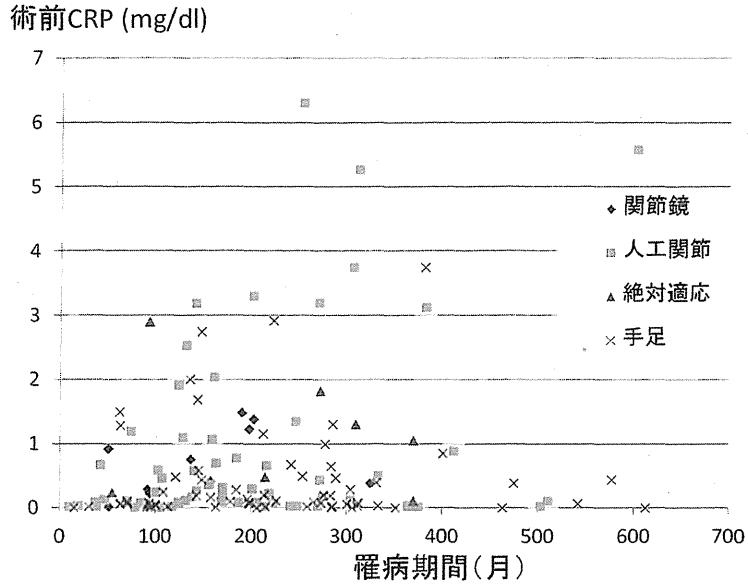

図2　生物学的製剤使用中手術の背景．2004年1月から2011年6月に行った生物学的製剤使用中手術155件を，人工関節置換術(肩，肘，膝，股関節)，手足の手術(指人工関節を含む)，関節鏡視下滑膜切除術，絶対的適応の手術(感染，脊椎脊髄障害，外傷)に分け，罹病期間，手術前CRP値(mg/dl)による分布を示した．

壊防止効果には期待できないとする意見が多い．今後問題となるのは生物学的製剤による治療に鏡視下滑膜切除術を併用することで長期的な治療効果が維持できるか否か，その限界はどこか，である．

今回調査した症例は関節形成術に併用した滑膜切除術を除く11例であり，全例が鏡視下滑膜切除術(膝9件，肘2件)であった．内訳は男性1例，女性10例，手術時平均年齢は53.2歳，平均罹病期間は6.7年と比較的若年で罹病期間が短かった．術前平均CRPは1.83 mg/dlであり，全例で薬物療法でも改善しない限局した滑膜炎が持続する場合に適応されていた．術後経過観察期間は平均32.8カ月であり，人工関節置換術をエンドポイントとしてKaplan-Meyer法による5年生存率は51.7%であった．人工関節置換術に移行した4例(3膝，1肘)はいずれも術前Larsen gradeはIIIおよびIVであり，軟骨破壊が進行すると，滑膜切除術の有効性は炎症の一時的な沈静化にとどまり，生物学的製剤使用によっても関節破壊の進行を防止することはできない場合が多い．一方，Larsen grade Iに対する滑膜切除術4例(2膝，2肘)は術後成績が維持されており，滑膜切除術は大関節では関節軟骨が障害される前の早期によりよい適応があると考えられる．

2) 人工関節置換術

人工関節置換術群51件の内訳は肩2件，肘8件，膝26件，股15件であり，平均罹病期間は215.3カ月であった．罹病期間10年未満の症例は10例14件であり，ほぼ全例で生物学的製剤導入前にすでに進行した関節破壊のある患者で，種々の程度の不可逆的な身体機能障害を有していた．平均CRP値は1.06 mg/dlであり，全身コントロールが得られている症例，生物学的製剤によっても低～中等度疾患活動性が残存した症例がほとんどであり，術前CRP高値例は生物学的製剤の二次無効例，休薬期間中の再燃であった．すでに関節破壊を有する例では，低疾患活動性にもかかわらず関節破壊の進行がゼロにできない例も認められ，生物学的製剤導入後にLarsen gradeがIIIからIVに進行して人工関節置換術に至った例やLarsen grade IVの同じGrade内で関節破壊が進行し，疼痛や不安定性が増強したために手術に至った例が含まれていた．一方，構造的破壊が軽度である早期～進行期RAの中には，経年的に関節破壊，変形が進行してくる症例も散見され，今後増加してくる患者群であると考えられた．

