Treat-to-target: not as simple as it appears

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Received and accepted on September 26, 2012.

Clin Exp Rheumatol 2012; 30 (Suppl. 73): S10-S20.

Key words: rheumatoid arthritis, remission, reliability, treat-to-target

T. Pincus has consulted for and received honoraria from Baxter, Janssen Pharmaceuticals and Medac, and receives support for an educational programme from Abbott, Amgen and UCB.
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Y. Yazici has consulted for and received honoraria from Abbott, Bristol-Myers Squibb, Centocor, Genentech, Celgene, Pfizer and UCB, and receives research support from Bristol-Myers Squibb, Genentech and Centocor.

ABSTRACT

Treat-to-target as a strategy for rheumatoid arthritis (RA) is now widely advocated based on strong evidence. Nonetheless, implementation of treat-to-target raises caveats, as is the case with all clinical care strategies. The target of remission or even low disease activity does not apply to all individual patients, some of whom are affected by concomitant fibromyalgia, other comorbidities, joint damage, and/or who simply prefer to maintain current status and avoid risks of more aggressive therapies. No single universal "target" measure or index exists for all individual RA patients. An emphasis in most studies on radiographic progression, rather than physical function or mortality, as the most important outcome to document the value of treat-to-target may be inappropriate. Many reports imply that the only limitation to treating all RA patients with biological agents involves costs, ignoring effective results in most patients with methotrexate and other disease-modifying anti-rheumatic drugs (DMARDs) and adverse events associated with biological agents. Indeed, the best outcomes in reported RA clinical trials result from tight control with DMARDs, rather than from biological agents, as does better overall status of RA patients at this time compared to previous decades. Pharmacoeconomic reports may ignore that RA patients are older, less educated, and have more comorbidities than the general population, as well as critical differences in patient status according to the gross domestic product of different countries. While treating to a target of remission or low disease activity, including with biological agents, is appropriate for many patients, awareness of these concerns could improve implementation of treat-to-target for optimal care of all RA patients.

Introduction

Treat-to-target is now advocated as an optimal treatment strategy for control of inflammation in patients with rheumatoid arthritis (RA) (1, 2). Treat-to-target is supported by a number of clinical trials summarised in this supplement, including FIN-RACo (3, 4), TICORA (5), CAMERA (6), CIMESTRA (7, 8), and BeSt (9) (Table I). These data indicate that the strategy appears far more important than any specific agent in achieving better RA outcomes (10).

Recommendations for treat-to-target in RA (Table II) direct that "measures of disease activity must be obtained and documented regularly" (1). Quantitative clinical rheumatology measures provide a welcome complement to traditional approaches, in which laboratory tests were (and often remain) the only quantitative information in most RA patient medical records. The senior author incorporated quantitative clinical rheumatology measurement into usual clinical care more than 25 years ago, with a 28 joint count (11, 12) and a patient questionnaire completed by each patient at each visit in the infrastructure of care (13-18).

Quantitative measurement in RA differs from prototype chronic diseases such as hypertension and diabetes, in the absence of a single "gold standard" biomarker which can be applied to all individual patients in diagnosis and treatment (19, 20). This matter has been addressed by an RA Core Data Set of 7 measures, and indices of 3–5 measures based on this Core Data Set (21, 22). The Core Data Set includes 3 quantitative measures from the patient history (in the format of a patient self-report questionnaire), 3 from a physical examination (in the format of a formal joint count), and only 1 laboratory test (21, 22), reflecting that the patient history and physical examination are more prominent in clinical decisions for RA than in most chronic diseases (23).

The senior author noted that 36% of RA patients seen in 2005 were taking biological therapies (as high as any reported setting at the time) (24), and

Table I. Rheumatoid arthritis clinical trials of treat-to-target strategy, guided by quantitative measurement.

Study, year (ref.)	Location	n	Strategy	Treatments
FIN-RACo 1999, 2005 (3,4)	Finland	195	Aim for remission	• SSZ + MTX + HCQ • Single SSZ or MTX
TICORA 2004 (5)	Scotland	111	DAS28 to change Rx	• Triple RX, q mo, inj • Routine DMARD
BeSt 2005, 2007 (9)	Netherlands	508	DAS28 to change Rx	• DMARD monotherapy • step-up combination • combo + high pred • combo + infliximab
CAMERA 2007 (6)	Netherlands	299	Computer-assisted management by pre-defined response criteria	• MTX-visit q month + CyA with computer decision model • MTX-visit q 3 months + CyA
CIMESTRA 2008, 2009 (7,8)	Denmark	160	DAS28 to change Rx	• Step-up MTX + CyA • Step-up MTX + PBO

CyA: cyclosporine A; DAS28: disease activity score with 28 joint count; DMARD: disease-modifying anti-rheumatic drug; HCQ: hydroxychloroquine; MTX: methotrexate; PBO: placebo; pred: prednisone; SSZ: sulfasalazine.

Table II. Ten recommendations on treating rheumatoid arthritis to target, based on both evidence and expert opinion (1).

1	The primary target for treatment of rheumatoid arthritis should be a state of clinical remission.
2	Clinical remission is defined as the absence of signs and symptoms of significant inflammatory disease activity.
3	While remission should be a clear target, based on available evidence low disease activity may be an acceptable alternative therapeutic goal, particularly in established long-standing disease.
4	Until the desired treatment target is reached, drug therapy should be adjusted at least every 3 months.
5	Measures of disease activity must be obtained and documented regularly, as frequently as monthly for patients with high/moderate disease activity or less frequently (such as every 3–6 months) for patients in sustained low disease activity or remission.
6	The use of validated composite measures of disease activity, which include joint assessments, is needed in routine clinical practice to guide treatment decisions.
7	Structural changes and functional impairment should be considered when making clinical decisions, in addition to assessing composite measures of disease activity.
8	The desired treatment target should be maintained throughout the remaining course of the disease.
9	The choice of the (composite) measure of disease activity and the level of the target value may be influenced by consideration of co-morbidities, patient factors and drug-related risks.
10	The patient has to be appropriately informed about the treatment target and the strategy planned to reach this target under the supervision of the rheumatologist.

recognises the immense value of these agents. Nonetheless, some concerns have emerged in implementation and "marketing" of treat-to-target in RA, which generally do not reflect the initial recommendations (Table II), but may compromise optimal patient care.

