Table 1. Continued

Survey Items	Median (30th to 70th percentile)†	Disagreement Index††
Swelling of associated bursa, as observed by the patient*	5 (4 to 6)	0.85
Warmth of skin overlying the affected joint, as observed by the patient*	5 (4 to 6)	0.85
Asymmetric joint involvement, as observed by the physician*	5 (4 to 6)	0.85
Patient has a high purine diet (i.e., consumes large amounts of red meat and shellfish)*	5 (4 to 6)	0.85
Patient is obese*	5 (4 to 6)	0.85
Patient has previously had a cardiovascular disease such as heart failure or myocardial infarction*	5 (4 to 6)	0.85
US power Doppler signal (PWD 2–3) in monoarthritis*	5 (4 to 6)	0.85
Elevated neutrophils within the synovial fluid*	5 (4 to 5)	0.32
Patient is middle aged (40–50 years old)*	5 (4 to 5)	0.32
Swelling in the joint, as observed by the patient*	5 (3 to 6)	0.97
Elevated leukocytes within the synovial fluid*	5 (3 to 5)	0.52
Inflammatory cells present in fluid aspirated from affected joint*	5 (3 to 5)	0.52
Pain is relieved by joint aspiration*	4.5 (3 to 5)	0.52
Patient also suffers from diabetes*	4 (4 to 5)	0.32
Elevated serum C-reactive protein*	4 (3.3 to 5)	0.47
Pain prevents walking*	4 (3 to 5.7)	0.81
Asymmetric joint involvement, as observed by the patient*	4 (3 to 5)	0.52
Acute uric acid nephropathy*	4 (3 to 5)	0.52
Elevated erythrocyte sedimentation rate*	4 (3 to 5)	0.52
Aspiration of previously affected joint shows elevated leukocyte count in joint fluid*	4 (3 to 4)	0.22
MRI synovitis (an area of synovial compartment is enhanced with contrast, and is thicker than the width of normal synovium)*	4 (3 to 4)	0.22
US calcium deposits (focal hyperechoic deposits within hyaline cartilage)*	4 (3 to 4)	0.22
Items agreed by physicians to be not discriminatory		
Polyarticular disease, as observed by the physician*	3.5 (3 to 4)	0.22
Fewer than 5 joints affected	3 (3 to 5)	0.52
Fever	3 (3 to 5)	0.52
Polyarticular disease, observed by the patient	3 (3 to 4)	0.22
Patient has hypertension*	3 (3 to 4)	0.22
Functional disability (difficulty with daily activities)	3 (2 to 5)	0.65
Loss of function of the joint (due to loss of joint motion)	3 (2 to 4.9)	0.62
MRI cartilage pathology (focal and diffuse narrowing)	3 (2 to 4.9)	0.62
Calcium nephrolithiasis	3 (2 to 4)	0.37
Radiographic joint space abnormalities (includes widening, narrowing, and ankylosis)	3 (2 to 4)	0.37
Patient complains of flu-like symptoms	3 (1.1 to 4)	0.48
Malaise	3 (1.1 to 4)	0.48
Elevated platelet count	2 (1.1 to 4)	0.48
Early morning stiffness lasting > 30 minutes	2 (1 to 2.9)	0.27
Spinal involvement	2 (1 to 2)	0.13

* Rating from final iteration. † Values of 1–3.5 indicate the item was considered not discriminatory for gout, 4–6.5 as uncertain, and 7–9 as discriminatory for gout. †† Disagreement index > 1 indicates disagreement[18]. US: ultrasound; CR: conventional radiology; CT: computed tomography; MRI: magnetic resonance imaging; MSU: monosodium urate.

agreement on all items during the second iteration so that a third iteration was not required. The final list of features (Table 1) contained 4 additional discriminatory items and 2 additional nondiscriminatory items. There were 52 items that were rated as uncertain (median rating 4–6).

There were 14 respondents to the first patient survey (16% response rate). Of these, 13 (93%) responded to the second iteration and 9 (69%) to the third iteration. Patients were a median age of 63 (range 38–89) years and the median duration of disease was 10 (range 4–25) years. In the first round, 46 features were identified by patients. In the second round, it was agreed that 2 of the features were not discriminatory for gout and that 22 of the features were discriminatory. Patients were uncertain of the diagnostic importance of 19 of the features or were in disagreement concerning 3 items and these were re-rated in the final iteration. After the final iteration of the patient survey (Table 2) there was agreement that 7 items were not discriminatory for gout, 25 items were discriminatory for gout, and 14 items were rated with uncertainty or disagreement.

Comparison of the patient and physician data showed consensus on the following general characteristics thought to be specific for gout: the suddenness of onset, redness and swelling of the affected joint, the marked tenderness of the joint, elevated serum urate levels, presence of tophi, the presence of MSU crystals in synovial fluid, and involvement of the first metatarsophalangeal joint (Figure 1).

Table 2. Final ratings following the third iteration of the patient survey.

Survey Items	Median (30th to 70th percentile) Rating†	Disagreement Index††
Items agreed by patients as being discriminatory		
Blood test shows an increase in uric acid in the blood	9 (9 to 9)	0
During an attack of gout the pain is so bad you find it hard to walk	9 (9 to 9)	0
During an attack of gout you cannot use the affected joint	9 (8.6 to 9)	0.05
During an attack of gout the pain is so bad it interrupts your sleep	9 (8.2 to 9)	0.1
During an attack of gout the joint is so sensitive you cannot even sleep with a sheet touching the affected area	9 (7.2 to 9)	0.26
Medication such as indomethacin, allopurinol, or colchicine keeps the gout attacks at bay	9 (6.6 to 9)	0.37
The pain is of a throbbing type	9 (5.6 to 9)	0.59
Presence of crystals from joint fluid under a microscope	9 (5.6 to 9)	0.59
An attack of gout often occurs after eating seafood/shellfish*	8 (7 to 9)	0.29
Onset of an attack is sudden	8 (6.6 to 9)	0.37
The big toe is affected	8 (6 to 9)	0.49
The affected joint is hot	8 (5.6 to 9)	0.59
The affected joint is red	8 (5.6 to 9)	0.59
Tophi (lumps) are present in areas such as the elbows, fingers, and toes	8 (5 to 9)	0.75
The pain is annoying	8 (4.2 to 8.4)	0.98
A flare-up of an attack of gout responds rapidly to medication such as prednisone or naproxen	7 (7 to 7.8)	0.13
The affected area is very sensitive to touch	7 (6.2 to 9)	0.45
The affected joint is swollen	7 (6 to 9)	0.49
An attack of gout often occurs after consuming alcohol*	7 (6 to 8.6)	0.45
Severe, sharp pain in the affected joint	7 (5.6 to 9)	0.59
The affected joint is enlarged	7 (5.6 to 8)	0.48
If you injure an area that has been affected by gout, it takes longer to heal than one that has not been affected by gout*	7 (5 to 9)	0.75
Only one foot is usually affected at a time	7 (5 to 9)	0.75
The pain is still present even when the affected joint is not being moved/used	7 (5 to 9)	0.75
There is a burning feeling in the affected area	7 (4.6 to 8.4)	0.83
Items agreed to be uncertain		
An attack of gout often occurs after eating red meat*	6 (5.4 to 7.2)	0.42
An increase in blood pressure may be observed*	5 (5 to 7.8)	0.63
Other members of your family have/have had gout*	5 (5 to 6.6)	0.45
The duration of an attack of gout is relatively short (1–2 days)*	5 (4.4 to 6.6)	0.71
Items agreed to be not discriminatory		
The affected joints appear deformed/have changed shape*	3 (2.4 to 5)	0.6
The elbows are affected*	3 (1.8 to 5)	0.67
The ball of the foot is affected*	3 (1.4 to 5.6)	0.91
The fingers are affected*	3 (1.4 to 4.2)	0.5
An attack of gout often occurs after eating asparagus	3 (1 to 5)	0.75
The knees are affected*	3 (1 to 4.2)	0.54
The pain is always present in the hands — even in the absence of an attack of gout	1 (1 to 5)	0.75
Items for which there was disagreement		
The pain may produce depression*	7 (4 to 9)	1.09
The joints in the middle of the foot are affected*	4 (2.4 to 6.2)	1.12
White lumps are observed on the fingers*	5 (3.8 to 8)	1.14
The area around the affected joint is swollen*	8 (3.8 to 9)	1.17
The pain is worse when you move the affected joint*	5 (3.4 to 8.6)	1.35
When these lumps are lanced they release a white substance*	1 (1 to 6.8)	1.45
Friction/rubbing makes the affected joint more painful*	5 (1.8 to 6.8)	1.47
The attack resolves quickly*	5 (2.4 to 7)	1.64
The affected joint is stiff*	3 (1.8 to 7.6)	2.07
The ankles are affected*	5 (2.4 to 7.6)	2.21

* Item re-rated during the third iteration. † Values of 1–3.5 indicate the item was considered not discriminatory for gout, 4–6.5 as uncertain, and 7–9 as discriminatory for gout. †† Disagreement index > 1 indicates disagreement[18].