これらの症例から生物学的製剤使用中患者の人工関節置換術のタイミングは，①生物学的製剤導入時にすでに破壊が進行して修復の見込みのない場合，②残存

する炎症により長期の間に関節破壊が進行する場合，③大関節においてはLarsen grade III以上となって軟骨が消失した場合(ただし，肩関節，足関節では関節のリモデリングをみることがある)，④上肢においては整容，トイレ動作など基本的ADLが障害され，下肢では歩行能力が著しく低下した場合，などであり，当然骨欠損が比較的軽度で，軟部組織の破綻(腱板，側副靱帯など)や拘縮(筋，関節包，靱帯など)を来す前の手術が成績もよい．

3) 手・足の手術

手・足の手術群は80件であり，大関節に比して疼痛によるVAS(visual analogue scale)は低く，術前CRPは平均0.72 mg/dlと他の手術群に比べてもっとも疾患活動性がコントロールされていた．しかし，手術時年齢や罹病期間は人工関節手術と同等であり，10年以上の長期罹病患者が80例中61例と4分の3を占めていた．臨床的寛解・低疾患活動性となった状態での残存HAQが認められる場合に手術を希望しており，そのタイミングとしては，①変形や可動域制限のため日常生活に困る場合，②機械的刺激による疼痛が強い場合，③腱断裂や末梢神経障害，④美容的愁訴が強い場合，④外傷，骨関節感染など，が認められた．われわれは，術後も生物学的製剤の関節破壊防止効果や修復効果を期待して，手関節においては橈骨月状骨間部分固定術やSauvé-Kapandji手術，中後足部選択的固定術，中足骨短縮骨切り術など，破壊を免れた周辺関節を温存する術式を選択するようにしており，今後もこういった症例が増加していくものと思われる．

今後の展望

生物学的製剤の登場により，RAに対する整形外科手術はより理想的な状況で行われるようになったことは疑いがない．炎症の状態がコントロールされることで，貧血は改善し，切除すべき炎症性滑膜の量は減少している場合が多い．人工関節の設置に際しては骨質もよく，長期成績の改善も期待できる．今後は術前からの合併症も減少傾向になるであろう．手術の対象となる関節以外の関節は比較的良好に保たれ，より円滑なリハビリテーションが施行できる．残存する障害された関節を再建する手術治療を薬物治療に組み合わせていくことは，生物学的製剤の有効性に限界があることからも，寛解や低疾患活動性を目指す治療(treat to target, T2T)[12]のためには必須の治療戦略と思われる．わが国においては，整形外科医が積極的にRA治療にかかわってきたという独自の背景がある．われわれ整形外科医は，海外よりもたらされたT2Tに対して，薬物治療に適宜手術療法・リハビリテーションを組み入れて行う“Japanese T2T”の構築を行っていく責務がある．

一方，こういった強力な免疫抑制療法下にある患者の手術に際しては，手術部位感染(surgical site infection, SSI)が最も重要な問題となる．日本整形外科学会リウマチ委員会では2004年1月から2008年11月の間に行ったRA関連手術について，全国研修施設を対象にアンケート調査を実施した．この中で，RA関連手術59807件中，生物学的製剤使用中の手術は3468件(5.8%)であった．これら手術を行ったのは1245施設中430施設(34.5%)であり，施設間の偏りはみられるが，今後も生物学的製剤使用下の手術は増加してくるものと考えられる．一方，SSIは46件(1.3%)で，生物学的製剤非使用群の感染合併率1.0%(56339件中567件)と有意な差を認めなかったが，人工関節置換術施行例ではオッズ比2.12で生物学的製剤使用中手術にSSIが多いことが判明しており，従来のRA関連手術の際以上の注意が必要である[12]．