A survey of 6,135 RA patients indicated that 64% would prefer to maintain clinical status and avoid risks of changing medications (25). Some of these established patients likely could benefit from education to accept and welcome more aggressive treatment. Nonetheless, this information reminds us that the recommendations for treat-to-target include that "the choice of the (composite) measure of disease activity and the level of the target value may be influenced by consideration of comorbidities, patient factors and drug-related risks (1)." This recommendation is sometimes forgotten in seminars and other "education" programmes for physicians.

A different survey of normal individuals over age of 50 in the general population of Finland (26) who completed a health assessment questionnaire (HAQ) indicated that 62% reported scores for pain >1 on a 0–10 visual analogue scale, or joint pain on a modified rheumatoid arthritis disease activity index (RADAI) (27) self-report joint count. Although remission was not analysed according to recently-revised remission criteria (28, 29), only 15% of these "control" subjects over age 50 met the 1981 American Rheumatism Association criteria for remission (30), and 28% met OMERACT Criteria for minimal disease activity (31). Therefore, it might be recognised that "normal" values for pain and patient global estimate may be greater than zero or even 1 or 2 on a 0–10 scale in many older individuals, and that an appropriate target for some older patients would not be remission or even low disease activity.

This information raises a concern of possible overtreatment of some patients in a treat-to-target strategy in RA, as has been reported in treat-to-target in hypertension and diabetes – one report indicated almost as many patients met criteria for overtreatment as for undertreatment (31). Historically, most RA patients often were undertreated, in part because of delays in diagnosis, overreliance on laboratory tests for diagnosis and management, and the severe toxicity of traditional DMARDS such as injectable gold salts and penicillamine. In a sense, it is a major advance that current treatment options in RA may even allow for overtreatment, but rheumatologists must be aware of this possibility at this time.

This article summarises some concerns about implementation of treat-to-target in RA at this time. The goals of the authors are identical to those of the Committee that formulated the initial treat-to-target recommendations (1), *i.e.* better patient care and outcomes for people with RA. These concerns (Table III) may be classified into 3 categories: **A**) the target of remission or even low disease activity does not apply to all individual patients; **B**) emphasis on biological agents and underestimation of methotrexate and other DMARDs; and **C**) pharmacoeconomic reports may neglect important issues about RA patients, as reviewed below.

Table III. Treat-to-target: 10 concerns about implementation, in 3 categories.

A)	**The target of remission or even low disease activity does not apply to all individual patients**
1	Many patients are content not to become worse and do not want to take risks of aggressive therapies, but nonetheless benefit greatly from rheumatology care.
2	The target of remission or even low disease activity is unrealistic for a large fraction of patients, who may also have fibromyalgia, other comorbidities, and/or joint damage.
3	No single universal target exists for all individual patients with RA.
4	An emphasis on radiographic progression An emphasis on radiographic progression rather than physical function or mortality as the most important outcome to document value of treat-to-target may be inappropriate.
B)	**Emphasis on biological agents and underestimation of methotrexate**
5	Effectiveness of methotrexate is often underestimated in the rheumatology literature.
6	Some reports imply that the only limitation to treating all RA patients with biological agents involves costs, ignoring effective results in most patients with methotrexate and other DMARDs and risks of these agents.
7	The best reported outcomes of treatment of RA in clinical trials do not result from biological agents.
8	Better status of RA patients at this time is not attributable primarily to biological agents.
C)	**Pharmacoeconomic reports may neglect important issues about RA patients**
9	Some analyses of disease costs may ignore that RA patients are older, less educated, and have more comorbidities than the general population.
10	Some reports may ignore critical differences in RA status according to the country in which the patient lives, which appear critical in the status of patients with RA.

A) The target of remission or even low disease activity does not apply to all individual patients

1) Many patients are content not to become worse and avoid risks of aggressive therapies, but nonetheless benefit greatly from rheumatology care: Treat-to-target guidelines state that "the level of the target value... must be based on a shared decision between patient and rheumatologist" (1). However, many marketing messages and "education" programmes, particularly for U.S. physicians, extol the benefits of biological agents in treat-to-target and ignore the "shared decision" concept. Of course, possibilities for remission in RA are available today that were unimaginable two or three decades ago, particularly for young, early patients with no comorbidities. Nonetheless, the risks of aggressive treatment are not appropriate for many patients, *e.g.* patients with long-standing disease or many comorbidities, and moderate or even high disease activity according to available indices, who may be content with their status and hope not to become more physically disabled.

As noted above, in a survey of 6,135 patients with RA, 64% agreed that "As long as I don't get worse I wouldn't want to change my arthritis medications" (25) (Table IV). Among all patients, 53% were "satisfied" with their therapy, and 73% agreed that "I don't want the risk of side effects that might come from taking new medications."

Of course, some patients are poorly informed regarding treatment options. Patient education can help patients recognise that the risks of RA progression – including frequent work disability

Table IV. Responses from a survey of 6,135 patients with RA to questions concerning treatment predictor variables and preferences for not changing therapy (25).

Question	All patients (n=6,135) (100.0%)*	Responses according to whether the statement "As long as I don't get worse I wouldn't want to change my arthritis medications" (question 1) was answered "true" or "false"		
		True (n=3,914) (63.8%)*	False (n=2,221) (36.2%)*	% difference (true – false) (95% CI)†
2. I don't need new medications because I am satisfied with the control I have over my arthritis.	53.3	73.6	17.4	56.5 (54.1–58.3)
3. I don't want the risk of side effects that might come from taking new medications.	72.5	87.1	46.2	40.1 (38.6–43.3)
4. I want to follow my doctor's suggestions, and my doctor thinks I don't need to change medications.	71.5	84.4	48.3	36.1 (33.3–38.8)
5. I am concerned that new treatments might not work as well and that I might lose control of my arthritis.	68.1	80.8	45.8	35.0 (32.5–37.3)
6. I don't think there are medications currently available that are better than the medications I am using now.	66.3	76.0	48.7	27.2 (24.9–26.7)
7. I don't want to take treatments that require injections or IVs.	35.7	41.5	25.5	16.0 (13.7–18.3)
8. I can't afford the cost of new medications.	42.7	45.7	35.7	8.1 (5.6–10.5)
9. Getting approval from my insurance company and the hassle of tests and medical visits for new drugs are important problems for me.	54.6	56.1	52.1	4.0 (1.0–6.8)

*Values are the percent of patients responding with agreement to the given question (questions 2-9) among the group of patients overall, the group responding "true" to question 1, and the group responding "false" to question 1.
†The greater the difference, the stronger the association with unwillingness to change therapy. 95% CI = 95% confidence interval. IVs = intravenous treatment.