DISCUSSION

This Delphi exercise identified 26 features of gout that expert physicians believed were potentially appropriate to distinguish gout from other rheumatic musculoskeletal diseases. Patients with chronic gout further supported these findings by identifying many of the same features as physicians.

One difference between patients and physicians was the

different emphasis on functional disability. Patients believed that the inability to carry out everyday tasks such as walking was an important diagnostic feature and rated it highly whereas physicians believed that it was not at all discriminatory. There was more emphasis by patients on the severity of the symptoms of gout such as red, hot, swollen, and tender joints that prevent sleep and normal everyday functioning. The response to treatment and the triggers for gout attacks were also seen by patients to be more important than physicians. In contrast, physicians tended to emphasize imaging, the pattern of joint involvement, and its behavior over time. Overall, physicians were more focused on diagnostic criteria and patients on disease severity criteria.

There was greater disagreement among patients regarding the specificity of features they suggested, compared to among physicians. This is consistent with substantial interindividual variation in how diseases manifest and how symptoms are interpreted by patients. Physicians are trained to recognize nomothetic commonalities, patterns, symptom clusters, and pathology, rather than idiographic variations of symptoms. An obvious key difference between patients and physicians that is relevant here is that physicians have experience in distinguishing between different rheumatic diseases, whereas patients have experience only in distinguishing between having and not having gout, and may not be able to easily determine when symptoms are due to gout and not some other rheumatic disease.

Many of the items for which there was agreement between patients and physicians already appear within existing classification criteria. This is not surprising, since such features are likely to be highly typical or characteristic of the disease. An improvement upon existing criteria may still be achievable with different criteria formats (for example, weighting of different features) and inclusion of new items (for example, modern imaging techniques).

Unfortunately, the patient response rate in our study was much lower than expected. Five patients did not complete all iterations and thus were considered nonrespondents, we received 8 "return to sender" letters due to incorrect addresses, and we received at least 1 letter and some telephone messages from patients who wanted to participate but had no access to a computer. But the reason for nonresponse was unknown for most nonrespondents. In light of the low response rate, the patient results cannot be considered representative of the gout patient population. In addition, the patients reported features such as tophi that may occur only in more severely affected patients. Also, it should be noted that all patient participants were from New Zealand whereas the physicians were from several countries. It would be of interest to obtain opinions from a larger number of patients from different countries. Finally, patients and physicians were hospital-based rather than recruited from primary care settings, which may tend to bias opinion toward more severe gout. Overall, it should not be considered that the patients in our study were representative of the gout population. Nonetheless, their opinions are of value.

This Delphi consensus methodology has provided some direction toward features that could be tested for possible new gout classification criteria. The next phase of this project is to conduct a case-control study to establish the most accurate combinations of these features for classifying gout when compared to the gold standard diagnostic procedure of MSU identification in tissue or synovial fluid.

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REFERENCES

1. Harrold LR, Saag KG, Yood RA, Mikuls TR, Andrade SE, Fouayzi H, et al. Validity of gout diagnoses in administrative data. Arthritis Care Res 2007;57:103-8.
2. Zhang W, Doherty M, Pascual E, Bardin T, Barskova V, Conaghan P, et al. EULAR evidence based recommendations for gout. Part I: Diagnosis. Report of a task force of the Standing Committee for International Clinical Studies Including Therapeutics (ESCISIT). Ann Rheum Dis 2006;65:1301-11.
3. Taylor WJ. Diagnosis of gout: Considering clinical and research settings. Curr Rheumatol Rev 2011;7:97-105.
4. Malik A, Schumacher R, Dinnella JE, Clayburne GM. Clinical diagnostic criteria for gout — Comparison with the gold standard of synovial fluid crystal analysis. J Clin Rheumatol 2009;15:22–4.
5. Decker JL. Report from the Subcommittee on Diagnostic Criteria for Gout. In: Bennett PH, Wood PHN, editors. Population studies of the rheumatic diseases — Proceedings of the Third International Symposium New York, June 5-10, 1966. Amsterdam: Excerpta Medica Foundation; 1968:385-7.
6. Wallace SL, Robinson H, Masi AT, Decker JL, McCarty DJ, Yu TF. Preliminary criteria for the classification of the acute arthritis of primary gout. Arthritis Rheum 1977;20:895-900.
7. Janssens H, Janssen M, van de Lisdonk EH, Fransen J, van Riel P. Limited validity of the American College of Rheumatology criteria for classifying patients with gout in primary care. Ann Rheum Dis 2010;69:1255–6.
8. Winnard D, Wright C, Taylor WJ, Jackson G, Te Karu L, Gow P, et al. National prevalence of gout derived from administrative health data in Aotearoa New Zealand. Rheumatology 2012;51:901-9.
9. Choi HK, Ford ES, Li C, Curhan G. Prevalence of the metabolic syndrome in patients with gout: The Third National Health and Nutrition Examination Survey. Arthritis Rheum 2007;57:109-15.
10. Gaffo AL, Edwards NL, Saag KG. Gout. Hyperuricemia and

cardiovascular disease: How strong is the evidence for a causal link? Arthritis Res Ther 2009;11:240.
11. Vazquez-Mellado J, Hernandez-Cuevas CB, Alvarez Hernandez E, Ventura-Rios L, Pelaez-Ballestas I, Casasola-Vargas J, et al. The diagnostic value of the proposal for clinical gout diagnosis (CGD). Clin Rheumatol 2012;31:429-34.
12. Janssens HJ, Fransen J, van de Lisdonk EH, van Riel PL, van Weel C, Janssen M. A diagnostic rule for acute gouty arthritis in primary care without joint fluid analysis. Arch Intern Med 2010;170:1120-6.
13. Kirwan JR, Tugwell PS. Overview of the patient perspective at OMERACT 10 — Conceptualizing methods for developing patient-reported outcomes. J Rheumatol 2011;38:1699-701.
14. Kirwan JR, Newman S, Tugwell PS, Wells GA. Patient perspective on outcomes in rheumatology — A position paper for OMERACT 9. J Rheumatol 2009;36:2067-70.
15. Ottewill R, Demain S, Ellis-Hill C, Greenyer CH, Kileff J. An expert patient-led approach to learning and teaching: The case of physiotherapy. Med Teach 2006;28:e120-6.
16. Abraham C, Gardner B. What psychological and behaviour changes are initiated by 'expert patient' training and what training techniques are most helpful? Psychol Health 2009;24:1153-65.
17. Schumacher HR Jr, Chen LX, Mandell BF. The time has come to incorporate more teaching and formalised assessment of skills in synovial fluid analysis into rheumatology training programs. Arthritis Care Res 2012;64:1271-3.
18. Fitch K, Bernstein SJ, Aguilar MS, Burnand B, LaCalle JR, Lazaro P, et al. The RAND/UCLA appropriateness method user's manual. Santa Monica, CA: RAND; 2001.
19. Graham B, Regher G, Wright J. Delphi as a method to establish consensus for diagnostic criteria. J Clin Epidemiol 2003;56:1150-6.

A Delphi Exercise to Identify Characteristic Features of Gout — Opinions from Patients and Physicians, the First Stage in Developing New Classification Criteria

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Concise report

A modified Delphi exercise to determine the extent of consensus with OMERACT outcome domains for studies of acute and chronic gout

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ABSTRACT

Objectives: To reach consensus with recommendations made by an OMERACT Special Interest Group (SIG).

Methods: Rheumatologists and industry representatives interested in gout rated and clarified, in three iterations, the importance of domains proposed by the OMERACT SIG for use in acute and chronic gout intervention studies. Consensus was defined as a value of less than 1 of the UCLA/RAND disagreement index.

Results: There were 33 respondents (61% response rate); all agreed the initial items were necessary, except "total body urate pool". Additional domains were suggested and clarification sought for defining "joint inflammation" and "musculoskeletal function". Items that demonstrated no clear decision were re-rated in the final iteration. There were six highly rated items (rating 1–2) with four slightly lower rating items (rating 3) for acute gout; and 11 highly rated items with eight slightly lower ratings for chronic gout.