文　献

1) van der Heijde D, Klareskog L, Rodriguez-Valverde V, et al. Comparison of etanercept and methotrexate, alone and combined, in the treatment of rheumatoid arthritis: two-year clinical and radiographic results from the TEMPO study, a double-blind, randomized trial. Arthritis Rheum 2006; 54: 1063-74.
2) Breedveld FC, Weisman MH, Kavanaugh AF, et al. The PREMIER study: A multicenter, randomized, double-blind clinical trial of combination therapy with adalimumab plus methotrexate versus methotrexate alone or adalimumab alone in patients with early, aggressive rheumatoid arthritis who had not had previous methotrexate treatment. Arthritis Rheum 2006; 54: 26-37.
3) Nishimoto N, Hashimoto J, Miyasaka N, et al. Study of active controlled monotherapy used for rheumatoid arthritis, an IL-6 inhibitor (SAMURAI): evidence of clinical and radiographic benefit from an X ray reader-blinded randomised controlled trial of tocilizumab. Ann Rheum Dis 2007; 66: 1162-7.
4) van der Kooij SM, le Cessie S, Goekoop-Ruiterman YP, et al. Clinical and radiological efficacy

of initial vs delayed treatment with infliximab plus methotrexate in patients with early rheumatoid arthritis. Ann Rheum Dis 2009; 68: 1153-8.
5) Emery P, Durez P, Dougados M, et al. Impact of T-cell costimulation modulation in patients with undifferentiated inflammatory arthritis or very early rheumatoid arthritis: a clinical and imaging study of abatacept (the ADJUST trial). Ann Rheum Dis 2009; 69: 510-6.
6) Fevang BT, Lie SA, Havelin LI, et al. Reduction in orthopedic surgery among patients with chronic inflammatory joint disease in Norway, 1994-2004. Arthritis Rheum 2007; 57: 529-32.
7) Pedersen AB, Johnsen SP, Overgaard S, et al. Total hip arthroplasty in Denmark: incidence of primary operations and revisions during 1996-2002 and estimated future demands. Acta Orthop 2005; 76: 182-9.
8) Sokka T, Kautiainen H, Hannonen P. Stable occurrence of knee and hip total joint replacement in Central Finland between 1986 and 2003: an indication of improved long-term outcomes of rheumatoid arthritis. Ann Rheum Dis 2007; 66: 341-4.
9) Weiss RJ, Ehlin A, Montgomery SM, et al. Decrease of RA-related orthopaedic surgery of the upper limbs between 1998 and 2004: data from 54,579 Swedish RA inpatients. Rheumatology (Oxford) 2008; 47: 491-4.
10) Yasui T, Nishino J, Kadono Y, et al. Impact of biologics on the prevalence of orthopedic surgery in the National Database of Rheumatic Diseases in Japan. Mod Rheumatol; 20: 233-7.
11) Momohara S, Tanaka S, Nakamura H, et al. Recent trends in orthopedic surgery performed in Japan for rheumatoid arthritis. Mod Rheumatol2011; 21: 337-42.
12) Suzuki M, Nishida K, Soen S, et al. Risk of postoperative complications in rheumatoid arthritis relevant to treatment with biologic agents: a report from the Committee on Arthritis of the Japanese Orthopaedic Association. J Orthop Sci 2011; 16: 778-84.

Mod Rheumatol (2012) 22:635–637
DOI 10.1007/s10165-012-0599-8

RAPID COMMUNICATION

Radiographic remodeling of the shoulder joint in a patient with rheumatoid arthritis after 4 years of treatment with etanercept

Toshifumi Ozaki · Kenzo Hashizume · Ryuichi Nakahara · Keiichiro Nishida

Received: 17 October 2011 / Accepted: 16 January 2012 / Published online: 10 February 2012

Keywords Rheumatoid arthritis · Shoulder joint · Remodeling · Healing · Etanercept