Table V. Rheumatoid arthritis (RA) indices in fibromyalgia patients: values for RA Core Data Set measures – and scores for indices DAS28, CDAI and RAPID3 – in two hypothetical patients with fibromyalgia. H = all index scores indicate high disease activity for rheumatoid arthritis.

	28 Tender joint count (0–28)	28 Swollen joint count (0–28)	Physician's global estimate (0–10)	ESR (mm/Hr)	Physical function (0–3)	Pain (0–10)	Patient global estimate (0–10)	Index Score
Patient n. 1	28	0	0	20	1	10	10	–
DAS 28 (0–10)	28	0	–	20	–	–	10	6.45 H
CDAI (0–76)	28	0	0	–	–	–	10	38 H
RAPID3 (0–10)	–	–	–	–	1	10	10	21 H
Patient n. 2	14	0	3	10	1	10	10	–
DAS 28 (0–10)	14	0	–	–	–	–	10	5.11 H
CDAI (0–76)	14	0	3	–	–	–	10	27 H
RAPID3 (0–10)	–	–	–	–	1	10	10	21 H

(33), radiographic progression (34), and premature mortality (35) – are usually greater than the risks of therapy (36).

Nonetheless, as noted above, overtreatment in treat-to-target of hypertension and diabetes is a recognised problem, and 65.5% of patients in the survey reported having experienced a side effect to an arthritis medication at some point during their lifetime (25). Furthermore, many healthy individuals in the general population over age 50 would not meet criteria for RA remission or even low disease activity (26). Many patients may have valid reasons to prefer maintenance of status, even with index scores indicating moderate or severe activity, rather than a "treat-to-target" approach, and this preference must be considered and respected. Physicians and sponsors of educational programs might emphasise to a greater extent the "shared decision" concept in their messages to rheumatologists.

2) The target of remission or even low disease activity is unrealistic for a large fraction of patients, who may also have fibromyalgia, other comorbidities, and/or joint damage: Treat-to-target guidelines also state that "the level of the target value may be influenced by considerations of comorbidities, patient factors and drug related risks" (1), but also state that "remission is an achievable goal in many patients in clinical trials and clinical practice... in a significant proportion of patients" (1). However, although remission and low disease activity may be seen at high levels in certain settings (37), at this time, remission is seen in only a small fraction of RA patients in usual care and clinical trials, and even low disease activity is not seen in the majority of patients in most rheumatology settings (38).

One explanation for limited levels of remission in clinical studies and even clinical research may be that this target is not achievable for many RA patients. Approximately 20%-30% of people who meet criteria for RA also have concomitant fibromyalgia (39;40), and most RA patients have comorbidities of varying severity (41-44). Patients with fibromyalgia (see n. 3 below) generally report a global status estimate greater than 5 (on a scale of 0–10), which would disqualify these patients from meeting any current criteria for remission, including SDAI ≤3.3 or patient global estimate of ≤1 in the Boolean definition of the ACR/EULAR committee (28, 29). Additional comorbidities and joint damage may limit meeting quantitative remission targets according to any current criteria.

Furthermore, some studies suggest that low disease activity, rather than remission, is sufficient to achieve the goals of preserving function and slowing radiographic progression. Of course, remission or even low disease activity is a laudable goal, but might be regarded as somewhat of a "platonic" ideal, possibly applicable primarily to the majority of patients with early RA, but not necessarily to all patients.

3) No single "gold standard" measure provides a universal target for all individual patients with RA: A single "gold standard" biomarker that can be applied to diagnosis and management of all individual patients is not available in RA (45), in contrast to hypertension, diabetes and other chronic diseases. Therefore, indices of 3–5 measures based on an RA Core Data Set of 7 measures (21, 22) are used in all clinical trials and treat-to-target. Prominent indices include the DAS28 (disease activity score with 28 joint count) (46), CDAI (clinical disease activity index) (47), SDAI (simplified disease activity index) (47), and RAPID3 (routine assessment of patient index data) (48).

The RA Core Data Set is a major advance. Nonetheless, the absence of a single gold standard measure leads to multiple criteria for a target – whether for low disease activity and/or for remission. Several possible targets will be available until a universal biomarker for all patients with RA is identified, or the definition of RA is revised to be based on such a biomarker (49). The clinical trials that established the value of "treat-to-target" (3-9) included earlier remission criteria, DAS, DAS 28, or a designated change as a primary target. DAS28 is recognised as insufficiently stringent by the most recent ACR/EULAR Committee, and even the recommendations of this committee for remission criteria provide two possible definitions (28, 29): Boolean criteria of scores ≤1 for tender and swollen 28 joint count, C-reactive protein (CRP), and patient global estimate of status; or SDAI ≤3.3.

One particular problem, noted above, is that all available criteria for RA remission necessarily include a patient

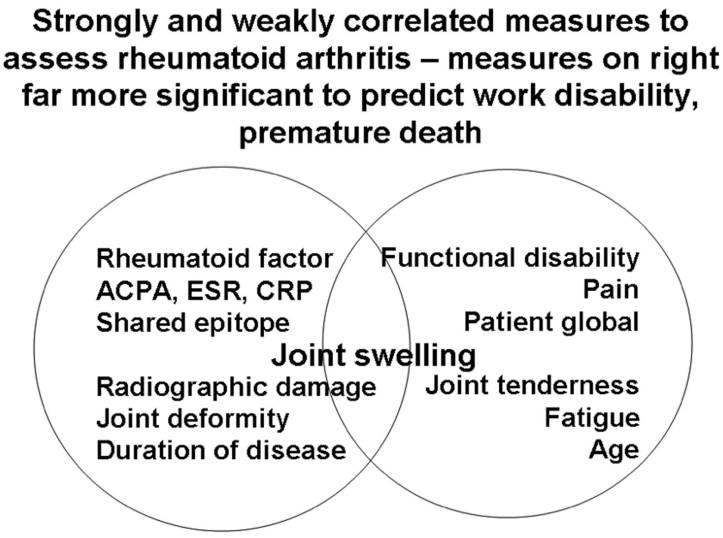

Fig. 1. Strongly and weakly correlated measures to assess rheumatoid arthritis. Early studies indicated that HLA haplotype, rheumatoid factor, ESR, and radiographic changes were associated at higher levels with each other than with joint count or patient questionnaire measures (50) and similar associations have been described in many studies (106;107). Although the former cluster of measures may appear the more substantial measures in RA (left circle), including for the prognosis of mortality, the patient questionnaire measures (right circle) generally have greater significance to predict mortality.