Conclusions: Consensus is that the following domains be considered mandatory for acute gout studies: pain, joint swelling, joint tenderness, patient global, physician global, functional disability; and for chronic gout studies: serum urate, gout flares, tophus regression, health-related quality of life, functional disability, pain, patient global, physician global, work disability and joint inflammation. Several additional domains were considered discretionary.

Gout is a systemic metabolic disease manifested by hyperuricaemia, acute and chronic arthritis, monosodium urate crystal deposits in connective tissue producing tophi, and uric acid nephrolithiasis. It is the most common inflammatory arthritis in men. It may be associated with the metabolic syndrome and with an increased risk of cardiovascular disease.

There has been renewed interest in the treatment of gout with recent reported intervention studies of new agents, including etoricoxib,[1] lumiracoxib[2] in acute gout or attacks of gout and febuxostat,[3] pegylated-uricase[4] in chronic gout. These studies have highlighted the relative paucity of validated outcome measures with which to judge efficacy. Gout has been discussed at OMERACT 7[5] and OMERACT 8[6] and a preliminary list of relevant domains has been developed by a Special Interest Group (SIG). These domains include: pain, inflammation, function, patient global, safety for acute gout studies; serum urate, gout flare recurrence, tophus regression, joint damage imaging, health-related quality of life (HRQOL), musculoskeletal function, patient global assessment, participation, safety and tolerability for chronic gout studies. A key aim of treatment for chronic gout is likely to include elimination of the deposited urate crystals.

The purpose of this study was to formally determine the extent of consensus with these recommendations using a Delphi approach. This technique iteratively and anonymously solicits opinions from participants, who have the opportunity to revise their opinion in the light of feedback on the opinion of the group as a whole.[7]

METHODS

Fifty-four rheumatologists and industry representatives interested in gout were identified from the OMERACT Gout mailing list and a previous Delphi exercise that examined the question of gout flare.[8] Respondents were asked to rate the importance of measuring domains in acute gout and chronic gout intervention studies on a seven-point scale (1 = definitely necessary to 7 = definitely not necessary), using a web-based questionnaire. Studies for acute gout refer to interventions that aim to limit the severity or duration of an acute gout flare. The precise definition of acute gout or gout flare is the subject of an ongoing study under the OMERACT umbrella.[9] Studies for chronic gout refer to interventions that aim to prevent recurrent episodes of acute gout or limit the overall impact of persistent symptoms, disease activity or functional consequences of persistent disease over an extended time period. The domains suggested by the OMERACT SIG were used for the first iteration, supplemented by domains of "physician global assessment" and "work disability" for acute gout and "work disability", "physician global assessment", "joint inflammation", "pain" and "total body urate pool" for chronic gout studies. These extra domains were selected on the basis of literature review and expert opinion. Additional domains felt to be of importance were also solicited from Delphi respondents. Consensus was defined by the UCLA/RAND disagreement index, whereby values of less than 1 indicated agreement.[10] This index is essentially calculated from the 30th and

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70th percentile of the respondents' ratings, adjusted for symmetry between the central point of the interpercentile range and the mid-point of the rating scale. The adjustment factor was derived from experimental work that compared different definitions of what constituted "disagreement" among panels of various sizes.

New items, re-worded items, and items for which there was disagreement and/or median rating of 4 (neither agreement nor disagreement) were re-rated in the second iteration. In the final (third) iteration, no new items were introduced and only items for which there was disagreement and/or median rating of 4 were re-rated. Reminders were emailed at 2 weeks following the start of each round and potential respondents were given a further week to respond before being declared a non-respondent.

According to the principles of the Delphi technique,[7] respondents were not known to each other during the survey and the group response (median and interpercentile range) was made known to respondents at the time any item was rated for a second or third time.

The study protocol was reviewed by the New Zealand Health and Disability Central Region Ethics Committee.

RESULTS

There were 33 respondents (61% response rate) to the first survey; 54% were from North America, 18% from Europe and 27% from Asia-Pacific. Of these, 29 (88%) responded to the second and third rounds of the survey. There were three participants from industry, all of whom had first-hand knowledge of design and conduct of pharmaceutical trials in gout.

All initial items were agreed as important (median rating 1–3), except for "total body urate pool" (median rating 4). Additional domains were suggested and clarification sought for the meaning of "joint inflammation" and "musculoskeletal function". Subsequently the new items and "total body urate pool" were (re)rated in the second and third (final) iteration.

For acute gout (table 1) the final list contained six items (median rating 1–2) and four items (median rating 3); and for chronic gout 11 items (median rating 1–2) and eight items (median rating 4) (table 2). Additional domains that this group of respondents felt were important for studies of chronic gout were health care utilisation, costs, patient utilities and comorbidities. Functional status should be assessed in terms of joint function (range of motion), activity limitation (disability) and participation restriction. It remained unclear whether an acute phase marker should be a core domain for studies of chronic gout.

DISCUSSION

This Delphi exercise has confirmed that the domains identified by the OMERACT SIG are important for studies of acute and chronic gout. However, additional domains were also seen as important, creating a list of outcome areas that might be too unwieldy for clinical trials. In addition, this exercise has clarified the meaning of "function" and "inflammation" listed in the OMERACT SIG recommendation, creating further domains. It is important to emphasise that identification of monosodium urate crystals was not considered sufficiently important by participants to be included in the final list, probably as it was a necessary prerequisite that the recommendations only applied to patients who had a confirmed diagnosis of gout.

One approach to resolving the tension between practical feasibility and desire to measure everything that is relevant, is to consider listing some items as mandatory for clinical trials and some items as discretionary (while still being seen as important). This approach has been successful for psoriatic arthritis,[11] lupus,[12] osteoporosis[13] and osteoarthritis.[14] Based on the results from this Delphi exercise, it is proposed that outcome domains for gout studies be organised into the groups shown in fig 1, and that this proposal be formally ratified at the OMERACT 9

Table 1 Final ratings for outcome domains in studies of acute gout

	Median rating (30th to 70th percentiles)‡	Disagreement index§
Pain*	1 (1 to 1)	0
Patient global*	2 (1 to 2)	0.22
Physician global	2 (2 to 3)	0.32
Work disability (absentee-ism or presentee-ism)	3 (2 to 3)	0.32
Inflammation of joint*†		
Joint erythema	3 (2 to 3)	0.32
Joint tenderness	1 (1 to 2)	0.22
Joint swelling	1 (1 to 2)	0.22
Acute phase marker	3 (2 to 4)	0.85
Function*†		
Functional disability (difficulty with daily activities)	2 (1 to 3)	0.52
Joint impairment (loss of joint motion)	3 (2 to 4)	0.85

*Items recommended by OMERACT SIG.
†These two items were rated highly in the first iteration (median 1) but respondents requested more precise clarification of meaning for subsequent iterations.
‡Ratings of 1–3 indicate item should be included in studies of gout; 4 indicates uncertainty; 5–7 indicate item should not be included in studies of gout.
§A disagreement index of less than 1 indicates no disagreement.[10]

Table 2 Final ratings for outcome domains in studies of chronic gout

	Median rating (30th to 70th percentiles)‡	Disagreement index§
Adverse effects of intervention*	1 (1 to 2)	0.22
Serum urate*	1 (1 to 1)	0
Gout flare recurrence*	1 (1 to 1)	0
Tophus regression*	2 (2 to 2)	0
Health-related quality of life*	2 (1.6 to 3)	0.41
Pain	2 (1 to 2.4)	0.33
Patient global*	2 (1 to 2)	0.22
Physician global	2 (1 to 3)	0.52
Work disability (absentee-ism or presentee-ism)	2 (2 to 3)	0.32
Joint inflammation	2 (2 to 4)	0.85
Physical function*†		
Functional disability (difficulty with daily activities)	2 (1 to 3)	0.52
Joint impairment (loss of joint motion)	3 (2 to 3)	0.32
Joint damage imaging*	3 (3 to 4)	0.32
Participation (life-role)*	3 (2 to 4)	0.85
Health care utilisation	3 (3 to 3)	0
Costs	3 (3 to 4)	0.32
Patient utility (value of current health state)	3 (2 to 3)	0.32
Comorbidities	3 (2 to 4)	0.85
Acute phase marker	4 (3 to 5)	0.52
Total body urate pool	5 (3.4 to 6)	0.53
Impact on family	5 (4 to 6)	0.37
Absence of urate crystals from knee synovial fluid	5 (4 to 6)	0.37
Depression	6 (4 to 6)	0.37

*Domain recommended by OMERACT SIG.
†This item was rated highly in the first iteration (median 2) but respondents requested more precise clarification of meaning for subsequent iterations.
‡Ratings of 1–3 indicate item should be included in studies of gout; 4 indicates uncertainty; 5–7 indicate item should not be included in studies of gout.
§A disagreement index of less than 1 indicates no disagreement.[10]