Introduction

The treatment strategy for rheumatoid arthritis (RA) has changed dramatically over the past decade with the introduction of biologic agents. One of the most intriguing effects of biologic agents is structural modification. It has been recognized that radiographic healing occurs even in patients with longstanding RA when clinical remission has been achieved [1–4]. Recent clinical trials have reported radiographic improvement of the affected joint (reappearance of the cortical plate or filling in of erosions) that was more often apparent with a combination of methotrexate (MTX) and biologic agents than with conventional disease-modifying antirheumatic drugs [5–9]. However, evidence of this phenomenon has been limited to small joints of the hand or foot, as evaluated by the van der Heijde- or Genant-modified Sharp scores [10, 11]. However, functional improvement generally depends on the condition of the large joints and is an important goal of treatment for RA. At present, reports on the structural modifying effect of biologic agents on large joints are rare, and the effect of these agents on the shoulder joint has not been documented in the literature.

Case report

A 59-year-old woman with a 20-year history of RA presented to our institution with progressively worsening left shoulder pain. There was swelling and tenderness of the left shoulder, with range of motion restricted to 30° of flexion, 10° of extension, and 0° of abduction due to severe pain. Plain radiographs showed erosions and an irregular humeral surface with bone destruction and atrophy, and a bone defect of the glenoid surface (Fig. 1a). Despite taking MTX (6 mg/week) and salazosulfapyridine (1,000 mg/day), she had a tender joint count of 4, a swollen joint count of 4, and a 91-mm rating on the patient's global assessment (PGA) scale. Laboratory findings were as follows: C-reactive protein (CRP), 1.67 mg/dL and erythrocyte sedimentation rate (ESR), 53 mm/h, resulting in a high disease activity score (DAS) 28-ESR of 5.73 and a DAS28-CRP of 4.96. We recommended total shoulder arthroplasty for this patient, as would be customary, but she declined and asked to be treated with a biologic agent. Four years of etanercept treatment (25 mg SC 2/week) effectively improved her clinical symptoms and laboratory readings. No swelling or tenderness of the left shoulder joint was noted, resulting in a PGA of 0 mm. The latest laboratory tests showed a CRP of 0.11 mg/dL and an ESR

Electronic supplementary material The online version of this article (doi:10.1007/s10165-012-0599-8) contains supplementary material, which is available to authorized users.

T. Ozaki · K. Hashizume · R. Nakahara · K. Nishida
Department of Orthopaedic Surgery, Okayama University Graduate School of Medicine, Dentistry and Pharmaceutical Sciences, 2-5-1 Shikata-cho, Okayama, Okayama 700-8558, Japan

K. Nishida (✉)
Department of Human Morphology, Science of Functional Recovery and Reconstruction, Okayama University Graduate School of Medicine, Dentistry and Pharmaceutical Sciences, 2-5-1 Shikata-cho, Okayama, Okayama 700-8558, Japan
e-mail: knishida@md.okayama-u.ac.jp