measure, reflecting that the clinical history is more important in diagnosis and management of RA that of many other chronic diseases (23). Patient-reported measures of pain or global estimate of status tend to be high in fibromyalgia, usually higher than seen in RA. Furthermore, a tender joint count is in part a "patient-reported" measure, for which many patients with fibromyalgia report many tender joints.

Two examples are illustrated in Table V of scores in patients with fibromyalgia on the DAS28, CDAI and RAPID3. Patient n. 1 has a tender joint count of 28, swollen joint count of 0, physician global estimate of 0, normal ESR of 20 mm/Hr, score for physical function of 1 on 0–10 scale, pain score of 10 on a 0–10 scale, and patient global estimate of 10 on a 0–10 scale; this patient's index scores are 6.45 for DAS28, 38 for CDAI, and 21 for RAPID3, all indicating high activity. A less severely-affected Patient n. 2 has a tender joint count of 14, swollen joint count of 0, physician global estimate of 3, normal ESR of 10 mm/Hr, score for physical function of 1 on 0–10 scale, pain score of 10 on a 0–10 scale, and patient global estimate of 10 on a 0–10 scale. This patient's index scores also indicate high activity, including 5.11 for DAS28, 27 for CDAI, and 21 for RAPID3. Since it is estimated that 20%–30% of patients with RA also are affected by fibromyalgia (39, 40), this may be an important but neglected matter to be considered by the rheumatology community.

4) An emphasis on radiographic progression rather than physical function or mortality as the most important outcome to document value of treat-to-target is not based on evidence: The treat-to-target recommendations state that "The primary goal of treating the patient with rheumatoid arthritis is to maximise long-term health-related quality of life through control of symptoms, prevention of structural damage, normalisation of function and social participation" (1). Nonetheless, radiographic progression, which has been viewed traditionally as the most important outcome in RA, is emphasised over physical function in most published reports.

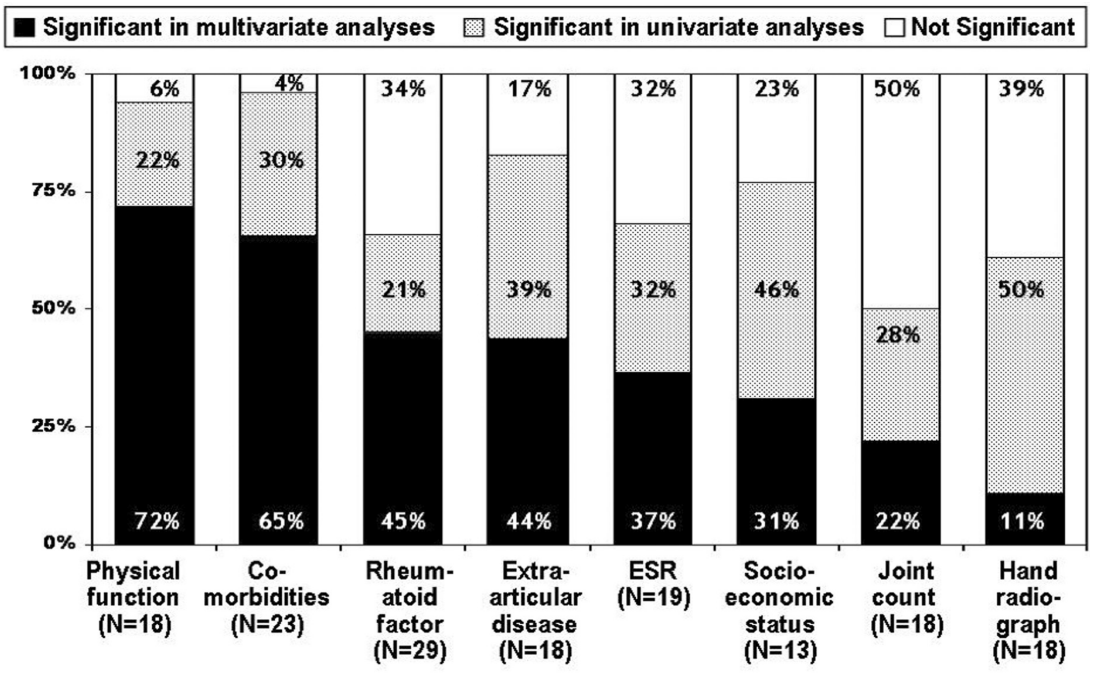

Fig. 2. Significance of 8 variables as predictors of mortality. In a review of 84 reports concerning mortality in RA, 53 cohorts presented predictors of mortality (64). For each variable, n = the number of reports that included the variable, and bars indicate the percentage of those reports in which the variable was a significant predictor of mortality in multivariate analyses (black), in univariate analyses (dotted), or not significant (white).

Table VI. Most significant predictor of rheumatoid arthritis (RA) outcomes, based on rigorous scientific method rather than beliefs.

Outcome	Time frame	Predictor measure
1. Radiographic progression	6-24 months	Laboratory tests: RF, ACPA, ESR, CRP, HLA, shared epitope
2. Work disability	5-15 years	Physical function on a patient self-report
3. Costs	5-15 years	questionnaire, not laboratory test or hand
4. Joint replacement surgery	5-15 years	radiograph
5. Death	5-15 years	

A focus on reduction of radiographic progression rather than functional disability as a primary goal of RA treatment may result from regarding radiographic scores as high-technology "objective" "scientific" data, while functional disability scores reported by a patient are regarded as "subjective" information. Furthermore, laboratory features of RA – including rheumatoid factor, ACPA, elevated ESR and CRP, as well as the shared epitope – are associated with higher levels of radiographic progression than with functional disability (50, 51) (Fig. 1).