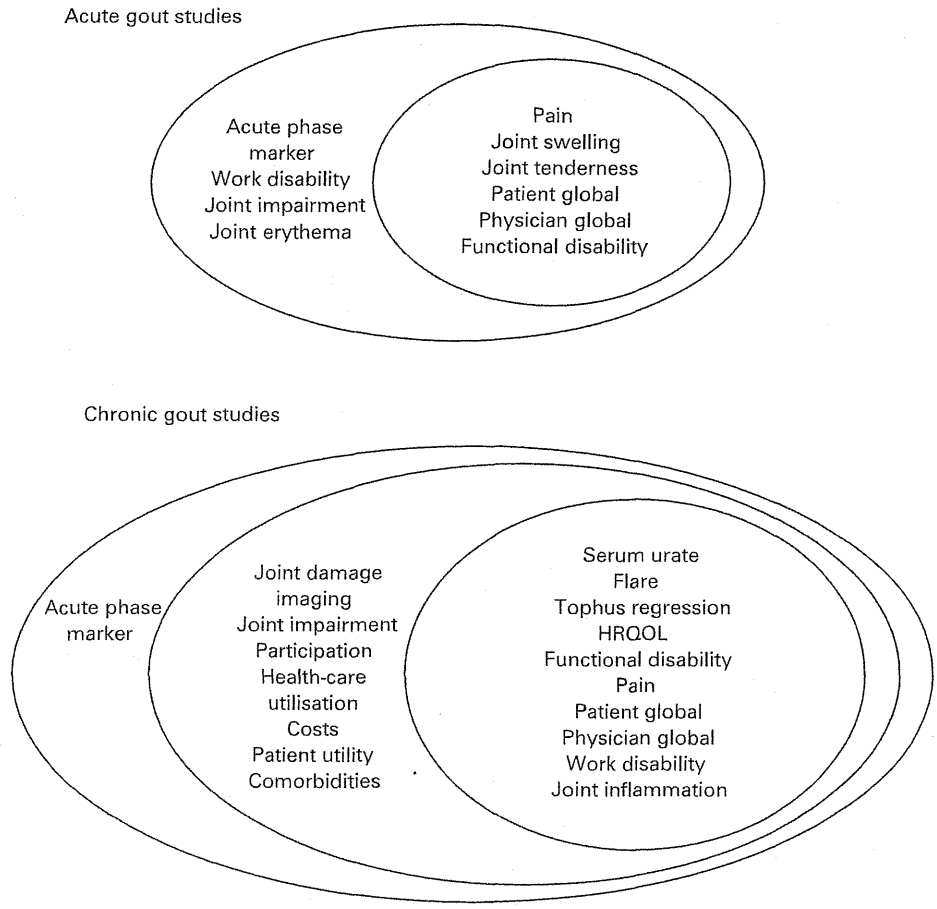

Figure 1 Proposed domains for gout studies. Items within inner ellipse are considered mandatory, within the next ellipse as discretionary and within the outermost ellipse as for further research.

meeting during 2008. Domains that scored a median of 1 or 2 were placed in the inner ellipse, domains that scored a median of 3 into the next ellipse and those that scored a median of 4 into the outermost ellipse. For all studies, it is mandated that safety and tolerability of investigational products also be assessed. Once core domains are agreed, a subsequent task is to identify or develop appropriate tools to measure each domain.

This exercise could be combined with the development of core sets for the International Classification of Functioning, Disability and Health (ICF), where core sets projects aim to identify those factors important for specific health states, including personal perspectives on activities and participation to complement the views of health professionals.[15]

It is important to recognise that the method or instrument to measure these domains was not addressed in this Delphi exercise. In particular, the rating of the importance of the domain by respondents reflected their own expert judgement, rather than the extent to which the domain could be measured in a way that satisfies the OMERACT filter (truth, discrimination, feasibility).[16] Specific outcome measures used in clinical trials of gout treatment were reviewed recently. This review describes currently used measures in terms of the OMERACT filter.[9] Other studies that address the measurement properties of instruments for some of these domains are currently in progress. It may be necessary to modify fig 1 in light of currently available tools for outcome measurement in gout, and this is likely to be a key area of discussion at the OMERACT 9 meeting. Even so, this Delphi exercise does point the way to where researchers should focus attention on producing validated outcome tools for gout studies.

A further limitation to this study is represented by the selected group of Delphi participants and non-response rate. This might limit the validity of the final recommendations; in particular, patients with gout were not invited to participate in this exercise. None the less, the initial response rate was actually very satisfactory in comparison with other similar Delphi exercises and the very broad geographical coverage of the panel does suggest adequate international representation.

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REFERENCES

1. **Schumacher HR Jr,** Boice JA, Daikh DI, Mukhopadhyay S, Malmstrom K, Ng J, *et al*. Randomised double blind trial of etoricoxib and indometacin in treatment of acute gouty arthritis. *BMJ* 2002;**324**:1488–92.
2. **Willburger RE,** Mysler E, Derbot J, Jung T, Thurston H, Kreiss A, *et al*. Lumiracoxib 400 mg once daily is comparable to indomethacin 50 mg three times daily for the treatment of acute flares of gout. *Rheumatology (Oxford)* 2007;**46**:1126–32.
3. **Becker MA,** Schumacher HR Jr, Wortmann RL, MacDonald PA, Eustace D, Palo WA, *et al*. Febuxostat compared with allopurinol in patients with hyperuricemia and gout. *N Engl J Med* 2005;**353**:2450–61.
4. **Sundy JS,** Becker MA, Baraf HS, Barkhuizen A, Moreland L, Huang B, *et al*. A Phase 2 study of multiple doses of intravenous polyethylene glycol (PEG)-uricase in patients with hyperuricemia and refractory gout. *Arthritis Rheum* 2005;**52**(Suppl 9):S679–80.
5. **Schumacher HR Jr,** Edwards LN, Perez, Ruiz F, Becker M, Chen LX, *et al*. Outcome measures for acute and chronic gout. *J Rheumatol* 2005;**32**:2452–5.
6. **Schumacher HR,** Taylor W, Joseph Ridge N, Perez Ruiz F, Chen LX, Schlesinger N, *et al*. Outcome evaluations in gout. *J Rheumatol* 2007;**34**:1381–5.
7. **Graham B,** Regehr G, Wright JG. Delphi as a method to establish consensus for diagnostic criteria. *J Clin Epidemiol* 2003;**56**:1150–6.
8. **Grainger R,** Harrison AA, Taylor WJ. Preliminary identification of potentials items for a definition of "gout flare" using Delphi methodology. *Arthritis Rheum* 2005;**52**(Suppl. 9):S105.
9. **Taylor WJ,** Schumacher Jr HR, Singh JA, Grainger R, Dalbeth N. Assessment of outcome in clinical trials of gout—a review of current measures. *Rheumatology (Oxford)* 2007;**46**:1751–6.
10. **Fitch K,** Bernstein SJ, Aguilar MD, Burnand B, LaCalle JR, Lazaro P, *et al*. *The RAND/UCLA Appropriateness Method User's Manual*. Santa Monica, CA: RAND, 2001.
11. **Gladman DD,** Mease PJ, Strand V, Healy P, Helliwell PS, Fitzgerald O, *et al*. Consensus on a core set of domains for psoriatic arthritis. *J Rheumatol* 2007;**34**:1167–70.
12. **Strand V,** Gladman D, Isenberg D, Petri M, Smolen J, Tugwell P, *et al*. Endpoints: consensus recommendations from OMERACT IV. *Lupus* 2000;**9**:322–7.
13. **Sambrook PN,** Cummings SR, Eisman JA, Genant HK, Eastell R, Reginster JY, *et al*. Guidelines for osteoporosis trials. *J Rheumatol* 1997;**24**:1234–6.
14. **Bellamy N,** Kirwan J, Boers M, Brooks P, Strand V, Tugwell P, *et al*. Recommendations for a core set of outcome measures for future phase III clinical trials in knee, hip, and hand osteoarthritis. Consensus development at OMERACT III. *J Rheumatol* 1997;**24**:799–802.
15. **Cieza A,** Ewert T, Ustun TB, Chatterjee S, Kostanjsek N, Stucki G. Development of ICF Core Sets for patients with chronic conditions. *J Rehabil Med* 2004;**Suppl. 44**:9–11.
16. **Boers M,** Brooks P, Strand V, Tugwell P. The OMERACT filter for outcome measures in rheumatology. *J Rheumatol* 1998;**25**:198–9.