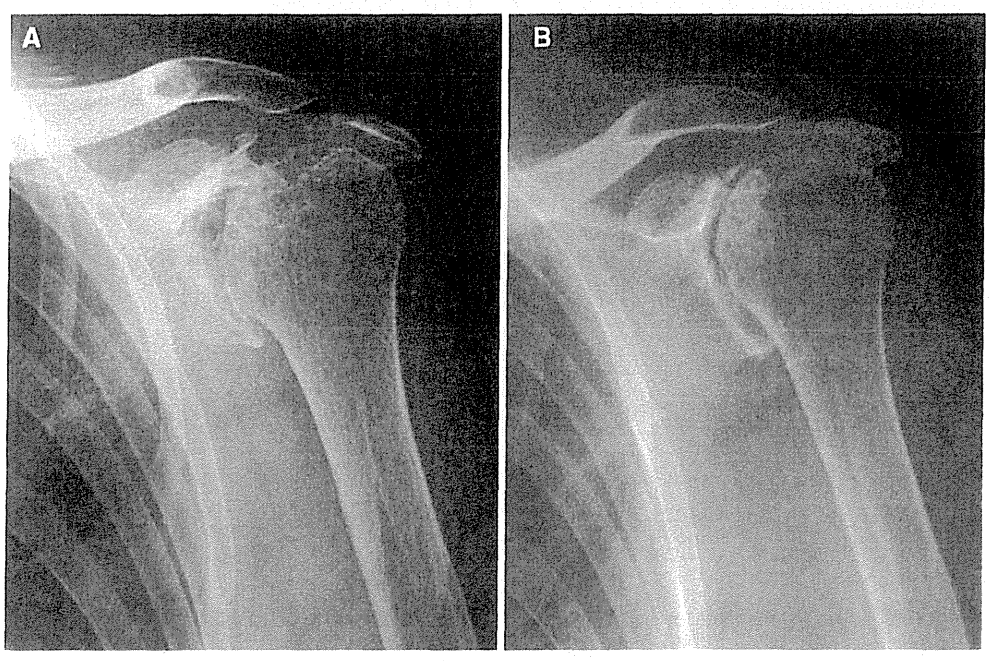

Fig. 1 Anteroposterior radiographic view of left shoulder joint at baseline (**a**) and at final follow up (**b**) after 4 years of treatment with etanercept (25 mg SC 2/week) in combination with methotrexate (6 mg/week)

of 22 mm/h, resulting in clinical remission with a DAS28-ESR of 2.16, and a DAS28-CRP of 1.23.

Recent follow-up radiographs of the left shoulder showed dramatic joint healing, a smooth humeral surface, marginal sclerosis of the glenoid cavity, and the reappearance of a clear joint space (Fig. 1b). Computed tomography (CT) revealed filling in of the erosions, subchondral bone sclerosis of the humeral and glenoid surfaces, and osteophyte formation at the posterior aspect of the glenoid, although the joint space had not been recovered (Fig. 2a, b). Although radiographically the humeral head still showed upper migration (suggesting rotator cuff tear), osteophyte formation at the superior aspect of the glenoid successfully covered the humeral surface, which was also evident in the coronal view of the CT (electronic supplementary material). Her shoulder pain has nearly resolved and her active range of motion has improved to 125° flexion, 30° extension, and 90° abduction.

Discussion

Joints affected by RA usually lack signs of repair, resulting in bone and joint destruction [12]. Our case indicates that radiographic healing may occur in an arthritic shoulder of RA treated with etanercept in combination with MTX, as a result of long-term clinical remission and disappearance of local inflammation. The question as to which stage of large joint destruction is beyond healing in RA remains to be answered. This limitation might depend on whether a joint is weight-bearing or non-weight-bearing. Seki et al. [13] reported that hip and knee joints with preexisting damage of Larsen grade III/IV showed apparent progression even in patients having good responses to biologic agents. They emphasized the need for the early introduction of anti-tumor necrosis factor (TNF) therapy when patients show early structural damage in their weight-bearing joints. Our patient's baseline radiograph showed late-stage joint destruction. The dramatic improvement of the joint structure might have been partly due to the nature of the shoulder joint as a suspended, non-weight-bearing joint, because mechanical force is one of the catabolic factors that promote bone destruction; furthermore, the wrist and elbow joints might compensate for overuse of a painful shoulder joint. Theoretically, hyaline cartilage regeneration, even with biologic agents, would not be expected after cartilage destruction; improvement toward a secondary osteoarthritic joint condition may be a more realistic goal. Thus, in the current era of biologic agents, a new radiographic grading system that evaluates the structural repair of large joints is necessary. In addition, a prospective study correlating the large joint score with disease activity and functional disability would add useful information for combining current therapy with biologic agents for joint destruction.