Extensive research over 30 years has documented that functional status is far more significant than radiographs (or laboratory tests) in the prognosis of all severe outcomes of RA – including work disability (52-56), costs (57), and premature death (35, 58-64) (Fig. 2) – other than radiographic progression itself (Fig. 1). Ironically, the value of treat-to-target appears as significant for functional status as for radiographic progression. Since functional status is far more significant to predict all severe long-term outcomes other than radiographic progression, perhaps functional status should be emphasised in documentation of the value of a treat-to-target strategy for RA.

A major rationale of treat-to-target in hypertension and diabetes was documentation that control of dysregulation to a target in the normal range was associated with a reduction of premature mortality seen in these diseases (65, 66). Unfortunately, few recent systematic studies of RA mortality have been reported, although available reports do suggest that effective treatment is associated with reduced mortality (67-69). A focus on reduction of radiographic progression rather than mortality as a primary goal of RA treatment may be attributed in part to the fact that radiographic progression can be analysed effectively over 3-6 months or any period of less than 5 years, while premature mortality requires at least 5 years of observation (Table V). However, studies over 5–15 years of reduction of mortality in RA according to significant predictive markers might help identify optimal targets for therapy as was accomplished in hypertension and diabetes, which provided an initial rationale for treat-to-target in RA.

B) Overestimation of biological agents and underestimation of methotrexate

5) The effectiveness of methotrexate is often underestimated in the rheumatology literature: Clinical trials document greater slowing of radiographic progression in groups of patients who took biological agents, compared to those who took methotrexate only (70, 71). Although the treat-to-target recommendations do not mention any specific agent in the context of discussions of treat-to-target, this observation is interpreted in some reports as suggesting that almost all patients should be treated with biological agents. For example, in 2008, two major rheumatology journals included the following statements: "When used as monotherapy, the structure-sparing effect of methotrexate is quite modest compared with that of TNF blockers, even if methotrexate is used in DMARD-naïve patients" (72) and "Studies of anti-TNF therapy plus methotrexate, compared with the effect with methotrexate alone, have shown that although methotrexate is relatively effective at relieving clinical symptoms, it has little or no effect on underlying radiological progression" (73).

Probability plots from reports that document greater slowing of radiographic progression with biological agents compared to methotrexate indicate that about 75% of patients who took methotrexate experienced no radiographic progression and 10–15% of patients who took biological agents did experience progression, even in combination with methotrexate (70). The documented differences in all patients are statistically significant in groups, but generally involve fewer than 10–20% of patients and less than 1% of the total score over one year (74). The findings would be undetectable clinically in individual patients, and could not be applied clinically to actual care of individual patients. Detectable radiographic changes are predicted by sustained clinical inflammatory activity, and radiographic progression tends to plateau over time (75). Clinically important radiographic progression is quite unusual in patients whose disease activity is controlled clinically by methotrexate

6) Some authors imply that the only limitation to treating all RA patients with biological agents involves costs: EULAR management recommendations state that patients who have incomplete responses to methotrexate+ glucocorticoids and have not met the target should receive biological agents, but all others should continue traditional DMARDs (76). Therefore, the treat-to-target recommendations do not suggest that all patients should be treated with biological agents. The treatment target of low disease activity or remission remains the same regardless of therapy (1).

Nonetheless, many authors suggest that, if money were no object, every RA patient should be treated with a biological agent. This may be reasonable for patients who have incomplete responses to methotrexate, who may comprise 15–40% of RA patients, but not for the 60–85% of patients with satisfactory responses to methotrexate and/or other DMARDs. Articles which suggest that the only barrier to biological therapies in RA involves costs ignore extensive evidence that many patients in remission have not taken biological agents, as well as adverse effects associated