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REVIEW ARTICLE

Management of rheumatoid arthritis: the 2012 perspective

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Abstract Management of rheumatoid arthritis (RA) has improved over the last 10 years. These changes have been monitored in the Institute of Rheumatology, Rheumatoid Arthritis (IORRA) observational cohort, and clinical remission has become a realistic goal. However, we should recognize that the ultimate goal of treatment is to improve long-term outcomes. These improvements have been achieved not only by new drugs, but also by the overall approach toward treating patients. Biologics in RA have been successful; however, safety concerns and pharmacoeconomical issues are still debated. Protein kinase inhibitors have been developed, and can be called "molecular-targeting antirheumatic drugs" (MTARDs), as opposed to "disease-modifying antirheumatic drugs." In comparison with biologics, oral MTARDs should be less expensive; however, their safety profile should be confirmed. Considering the limitations of randomized trials, it is encouraged to conduct studies based on daily practice. It is time to consider the application of the evidence generated from "our" patients to patients in daily practice, namely institute-based medicine as opposed to evidence-based medicine, of which "IORRA-based medicine" would be representative. Finally, there remains much for us rheumatologists to do for our patients, including patient-perspective approaches.

Keywords Outcome · Observational cohort · Biologics · MTARDs · Patient perspective

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What have we achieved since 2000?

The readers of *Modern Rheumatology* know that, over the last 10 years, care of patients with rheumatoid arthritis (RA) has seen impressive improvements. New drugs with novel modes of action have led to improvements not only in signs and symptoms, but also in long-term outcomes, including joint destruction and disability. Therefore, the goal of RA treatment has changed from improving outcomes over the short term to outcomes over the long term. The proposal that there should be a paradigm shift from "care to cure" has become realistic.

The changes generated in the last 10 years have been carefully monitored since 2000 in the Institute of Rheumatology, Rheumatoid Arthritis (IORRA) observational cohort [1, 2]. We previously reported that disease activity in the IORRA cohort improved significantly from 2000 to 2007 [3]; subsequently, there has been constant improvement along with the changes in the drugs employed for therapy (Fig. 1). Clinical remission has become a realistic goal. By any of the 2010 criteria for remission proposed by the European League Against Rheumatism/American College of Rheumatology (EULAR/ACR), the number of patients in remission has increased [4, 5] (Fig. 2). This progress has been the result of the increased use of methotrexate and biologics. Based on data mainly from IORRA, the maximum dose of methotrexate has been raised [6, 7], and this will lead to better patient outcomes over the next decade. It is amazing that changes in disease control have resulted from the use of nonsteroidal anti-inflammatory drugs as well as gastrointestinal medications (Fig. 3).

An IORRA study conducted in the prebiologic era found a standardized mortality ratio (SMR) of 1.46-1.90, which was consistent with findings from Western countries [8]. Advances in drug therapy may improve the survival of RA

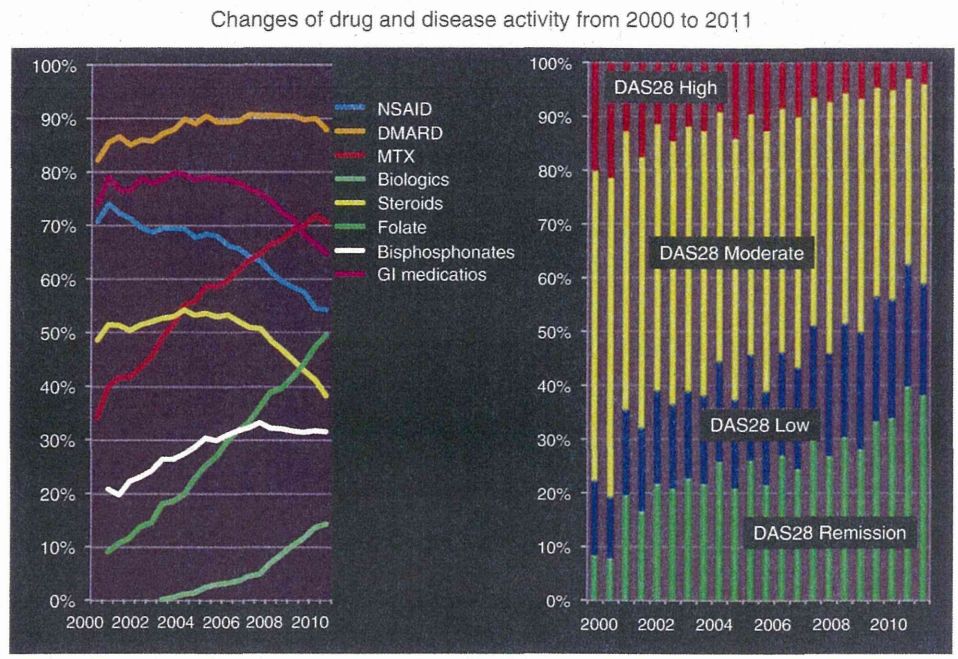

Fig. 1 Changes of drug and disease activity from 2000 to 2011. Changes of drug use and disease activity of RA patients in the IORRA cohort from 2000 to 2011 are shown. Disease activity was categorized by DAS28 according to the standard method

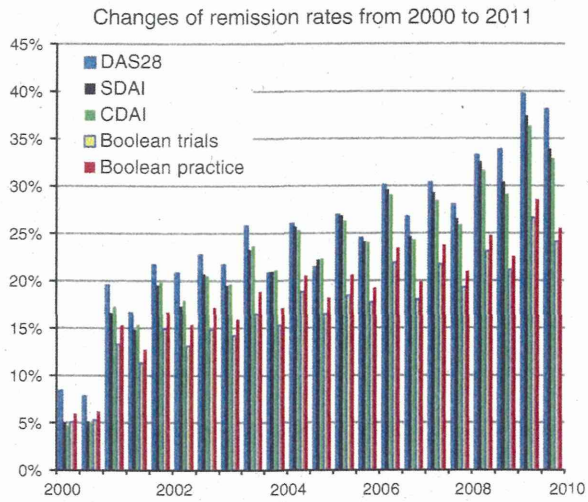

Fig. 2 Changes of remission rates from 2000 to 2011, defined by 5 methods including DAS28, simplified disease activity index (SDAI), clinical disease activity index (CDAI), Boolean trials, and Boolean practice. Definition of remission is based on each criterion

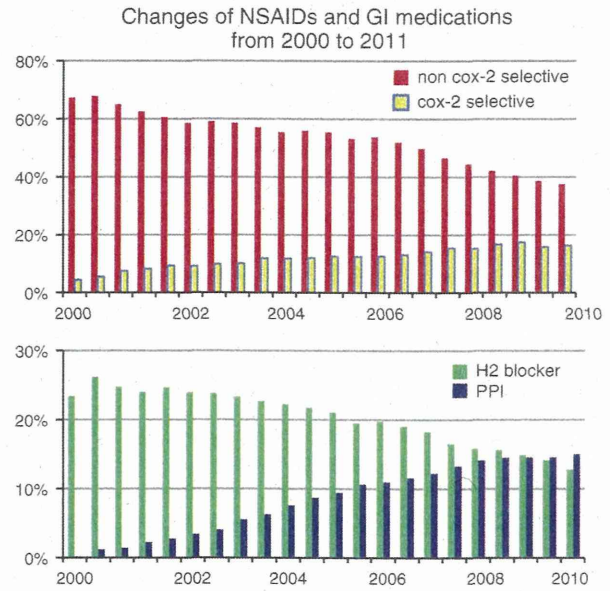

Fig. 3 Changes of use of NSAIDs (*upper column*) and gastrointestinal (GI) medications (*lower column*) from 2000 to 2011. NSAIDs were categorized by cyclooxygenase-2 (COX-2) selectivity as COX-2 selective (celecoxib, meloxicam, and etodolac) or non-COX-2 selective (others). Categorizations of proton pomp inhibitor (PPI) and H2 blocker are based on label information

patients [9]. We recently undertook a nationwide study to estimate the mortality rate of RA patients treated using biologics (Nakajima A, et al. submitted); our findings need confirmation by a more precise study. It is extremely important to recognize that the ultimate goal of the treatment of patients with RA is to improve long-term outcomes, including mortality and quality-adjusted life years (QALYs) [10].

We would like to emphasize that improvements in patient management have been achieved not only by new drugs. It is apparent that new drugs initiated these changes, but in addition, major improvements have been achieved in the overall approach toward treating patients with RA. The establishment of treatment recommendations [11, 12] for management of RA, and the introduction of new criteria for classification [13] and remission [4, 5], are important

platforms for introducing novel treatments into daily practice.