Another question arises over the potential effects of biologic agents on anabolic bone metabolism. Tumor necrosis factor (TNF) promotes bone destruction by inducing bone-resorbing osteoclasts and decreasing the number of bone-forming osteoblasts. TNF also upregulates

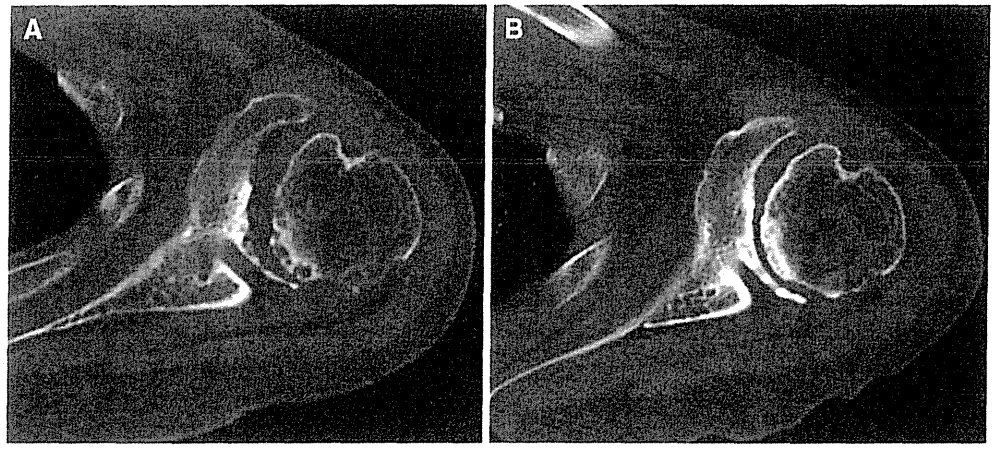

Fig. 2 Horizontal and coronal views of computed tomography (CT) scan of left shoulder joint at baseline (**a**) and at final follow up (**b**)

Dickkopf-1 (DKK-1), a natural inhibitor of wingless signaling that is essential for joint remodeling [14]. Thus, targeted TNF inhibition by biologic disease-modifying antirheumatic drugs might effectively interfere with the catabolic pathways of joint destruction and promote anabolic repair mechanisms by inhibiting DKK-1 expression. More recently, Wang et al. [15] reported that the serum DKK-1 level was significantly decreased in RA patients treated with a TNF-α inhibitor. Furthermore, increased DKK-1 was associated with a higher risk of bone erosion progression, assessed by changes in the radiological Sharp score, in patients treated with etanercept when compared with patients treated with methotrexate (MTX) alone [16]. However, these studies did not focus on the relationship between DKK-1 and joint remodeling. As large-joint remodeling takes years, it would be tempting to investigate whether direct inhibition of DKK-1 contributes to acceleration of the joint remodeling process.

Conflict of interest K.N. received lecture fees from Pfizer Japan, Inc. and Takeda Pharmaceutical Co. Ltd. The other authors have no conflicts of interest to declare.