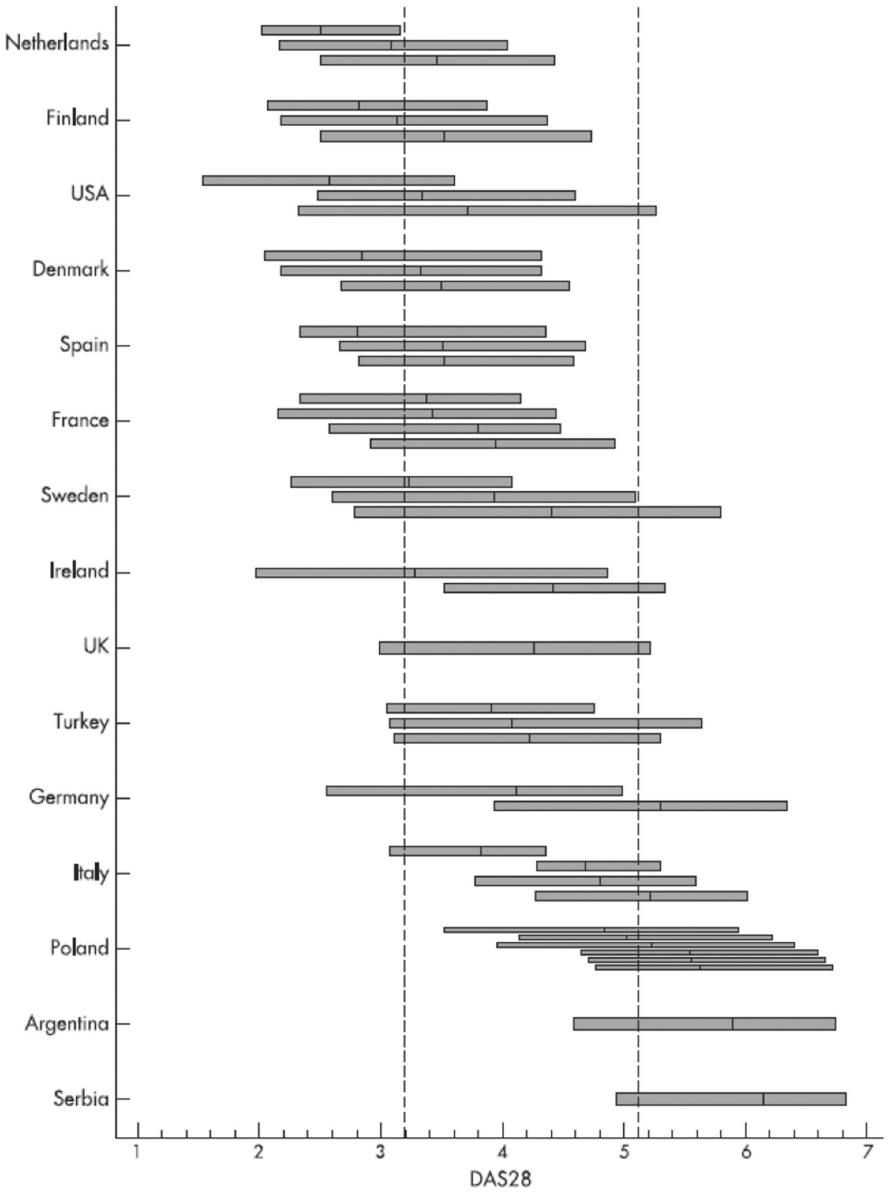

Fig. 3. Disease activity according to DAS28 (disease activity score on 28-joint count; median, interquartile range) in QUEST-RA by country and site (96). Reference lines indicate cut-offs for low (DAS28 <3.2) and high (DAS28 >5.1) disease activity.

with biological agents, which are not uncommon (25). It is inappropriate to suggest that all RA patients should be treated with biological agents, even if costs were not a consideration.

7) The best reported results of treatment of RA in clinical trials do not include biological agents: The highest rates of remission and/or low disease activity have been seen in the trials of strategy (3-9), in which traditional DMARDs rather than biological agents were used in a tight control strategy (Table I). [The BeSt trial included one arm with infliximab, with similar results to tight control without infliximab (9).] Indeed, these reports, rather than reports of clinical trials involving biological agents, form the intellectual and scientific foundation for treat-to-target (2).

Most physicians, including many rheumatologists, are not aware of these trials based on a strategy of tight control or treat-to-target. Evidence that biological agents have greater potential for remission or low disease activity outcomes in groups of patients has been promoted to suggest that biological agents are superior to traditional DMARDs in all individual patients, including the comments cited above. However, most patients (about 60–80%) achieve similar control with methotrexate (see below). Pharmaceutical companies must report two pivotal clinical trials to document that an agent is superior to placebo for registration. Therefore, early trials of biological agents could not allow medication and dosage adjustments that characterise a treat-to-target strategy. Further post-marketing trials to document better results using more stringent treat-to-target strategies have only recently been initiated under sponsorship of companies that market biological agents (77, 78). At this time, the best results in the rheumatology literature remain those from clinical trials that did not involve biological agents (3-9).

8) Better status of RA patients at this time is not attributable primarily to biological agents: Patients seen in recent years have substantially better clinical status than in earlier years, documented at some settings (68, 79-85) but unfortunately not at most rheumatology care sites. Many statements in the rheumatology literature attribute this improved status to biological agents. However, better RA status was noted in the 1990s, before biological agents were introduced.

Biological agents certainly provide a major treatment advance for certain individual patients. Nonetheless, most of the differences in patient status at this time compared to earlier decades are not attributable to these agents, but rather to early treatment; low-dose methotrexate – adjusted to optimal levels of up to 20 mg/week along with concomitant folic acid (68, 79, 80, 86, 87); low-dose prednisone ≤5 mg/day (88); and possible secular trends to milder disease (89-91).

C) Pharmacoeconomic reports may neglect important issues about RA patients

9) Some analyses of disease costs may ignore that RA patients are older, less educated, and have more comorbidities than seen in the general population: Pharmacoeconomic analyses report income losses in patients with RA as indirect costs, which historically have been greater than direct costs of medications and other treatments, although that may no longer be the case for some patients

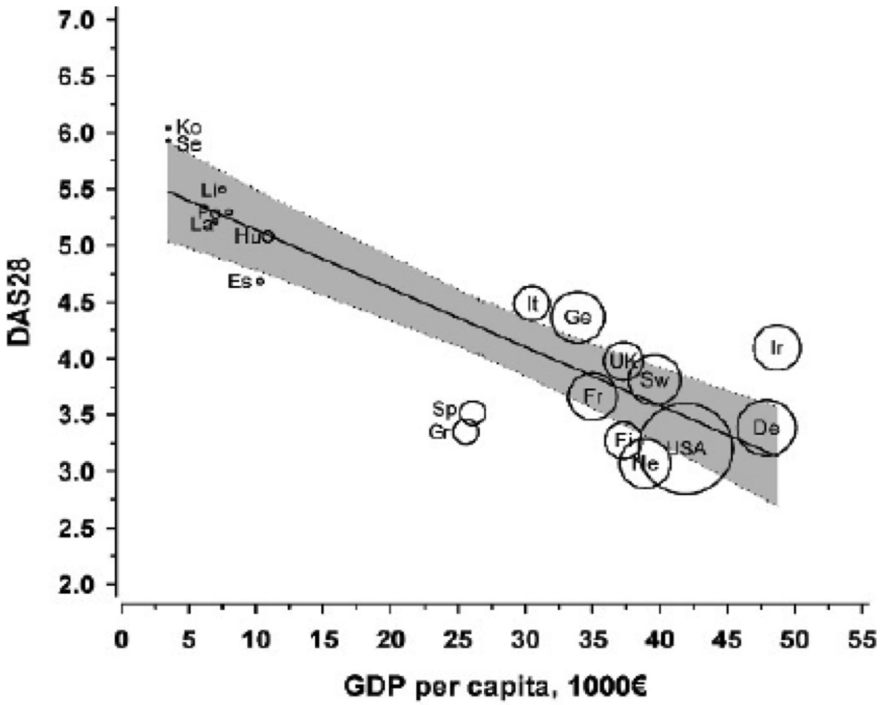

Fig. 4. Association between gross domestic product (GDP) per capita and disease activity score in 28 joints (DAS28) in 18 European countries and the USA in the QUEST–RA study (97). The correlation of GDP with DAS28 is rho = -0.85 (95% confidence interval, -0.63 to -0.94), indicated with color. GDP is expressed as 1000€ per capita. DAS28 ranges from 0 to 9.1 (low–high disease activity). The area of the disk is proportional to the total national health expenditure of each country in 2004. De, Denmark; Es: Estonia; Fi: Finland; Fr: France; Ge: Germany; Gr: Greece; Hu: Hungary; Ir: Ireland; It: Italy; Ko: Kosovo; La: Latvia; Li: Lithuania; Ne: The Netherlands; Po: Poland; Se: Serbia; Sp: Spain; Sw: Sweden.

who take biological agents. However, some reports do not include recognition that RA patients are older, less educated, and more likely to have comorbidities than the general population (92). Therefore, elimination of the clinical consequences of RA entirely, with a status of "remission," and continued employment, would eliminate only about half of the losses of wages associated with RA compared to age- and sex-matched individuals in the general population.