We previously reported several findings that support the concept that strict control of disease activity by maintaining the disease activity score using 28 joint count (DAS28) at a low value can inhibit the progression of disability in patients with RA [3, 14]. This target-driven therapeutic strategy ("treat to target") has become familiar as the T2T movement since recommendations for achieving optimal outcomes were published in 2010 [15]; we first reported on use of "treat to target" in 2007 [3].

Progress in the technology of imaging modalities, including ultrasound and magnetic resonance imaging (MRI), has led to increased accuracy of diagnosis. As suggested by the new classification criteria for polymyalgia rheumatica [16], the addition of ultrasound information will increase the sensitivity and specificity of the diagnosis of early rheumatoid arthritis. Although there remains the problem of feasibility, ultrasound should be widely implemented for routine care of RA patients [17]. These diagnostic strategies were established based on the results of several clinical studies, predominantly randomized controlled trials (RCTs) [18]. Comparing the study patients in RCTs with patients in daily practice is debatable, which we return to later in this review.

When we consider the changes that have occurred over the last 10 years, we can see that the strategies of RA treatment have changed dramatically as a result of the productive collaboration of academic expertise and innovative companies.

The future of the biologic era

Everyone can agree that molecular targeting is one of the best ways to control disease activity for a disease in which the target molecule has been identified. RA is phenotypically a quite heterogeneous disease, but the pathophysiology is quite uniform. Although many molecules are involved in the pathogenesis of RA, there are only a few key molecules that can be targeted for treatment. Tumor necrosis factor-alpha (TNF-α) and interleukin-6 (IL-6) have been most successfully targeted, and the introduction of monoclonal antibodies and receptor-fusion proteins has successfully led to suppression of RA disease activity [19, 20].

There are several other candidate molecules that may be targeted for RA treatment, including CD86, CD20, CD22, and B cell activating factor (BAFF), which are functional surface molecules of T cells or B cells; and IL-17 and IL-12/23, which are proinflammatory cytokines [21, 22]. Antibodies and/or fusion proteins with activity against those molecules have been developed and are in clinical trials. In the near future, we may have more than 10 effective drugs for treatment of RA. The efficacy and safety profiles of these biologics may differ according to their target molecules, but an essential characteristic of these drugs is their ability to suppress joint destruction and improve long-term outcomes. Improvement in the signs and symptoms of each RA patient is a minimum requirement, but will not be sufficient for a candidate drug to become a useful therapeutic option.

It should be recognized that these macromolecular drugs cannot cross cell membranes, and are active extracellularly. Therefore, these biologics are quite safe with regard to hepatotoxicity, nephrotoxicity, and hematotoxicity. Concerns regarding the safety of biologics focus on the immunogenic reactions against exogenous proteins and the results of the suppression of target molecules. Preclinical and clinical data accumulated over the last 10 years have demonstrated that hypersensitivity to these macromolecules occurs at a tolerable level, and is manageable in daily practice. However, suppression of target molecules is a major problem affecting the safety profiles of these biologics; For example, TNF-α is part of the endogenous line of defense against tuberculosis infection, and suppression of TNF-α has resulted in increases in reactivation of occult tuberculosis infection [23]. Thus, it very important to predict the possible side-effects of any biologic by considering the role of its target molecule. However, all of the target molecules of the biologics used to treat RA are associated with the immune system of the host, and therefore susceptibility to infection is an unavoidable issue. Efforts have been made to identify patients highly susceptible to infection, so that an effective prophylactic regimen can be instituted; however, prevention of opportunistic infections, including pneumocystis pneumonia, remains an important concern [24].

Use of biologics to treat RA is a pharmacoeconomical issue. These macromolecules are quite expensive compared with other drug classes, because they are produced using advanced technology. The outpatient costs incurred from 2000 to 2007 for 8,982 RA patients (34,839 patient-years) enrolled in the IORRA study were evaluated. The mean annual outpatient cost increased from 287,626 JPY in 2000 to 366,964 JPY in 2007 (+27.6 %). The cost of medications and injections over those 7.5 years increased 39.0 and 1215 %, respectively. Costs increased in association with aging, increased DAS28 values, and increased Japanese Health Assessment Questionnaire (J-HAQ) scores. Levels of disability and use of biologics were the most significant factors associated with cost increases. Outpatient care costs for patients with RA also increased over the last 7.5-year period, especially after the introduction of biologics [25].

Extensive pharmacoeconomical analysis has demonstrated that biologics are cost-effective when work

productivity is taken into consideration, but cost is an obvious barrier to RA patients who have lost their job because of their disease. Our recent data have shown that biologics are most cost-effective when used in patients with early RA and with moderate disability (J-HAQ = 1.0–1.5) (Tanaka E, et al. submitted). In the effort to improve patient quality of life (QOL), this use of biologics for earlier disease is needed for effective utilization of limited medical resources.

Another promising approach for improving the cost benefits of biologics is the development of generic biologics, also known as biosimilar products [26]. Clinical studies of these biosimilar products are now being conducted in many countries, including Japan.

Antirheumatic drugs: DMARD to MTARD

Control of disease activity in RA had its origins in the empirical use of gold compounds in clinical practice, and was not the result of scientific evaluations. Gold compounds belong to the class of drugs called disease-modifying antirheumatic drugs (DMARDs). The target molecules of DMARDs, including gold compounds, D-penicillamine, sulfasalazine, bucillamine, and actarit, have not been clearly identified, but the targets of methotrexate, leflunomide, mizoribine, and tacrolimus have been well defined. Now there is a new class of drugs, including protein kinase inhibitors, which target unique molecules that regulate cell functions. Many of these drugs have been classified as immunosuppressive drugs. We propose a tentative generation-based classification of these immunosuppressive drugs according to when they were discovered (Table 1).

The molecular targets of the drugs in the 1st to 3rd generations were identified after discovery of the drug; however, the 4th generation of immunosuppressive drugs is a novel class of antirheumatic drugs that have been developed based on molecular targets. Thus, we would like to propose the designation "molecular-targeting antirheumatic drugs" (MTARDs), as opposed to "disease-modifying antirheumatic drugs" (DMARDs).

Thus far, five oral compounds including kinase inhibitors (tofacitinib, fostamatinib, VX-509), an S1P lyase inhibitor (LX 3305), and a chemokine receptor-1 antagonist (CCX354-C) have been developed [27, 28]. Because there are many target molecules involved in regulating cell function in the immune system, many novel drugs classified as MTARDs should be discovered (Table 2).

MTARDs are small-molecule compounds with high specificity for the target molecule. In comparison with biologics, MTARDs are administered orally, and their production should be less expensive. Therefore, if they are noninferior to DMARDs, MTARDs would provide advantages over biologics, since biologics are not administered orally and are expensive.

Table 1 Immunosuppressants

Generation	Mode of action	Drugs
1st	DNA damaging agents	Cyclophosphamide, alkylating agents
2nd	Purine/pyrimidine antimetabolites	Methotrexate, leflunomide, mizoribine, azathioprine
3rd	Calcineurin inhibitors	Cyclosporine, tacrolimus
4th	Protein kinase inhibitors	Tofacitinib, fostamatinib

Table 2 Comparison of DMARDs and MTARDs

Class		Definition	Drugs
DMARDs	Disease-modifying antirheumatic drugs	Target molecule is unknown, or was identified after drug development	Gold, D-penicillamine, sulfasalazine, bucillamine, methotrexate, leflunomide, tacrolimus, etc.
MTARDs	Molecular-targeting antirheumatic drugs	Drug was developed directly to target the molecule	Tofacitinib, fostamatinib, etc.

The safety profile of MTARDs is a concern. MTARD actions occur intracellularly, and MTARDs must cross the cell membrane. Thus, cytotoxicity may be inevitable if MTARDs must be administered in high concentrations. In addition, regulation of intracellular protein kinases, the target molecules, is thought to be sensitive to concentration; therefore, changes in levels of protein kinases may lead to side-effects [29]. Since kinases are phosphotransferases, these kinase-inhibiting drugs will inhibit adenosine triphosphate (ATP) binding at the catalytic sites of kinases [30], and may nonspecifically inhibit ATP binding. In vivo and in vitro experiments should be performed for clarification. The results of phase 1–3 clinical trials of the first MTARD, tofacitinib, indicate that it was relatively well tolerated, and it has been submitted for approval in the USA, European Union, and Japan [31].