References

1. Rau R, Wassenberg S, Herborn G, Perschel WT, Freitag G. Identification of radiologic healing phenomena in patients with rheumatoid arthritis. J Rheumatol. 2001;28:2608–15.
2. Rau R. Is remission in rheumatoid arthritis associated with radiographic healing? Clin Exp Rheumatol. 2006;24:S-41–4.
3. Wassenberg S, Rau R. Radiographic healing with sustained clinical remission in a patient with rheumatoid arthritis receiving methotrexate monotherapy. Arthritis Rheum. 2002;46:2804–7.
4. Sokka T, Hannonen P. Healing of erosions in rheumatoid arthritis. Ann Rheum Dis. 2000;59:647–9.
5. van der Heijde D, Klareskog L, Rodriguez-Valverde V, et al. Comparison of etanercept and methotrexate, alone and combined, in the treatment of rheumatoid arthritis: two-year clinical and radiographic results from the TEMPO study, a double-blind, randomized trial. Arthritis Rheum. 2006;54:1063–74.
6. Breedveld FC, Weisman MH, Kavanaugh AF, et al. The PREMIER study: A multicenter, randomized, double-blind clinical trial of combination therapy with adalimumab plus methotrexate versus methotrexate alone or adalimumab alone in patients with early, aggressive rheumatoid arthritis who had not had previous methotrexate treatment. Arthritis Rheum. 2006;54:26–37.
7. Nishimoto N, Hashimoto J, Miyasaka N, et al. Study of active controlled monotherapy used for rheumatoid arthritis, an IL-6 inhibitor (SAMURAI): evidence of clinical and radiographic benefit from an X-ray reader-blinded randomised controlled trial of tocilizumab. Ann Rheum Dis. 2007;66:1162–7.
8. van der Kooij SM, le Cessie S, Goekoop-Ruiterman YP, et al. Clinical and radiological efficacy of initial vs delayed treatment with infliximab plus methotrexate in patients with early rheumatoid arthritis. Ann Rheum Dis. 2009;68:1153–8.
9. Emery P, Durez P, Dougados M, et al. Impact of T-cell costimulation modulation in patients with undifferentiated inflammatory arthritis or very early rheumatoid arthritis: a clinical and imaging study of abatacept (the ADJUST trial). Ann Rheum Dis. 2009;69:510–6.
10. van der Heijde D. How to read radiographs according to the Sharp/van der Heijde method. J Rheumatol. 1999;26:743–5.
11. Genant HK. Methods of assessing radiographic change in rheumatoid arthritis. Am J Med. 1983;75:35–47.
12. Walsh NC, Crotti TN, Goldring SR, Gravallese EM. Rheumatic diseases: the effects of inflammation on bone. Immunol Rev. 2005;208:228–51.
13. Seki E, Matsushita I, Sugiyama E, et al. Radiographic progression in weight-bearing joints of patients with rheumatoid arthritis after TNF-blocking therapies. Clin Rheumatol. 2009;28:453–60.
14. Diarra D, Stolina M, Polzer K, et al. Dickkopf-1 is a master regulator of joint remodeling. Nat Med. 2007;13:156–63.
15. Wang SY, Liu YY, Ye H, et al. Circulating Dickkopf-1 is correlated with bone erosion and inflammation in rheumatoid arthritis. J Rheumatol. 2011;38:821–7.
16. Garnero P, Tabassi NC, Voorzanger-Rousselot N. Circulating dickkopf-1 and radiological progression in patients with early rheumatoid arthritis treated with etanercept. J Rheumatol. 2008;35:2313–5.

The Journal of
Rheumatology

The Journal of Rheumatology Volume 39, no. 3

Safety and Efficacy of Various Dosages of Ocrelizumab in Japanese Patients with Rheumatoid Arthritis with an Inadequate Response to Methotrexate Therapy: A Placebo-controlled Double-blind Parallel-group Study

MASAYOSHI HARIGAI, YOSHIYA TANAKA, SHINGO MAISAWA and the JA21963 Study Group

J Rheumatol 2012;39;486-495
http://www.jrheum.org/content/39/3/486

Safety and Efficacy of Various Dosages of Ocrelizumab in Japanese Patients with Rheumatoid Arthritis with an Inadequate Response to Methotrexate Therapy: A Placebo-controlled Double-blind Parallel-group Study

MASAYOSHI HARIGAI, YOSHIYA TANAKA, SHINGO MAISAWA, and the JA21963 Study Group

ABSTRACT. ***Objective.*** To evaluate the safety and efficacy of ocrelizumab (OCR) in Japanese patients with rheumatoid arthritis (RA) with an inadequate response to methotrexate (MTX).

Methods. RA patients with an inadequate response to MTX 6–8 mg/week received an infusion of 50, 200, or 500 mg OCR or placebo on Days 1 and 15 and were observed for 24 weeks. The double-blind period was prematurely terminated because of a possible risk for serious infection from OCR.