For example, in a report published more than 20 years ago, it was noted that earnings of women with symmetric polyarthritis, a surrogate for RA, were 26.5% of those of women in the general population, while earnings of men with RA were 47.5% of those of men in the general population (92). However, only 35.5% and 38% of these earnings gaps in women and men were attributable to symmetric polyarthritis. The majority of the earnings gap is attributable to older age, lower education, and comorbidities seen in patients with RA compared to the general population (92). Indeed, low education level is more significant to identify poor clinical status in RA patients than age and duration of disease (93). These "human capital" aspects of RA patients compared to the general population are not considered in some analyses of the costs of RA to society and possible benefits of expensive therapies.

10) Some reports may ignore critical differences in RA status according to the country in which the patient lives, which appear critical in the status of patients with RA: An important pharmacoeconomic consideration involves significant differences in the clinical status of patients with RA in various countries according to the wealth of the individual country. The QUEST-RA international database was established to include 100 consecutive patients of 3 rheumatologists in each included country (94), who were evaluated according to a "standard protocol to evaluate rheumatoid arthritis" (SPERA) (95) that included the 7 RA Core Data Set measures (21, 22). Mean DAS28 scores varied substantially in 15 countries analysed in a 2007 report, from low disease activity in the Netherlands, Finland and the United States to high disease activity in Latvia, Poland, Argentina, Lithuania, and Serbia (Fig. 3) (96). A correlation value of rho=0.85 (far higher than rho=0.5 for correlation of the ESR with CRP) was seen between DAS28 and per capita gross domestic product (GDP) in 18 European countries analysed in 2009 (Fig. 4) (97).

The data suggest that country of residence may be as or more important as a determinant of clinical status and disease activity than any other variable specific to a given patient. It is recognised that most patients in certain settings in the United States did not meet criteria to be included even in early clinical trials of biological agents before 2000 (98, 99). Therefore, most clinical trials in RA patients sponsored by pharmaceutical companies at this time are conducted in Eastern Europe, South America, and countries where a large fraction of the population is disadvantaged.

These results reinforce the concept that patients with RA cannot be analysed solely according to a strict "biomedical model," and that a complementary "biopsychosocial model" is needed to fully understand and account for clinical status of patients (100-102). Rigorous pharmacoeconomic analyses recognise differences among different countries, but some reports do not. Indeed, it is possible that the greatest challenges to optimal treatment of patients with RA at this time, including "treat-to-target" with a goal of remission, are more in the domain of psycho/socio/economic issues rather than biochemical/immunologic matters.

Conclusion

Treat-to-target is promoted to guide management of RA. The requirement for quantitative variables in patient care beyond laboratory tests to provide a suitable clinical target is an unquestioned advance. Without quantitative clinical data, rheumatologists were taught into the 1980s that "RA is, in the majority of instances a disease with a good prognosis" (103) and that "the majority of patients can control RA satisfactorily

with well-accepted conservative regimens" (104). By contrast, quantitative data indicated underestimation of severe long-term outcomes of RA such as work disability (33), premature mortality (35), and radiographic progression (34), while sustained remission was rare (105). Among quantitative measures, patient-self-report measures were the primary predictors of severe outcomes of work disability and premature mortality (35, 52-64).

A target of low disease activity or remission according to recognised quantitative criteria is not applicable to all patients, on the basis of patient choice, comorbidities including fibromyalgia, joint damage and other variables, and even older age. These characteristics may explain in large part why the majority of patients in usual clinical care and even clinical research studies do not meet criteria for remission or even for low disease activity. The rheumatology community should be aware of some of these complexities concerning a treat-to-target strategy in approaching care of individual patients. Further analysis of barriers to remission and low disease activity in patients with RA should lead to more informed application of treat-to-target and better patient outcomes.