Importance of practice-based clinical studies

As mentioned earlier in this review, there are many guidelines and recommendations regarding therapeutic strategies for daily practice that have been established, including the most recent ACR recommendation [12]; however, it is important that these have been established based on the results of many clinical studies, including

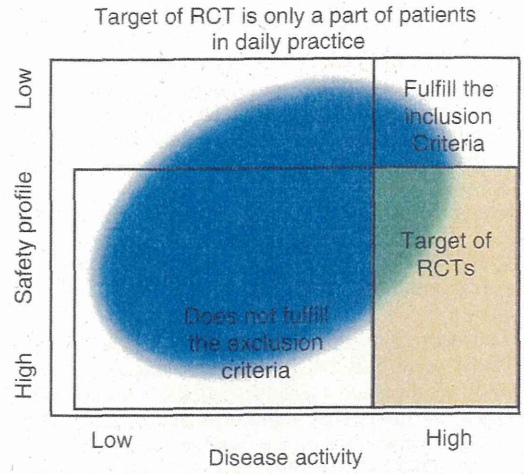

Fig. 4 The target of a RCT is only a part of the patients in daily practice. The target population of most randomized controlled trials (RCTs) is limited by the inclusion and exclusion criteria of the study. In most RCTs for RA, patient inclusion is dependent on disease activity and exclusion is dependent on safety profiles

many RCTs. RCTs are quite appropriate for determining the efficacy and safety profile of a drug or therapeutic strategy, but the population of study patients is usually restricted because of the study inclusion and exclusion criteria (Fig. 3).

It has been argued that only a small fraction of patients in daily practice would satisfy the inclusion and exclusion criteria of the clinical studies of biologics [17]; therefore, the therapeutic strategies established by clinical studies are acceptable but not ideal for implementation in daily practice. As Professor Furst has commented, "Well-designed clinical studies and observational cohorts, we need them both" [32]. Many RCTs have been conducted by pharmaceutical companies, but it is extremely difficult for a company to organize and maintain an observational cohort based on daily practice. There are many registries and observational cohorts of RA patients, including IORRA, CORRONA [33], NOR [34], and SRR [35]. We believe that consideration should be given to basing the guidelines and recommendations for RA therapeutic strategies on these practice-oriented databases. In addition, we would like to encourage clinical studies based on all the patients seen in daily practice (Fig. 4).

One of the pitfalls of evidence-based medicine (EBM) has been the application of the results of clinical studies that were conducted under medical conditions different from those of the patients in our daily practice. Even if the essential baseline characteristics are similar, the study patients might be of different ethnicities, with different comorbid diseases, concomitant medications, methotrexate doses, financial support, or medical insurance. These are the limitations of EBM, and we have to think about the application of evidence generated from "our" patients to patients in daily practice. We have established a large cohort of IORRA patients with RA, and various evidence-based findings can be generated by appropriate analyses; therefore, it is possible to apply the data from the IORRA cohort to our patients in IORRA. We call this approach "institute-based medicine" (IBM) or "IORRA-based medicine" (also IBM). It may not be feasible to apply this concept to all patients in all clinical situations, but we think that we have to try to improve the quality of evidence by considering the medical circumstances of each patient.

Thoughts on a patient-friendly program

The aim of RA treatment is the well-being of RA patients. Patient self-care is needed to prevent disease progression; however, RA is essentially not a lifestyle-related disease where patient effort yields a better outcome. Thus, medical professionals, including rheumatologists, must modify the course of the disease so that it leads to the best outcome. If patients are not educated about their disease, or are depressed by a poor disease outcome, effective treatment cannot be delivered. As treatment goals have become more optimistic over the years since the introduction of rigorous control of disease activity, there is also a tendency to administer stronger immunosuppression to patients. Both patients and health professionals have to be acutely aware of the early signs and symptoms of adverse events, including opportunistic infections, since anticytokine therapy may sometimes mask those signs [36].

Considering these issues, our IORRA cohort has been established essentially based on information from patients [1–3]. OMERACT has been conducting workshops on patients' perspectives for over 10 years [37], which has led to a recently published definition of RA remission from the patient perspective [38]. Thus, patient education and participation has become increasingly important. As a part of the T2T program, the patient version of the T2T program has been published [37] and translated into many languages, including Japanese. Furthermore, product-specific campaigns that focus on patients who are prescribed a specific drug have been developed, with an aim of specifying the important issues of care in daily life. These are welcome developments in the management of RA and may lead to better patient outcomes. Thus, rheumatologists must share their experience with their patients.

Future perspectives

It has been proposed that medicine of the future should be described by the 4 Ps: predictive, personalized, preventive,

and participatory [39]. Using this perspective, what we have to develop for management of rheumatoid arthritis is: better prediction of disease onset, progression, and response to treatment; a personalized therapeutic strategy; prevention of disease onset, worse outcomes, and side-effects; and participation of all rheumatologists and patients. In the future, use of genomic information [39–47] from individual patients should become important for predicting the disease and its course in each patient.

Furthermore, when thinking about the characteristics of medicine in 2020, we should include the developments of a postgenomic society, and of nanotechnology, smart IT, and enhanced performance [48]. It has been suggested that both medicine and healthcare should be incorporated into the big wave of technology investment.

In conclusion, management of RA has progressed remarkably over the last 10 years. However, there remains much for us rheumatologists to do for our patients.

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References

1. Yamanaka H, Tohma S. Potential impact of observational cohort studies in Japan on rheumatoid arthritis research and practice. Mod Rheumatol. 2006;16(2):75–6.
2. Yamanaka H. A cohort study of clinical care in rheumatoid arthritis: the IORRA study. JMAJ. 2009;52(1):54–6.
3. Yamanaka H, Inoue E, Singh G, Tanaka E, Nakajima A, Taniguchi A, et al. Improvement of disease activity of rheumatoid arthritis patients from 2000 to 2006 in a large observational cohort study IORRA in Japan. Mod Rheumatol. 2007;17(4):283–9.
4. Felson DT, Smolen JS, Wells G, Zhang B, van Tuyl LH, Funovits J, American College of Rheumatology; European League Against Rheumatism, et al. American College of Rheumatology/European League Against Rheumatism provisional definition of remission in rheumatoid arthritis for clinical trials. Arthritis Rheum. 2011;63(3):573–86.
5. Felson DT, Smolen JS, Wells G, Zhang B, van Tuyl LH, Funovits J, et al. American College of Rheumatology/European League against Rheumatism provisional definition of remission in rheumatoid arthritis for clinical trials. Ann Rheum Dis. 2011;70(3):404–13.
6. Yamanaka H, Inoue E, Tanaka E, Nakajima A, Taniguchi A, Terai C, et al. Influence of methotrexate dose on its efficacy and safety in rheumatoid arthritis patients: evidence based on the variety of prescribing approaches among practicing Japanese rheumatologists in a single institute-based large observational cohort (IORRA). Mod Rheumatol. 2007;17(2):98–105.
7. Seto Y, Tanaka E, Inoue E, Nakajima A, Taniguchi A, Momohara S, et al. Studies of the efficacy and safety of methotrexate at dosages over 8 mg/week using the IORRA cohort database. Mod Rheumatol. 2011;21(6):579–93.
8. Nakajima A, Inoue E, Tanaka E, Singh G, Sato E, Hoshi D, et al. Mortality and cause of death in Japanese patients with rheumatoid arthritis based on a large observational cohort, IORRA. Scand J Rheumatol. 2010;39(5):360–7.
9. Myasoedova E, Davis JM 3rd, Crowson CS, Gabriel SE. Epidemiology of rheumatoid arthritis: rheumatoid arthritis and mortality. Curr Rheumatol Rep. 2010;12(5):379–85.
10. Adams R, Walsh C, Veale D, Bresnihan B, FitzGerald O, Barry M. Understanding the relationship between the EQ-5D, SF-6D, HAQ and disease activity in inflammatory arthritis. Pharmacoeconomics. 2010;28(6):477–87.
11. Smolen JS, Landewé R, Breedveld FC, Dougados M, Emery P, Gaujoux-Viala C, et al. EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs. Ann Rheum Dis. 2010;69(6):964–75.
12. Singh JA, Furst DE, Bharat A, Curtis JR, Kavanaugh AF, Kremer JM, et al. 2012 Update of the 2008 American College of Rheumatology recommendations for the use of disease-modifying antirheumatic drugs and biologic agents in the treatment of rheumatoid arthritis. Arthritis Care Res. 2012;64(5):625–39.
13. Aletaha D, Neogi T, Silman AJ, Funovits J, et al. 2010 Rheumatoid arthritis classification criteria: an American College of Rheumatology/European League Against Rheumatism collaborative initiative. Ann Rheum Dis. 2010;69(9):1580–8.
14. Tanaka E, Mannalithara A, Inoue E, Hara M, Tomatsu T, Kamatani N, et al. Efficient management of rheumatoid arthritis significantly reduces long-term functional disability. Ann Rheum Dis. 2008;67(8):1153–8.
15. Smolen JS, Aletaha D, Bijlsma JW, Breedveld FC, Boumpas D, Burmester G, T2T Expert Committee, et al. Treating rheumatoid arthritis to target: recommendations of an international task force. Ann Rheum Dis. 2010;69(4):631–7.
16. Dasgupta B, Cimmino MA, Kremers HM, Schmidt WA, Schirmer M, Salvarani C, et al. 2012 Provisional classification criteria for polymyalgia rheumatica: a European League Against Rheumatism/American College of Rheumatology collaborative initiative. Arthritis Rheum. 2012;64(4):943–54.
17. Fukae J, Kon Y, Henmi M, Sakamoto F, Narita A, Shimizu M, et al. Change of synovial vascularity in a single finger joint assessed by power Doppler sonography correlated with radiographic change in rheumatoid arthritis: comparative study of a