Results. A total of 152 patients were randomized into the study. The incidence of infection was 37.7% (43/114) in the OCR groups combined, compared to 18.9% (7/37) in the placebo group. Serious infections occurred in 7 patients in the OCR groups combined; there were no serious infections in the placebo group. Among the serious infections, *Pneumocystis jirovecii* pneumonia occurred in 2 patients in the OCR 200 mg group. The American College of Rheumatology 20% response rates at Week 24 (the primary endpoint) of the OCR 50, 200, and 500 mg groups were 54.1% ($p = 0.0080$), 55.6% ($p = 0.0056$), and 47.2% ($p = 0.044$), respectively, all significantly higher than that of the placebo group (25.0%).

Conclusion. These results suggest inappropriate benefit-risk balance of OCR in this patient population. Because rituximab is not approved for treatment of RA in Japan, it will be necessary to investigate safety and efficacy of other anti-B cell therapies in Japanese patients with RA. (ClinicalTrials.gov NCT00779220). (First Release Jan 15 2012; J Rheumatol 2012;39:486–95; doi:10.3899/jrheum.110994)

Key Indexing Terms:
OCRELIZUMAB
B CELL DEPLETION
RHEUMATOID ARTHRITIS
CLINICAL TRIALS

From the Departments of Pharmacovigilance, and Medicine and Rheumatology, Graduate School of Medical and Dental Sciences, and the Clinical Research Center, Tokyo Medical and Dental University, Tokyo; the First Department of Internal Medicine, School of Medicine, University of Occupational and Environmental Health, Kitakyushu; and Chugai Pharmaceutical Co. Ltd., Tokyo, Japan.

Supported by Chugai Pharmaceutical Co. Ltd. M. Harigai has received research grants, consultant fees, and/or speakers' bureau honoraria from Abbott Japan, Bristol-Myers Japan, Chugai Pharmaceutical Co. Ltd., Eisai Co. Ltd., Janssen Pharmaceutical KK, Mitsubishi Tanabe Pharma, Pfizer Japan Inc., and Takeda Pharmaceutical Co. Ltd. Y. Tanaka has received consulting fees, speaking fees, and/or honoraria from Chugai, Mitsubishi-Tanabe, Eisai, Takeda, Astellas, and Abbott and has received research grant support from Chugai, Mitsubishi-Tanabe, Takeda, MSD, Pfizer, Astellas, Abbott, and Eisai.

M. Harigai, MD, PhD, Departments of Pharmacovigilance, Medicine and Rheumatology, and the Clinical Research Center, Graduate School of Medical and Dental Sciences, Tokyo Medical and Dental University; Y. Tanaka, MD, PhD, First Department of Internal Medicine, School of Medicine, University of Occupational and Environmental Health; S. Maisawa, BSc, Chugai Pharmaceutical Co. Ltd.

Address correspondence to Dr. M. Harigai, Department of Pharmacovigilance, Graduate School of Medical and Dental Sciences, Tokyo Medical and Dental University, 1-5-45 Yushima, Bunkyo-ku, Tokyo, 113-8519, Japan. E-mail: mharigai.mpha@tmd.ac.jp

Full Release Article. For details see Reprints/Permissions at jrheum.org

Accepted for publication October 13, 2011.

The possible involvement of B cells in the pathogenesis and progression of RA, including autoantibody production, autoantigen presentation, T cell activation, and production of proinflammatory cytokines and chemokines, has been suggested[1,2,3,4,5,6]. Based on these reports, clinical trials of rituximab (RTX), a chimeric anti-CD20 monoclonal antibody (mAb) targeting CD20 molecules, were conducted in patients with rheumatoid arthritis (RA)[7,8]. Subsequently, RTX was approved for treatment of RA in Europe and the United States.

Ocrelizumab (OCR) is a humanized mAb that also targets CD20[9,10] and eliminates B cells by inducing antibody-dependent cell-mediated cytotoxicity (ADCC), complement-dependent cytotoxicity (CDC), and apoptosis. While the epitopes recognized by OCR and RTX on the extracellular domain of the CD20 molecule partially overlap, OCR offers some advantages over RTX. First, OCR is expected to be better tolerated over repeated and longterm administration because OCR induced higher ADCC activity and lower CDC activity than RTX *in vitro*; this has clinical relevance because CDC activation has been associated with