novel quantitative score with a semiquantitative score. Arthritis Care Res (Hoboken). 2010;62(5):657–63.
18. Kievit W, Fransen J, Oerlemans AJ, Kuper HH, van der Laar MA, de Rooij DJ, et al. The efficacy of anti-TNF in rheumatoid arthritis, a comparison between randomised controlled trials and clinical practice. Ann Rheum Dis. 2007;66(11):1473–8.
19. Aaltonen KJ, Virkki LM, Malmivaara A, Konttinen YT, Nordström DC, Blom M. Systematic review and meta-analysis of the efficacy and safety of existing TNF blocking agents in treatment of rheumatoid arthritis. PLoS One. 2012;7(1):e30275.
20. Singh JA, Beg S, Lopez-Olivo MA. Tocilizumab for rheumatoid arthritis. Cochrane Database Syst Rev. 2010;(7):CD008331.
21. Tak PP, Kalden JR. Advances in rheumatology: new targeted therapeutics. Arthritis Res Ther. 2011;25(13 Suppl 1):S5.
22. Buch MH, Emery P. New therapies in the management of rheumatoid arthritis. Curr Opin Rheumatol. 2011;23(3):245–51.
23. Gómez-Reino JJ, Carmona L, Angel Descalzo M; Biobadaser Group. Risk of tuberculosis in patients treated with tumor necrosis factor antagonists due to incomplete prevention of reactivation of latent infection. Arthritis Rheum. 2007;57(5):756–61.
24. Harigai M, Koike R, Miyasaka N, Pneumocystis Pneumonia under Anti-Tumor Necrosis Factor Therapy (PAT) Study Group. Pneumocystis pneumonia associated with infliximab in Japan. N Engl J Med. 2007;357(18):1874–6.
25. Tanaka E, Inoue E, Hoshi D, Nakajima A, Momohara S, Taniguchi A, et al. Analysis of medical cost for care of rheumatoid arthritis patients before and after usage of the biologics using a large cohort database, IORRA (abstract). Mod Rheumatol. 2009;19(Suppl):S46.
26. Gu N, Yi S, Kim TE, Kim J, Shin SG, Jang IJ, et al. Comparative pharmacokinetics and tolerability of branded etanercept (25 mg) and its biosimilar (25 mg): a randomized, open-label, single-dose, two-sequence, crossover study in healthy Korean male volunteers. Clin Ther. 2011;33(12):2029–37.
27. Fleischmann R. Novel small-molecular therapeutics for rheumatoid arthritis. Curr Opin Rheumatol. 2012 (Epub ahead of print).
28. Yazici Y, Regens AL. Promising new treatments for rheumatoid arthritis—the kinase inhibitors. Bull NYU Hosp Jt Dis. 2011;69(3):233–7.
29. Okamoto H, Kobayashi A. Spleen tyrosine kinase (Syk) inhibitor for rheumatoid arthritis. N Engl J Med. 2011;364(1):83–4.
30. Lucet IS, Fantino E, Styles M, Bamert R, Patel O, Broughton SE, et al. The structural basis of Janus kinase 2 inhibition by a potent and specific pan-Janus kinase inhibitor. Blood. 2006;107(1):176–83.
31. Kremer JM, Cohen S, Wilkinson BE, Connell CA, French JL, Gomez-Reino J, et al. A phase 2B dose-ranging study of the oral JAK inhibitor tofacitinib (CP-690,550) versus placebo in combination with background methotrexate in patients with active rheumatoid arthritis and inadequate response to methotrexate alone. Arthritis Rheum. 2012;64(4):970–81.
32. Furst DE. Observational cohort studies and well controlled clinical trials–we need them both! J Rheumatol. 2004;31(8):1476–7.
33. Greenberg JD, Kremer JM, Curtis JR, Hochberg MC, Reed G, Tsao P, CORRONA Investigators, et al. Tumour necrosis factor antagonist use and associated risk reduction of cardiovascular events among patients with rheumatoid arthritis. Ann Rheum Dis. 2011;70(4):576–82.
34. Camacho EM, Lunt M, Farragher TM, Verstappen SM, Bunn DK, Symmons DP. The relationship between oral contraceptive use and functional outcome in women with recent-onset inflammatory polyarthritis: results from the Norfolk Arthritis Register. Arthritis Rheum. 2011;63(8):2183–91.
35. Ljung L, Simard JF, Jacobsson L, Rantapää-Dahlqvist S, Anti-Rheumatic Therapy in Sweden (ARTIS) Study Group. Treatment with tumor necrosis factor inhibitors and the risk of acute coronary syndromes in early rheumatoid arthritis. Arthritis Rheum. 2012;64(1):42–52.
36. Baghai M, Osmon DR, Wolk DM, Wold LE, Haidukewych GJ, Matteson EL. Fatal sepsis in a patient with rheumatoid arthritis treated with etanercept. Mayo Clin Proc. 2001;76(6):653–6.
37. Kirwan J, Heiberg T, Hewlett S, Hughes R, Kvien T, Ahlmèn M, et al. Outcomes from the patient perspective workshop at OMERACT 6. J Rheumatol. 2003;30(4):868–72.
38. van Tuyl LH, Smolen JS, Wells GA, Scholte-Voshaar M, Hoogland W, Boers M. Patient perspective on remission in rheumatoid arthritis. J Rheumatol. 2011;38(8):1735–8.
39. de Wit MP, Smolen JS, Gossec L, van der Heijde DM. Treating rheumatoid arthritis to target: the patient version of the international recommendations. Ann Rheum Dis. 2011;70(6):891–5.
40. Hood L. A personal journey of discovery: developing technology and changing biology. Annu Rev Anal Chem (Palo Alto Calif). 2008;1:1–43.
41. Hood L, Friend SH. Predictive, personalized, preventive, participatory (P4) cancer medicine. Nature Rev Clin Oncol. 2011;8:184–7.
42. Okada Y, Terao C, Ikari K, Kochi Y, Ohmura K, Suzuki A, et al. Meta-analysis identifies nine new loci associated with rheumatoid arthritis in the Japanese population. Nat Genet. 2012;25;44(5):511–6.
43. Terao C, Ohmura K, Kochi Y, Ikari K, Maruya E, Katayama M, et al. A large-scale association study identified multiple HLA-DRB1 alleles associated with ACPA-negative rheumatoid arthritis in Japanese subjects. Ann Rheum Dis. 2011;70(12):2134–9.
44. Nishimoto K, Ikari K, Kaneko H, Tsukahara S, Kochi Y, Yamamoto K, et al. Association of EMCN with susceptibility to rheumatoid arthritis in a Japanese population. J Rheumatol. 2011;38(2):221–8.
45. Kochi Y, Okada Y, Suzuki A, Ikari K, Terao C, Takahashi A, et al. A regulatory variant in CCR6 is associated with rheumatoid arthritis susceptibility. Nat Genet. 2010;42(6):515–9.
46. Shimane K, Kochi Y, Horita T, Ikari K, Amano H, Hirakata M, et al. The association of a nonsynonymous single-nucleotide polymorphism in TNFAIP3 with systemic lupus erythematosus and rheumatoid arthritis in the Japanese population. Arthritis Rheum. 2010;62(2):574–9.
47. Nishimoto K, Kochi Y, Ikari K, Yamamoto K, Suzuki A, Shimane K, et al. Association study of TRAF1-C5 polymorphisms with susceptibility to rheumatoid arthritis and systemic lupus erythematosus in Japanese. Ann Rheum Dis. 2010;69(2):368–73.
48. Carton J. The extreme future. London: A Plume Book; 2007.