References

1. SMOLEN JS, ALETAHA D, BIJLSMA JW *et al*.: Treating rheumatoid arthritis to target: recommendations of an international task force. *Ann Rheum Dis* 2010; 69: 631-7.
2. SCHOELS M, KNEVEL R, ALETAHA D *et al*.: Evidence for treating rheumatoid arthritis to target: results of a systematic literature search. *Ann Rheum Dis* 2010; 69: 638-43.
3. MÖTTÖNEN T, HANNONEN P, LEIRISALO-REPO M *et al*.: Comparison of combination therapy with single-drug therapy in early rheumatoid arthritis: A randomised trial. FIN-RACo trial group. *Lancet* 1999; 353: 1568-73.
4. PUOLAKKA K, KAUTIAINEN H, MÖTTÖNEN T *et al*.: Early suppression of disease activity is essential for maintenance of work capacity in patients with recent-onset rheumatoid arthritis: five-year experience from the FIN-RACo trial. *Arthritis Rheum* 2005; 52: 36-41.
5. GRIGOR C, CAPELL H, STIRLING A *et al*.: Effect of a treatment strategy of tight control for rheumatoid arthritis (the TICORA study): a single-blind randomised controlled trial. *Lancet* 2004; 364: 263-9.
6. VERSTAPPEN SMM, JACOBS JWG, VAN DER VEEN MJ *et al*.: Intensive treatment with methotrexate in early rheumatoid arthritis: aiming for remission. Computer Assisted Management in Early Rheumatoid Arthritis (CAMERA, an open-label strategy trial). *Ann Rheum Dis* 2007; 66: 1443-9.
7. HETLAND ML, STENGAARD-PEDERSEN K, JUNKER P *et al*.: Aggressive combination therapy with intra-articular glucocorticoid injections and conventional disease-modifying anti-rheumatic drugs in early rheumatoid arthritis: second-year clinical and radiographic results from the CIMESTRA study. *Ann Rheum Dis* 2008; 67: 815-22.
8. HETLAND ML, OSTERGAARD M, EJBJERG B *et al*.: Short- and long-term efficacy of intra-articular injections with betamethasone as part of a treat-to-target strategy in early rheumatoid arthritis: impact of joint area, repeated injections, MRI findings, anti-CCP, IgM-RF and CRP. *Ann Rheum Dis* 2012; 71: 851-6.
9. GOEKOOP-RUITERMAN YPM, DE VRIES-BOUWSTRA JK, ALLAART CF *et al*.: Comparison of treatment strategies in early rheumatoid arthritis: a randomized trial. *Ann Intern Med* 2007; 146: 406-15.
10. SOKKA T, PINCUS T: Rheumatoid arthritis: strategy more important than agent. *Lancet* 2009; 374: 430-2.
11. FUCHS HA, BROOKS RH, CALLAHAN LF, PINCUS T: A simplified twenty-eight joint quantitative articular index in rheumatoid arthritis. *Arthritis Rheum* 1989; 32: 531-7.
12. FUCHS HA, PINCUS T: Reduced joint counts in controlled clinical trials in rheumatoid arthritis. *Arthritis Rheum* 1994; 37: 470-5.
13. PINCUS T, SUMMEY JA, SORACI SA, JR., WALLSTON KA, HUMMON NP: Assessment of patient satisfaction in activities of daily living using a modified Stanford health assessment questionnaire. *Arthritis Rheum* 1983; 26: 1346-53.
14. WOLFE F, MICHAUD K, PINCUS T: Development and validation of the health assessment questionnaire II: a revised version of the health assessment questionnaire. *Arthritis Rheum* 2004; 50: 3296-305.
15. PINCUS T, SWEARINGEN C, WOLFE F: Toward a multidimensional health assessment questionnaire (MDHAQ): Assessment of advanced activities of daily living and psychological status in the patient friendly health assessment questionnaire format. *Arthritis Rheum* 1999; 42: 2220-30.
16. PINCUS T, SOKKA T, KAUTIAINEN H: Further development of a physical function scale on a multidimensional health assessment questionnaire for standard care of patients with rheumatic diseases. *J Rheumatol* 2005; 32: 1432-9.
17. PINCUS T, WOLFE F: An infrastructure of patient questionnaires at each rheumatology visit: Improving efficiency and documenting care. *J Rheumatol* 2000; 27: 2727-30.
18. PINCUS T, YAZICI Y, BERGMAN M: Development of a multi-dimensional health assessment questionnaire (MDHAQ) for the infrastructure of standard clinical care. *Clin Exp Rheumatol* 2005; 23: S19-S28.
19. PINCUS T, GIBOFSKY A, WEINBLATT ME: Urgent care and tight control of rheumatoid arthritis as in diabetes and hypertension: better treatments but a shortage of rheumatologists. *Arthritis Rheum* 2002; 46: 851-4.
20. CASTREJÓN I, PINCUS T: Differences in treat-to-target in patients with rheumatoid arthritis versus hypertension and diabetes: consequences for clinical care. *Bull NYU Hosp Jt Dis* 2011; 69: 104-10.
21. FELSON DT: Choosing a core set of disease activity measures for rheumatoid arthritis clinical trials. *J Rheumatol* 1993; 20: 531-4.
22. VAN RIEL PLCM: Provisional guidelines for measuring disease activity in clinical trials on rheumatoid arthritis (Editorial). *Br J Rheumatol* 1992; 31: 793-4.
23. CASTREJÓN I, MCCOLLUM L, DURUSU TANRIOVER M, PINCUS T: Importance of patient history and physical examination in rheumatoid arthritis compared to other chronic diseases: Results of a physician survey. *Arthritis Care Res* 2012; 64: 1250-5.
24. PINCUS T, YAZICI Y, YAZICI H, KAVANAUGH AF, KREMER JM, WOLFE F: Radiographic benefit without clinical improvement in infliximab-treated patients with rheumatoid arthritis: comment on the article by Smolen et al. *Arthritis Rheum* 2005; 52: 4044-5.
25. WOLFE F, MICHAUD K: Resistance of rheumatoid arthritis patients to changing therapy: discordance between disease activity and patients' treatment choices. *Arthritis Rheum* 2007; 56: 2135-42.
26. SOKKA T, MAKINEN H, HANNONEN P, PINCUS T: Most people over age 50 in the general population do not meet ACR remission criteria or OMERACT minimal disease activity criteria for rheumatoid arthritis. *Rheumatology* (Oxford) 2007; 46: 1020-3.
27. STUCKI G, LIANG MH, STUCKI S, BRÜHLMANN P, MICHEL BA: A self-administered rheumatoid arthritis disease activity index (RADAI) for epidemiologic research. *Arthritis Rheum* 1995; 38: 795-8.
28. FELSON DT, SMOLEN JS, WELLS G *et al*.: American College of Rheumatology/European League Against Rheumatism provisional definition of remission in rheumatoid arthritis for clinical trials. *Arthritis Rheum* 2011; 63: 573-86.
29. FELSON DT, SMOLEN JS, WELLS G *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: 404-13.
30. PINALS RS, MASI AT, LARSEN RA *et al*.: Preliminary criteria for clinical remission in rheumatoid arthritis. *Arthritis Rheum* 1981; 24: 1308-15.
31. WOLFE F, RASKER JJ, BOERS M, WELLS GA, MICHAUD K: Minimal disease activity, remission, and the long-term outcomes of rheumatoid arthritis. *Arthritis Rheum* 2007; 57: 935-42.
32. KERR EA, LUCATORTO MA, HOLLEMAN R, HOGAN MM, KLAMERUS ML, HOFER TP: Monitoring performance for blood pressure management among patients with diabetes mellitus: too much of a good thing? *Arch Intern Med* 2012; 172: 938-45.
33. YELIN E, MEENAN R, NEVITT M, EPSTEIN W: Work disability in rheumatoid arthritis: effects of disease, social, and work factors. *Ann Intern Med* 1980; 93: 551-6.

34. SCOTT DL, GRINDULIS KA, STRUTHERS GR, COULTON BL, POPERT AJ, BACON PA: Progression of radiological changes in rheumatoid arthritis. *Ann Rheum Dis* 1984; 43: 8-17.
35. PINCUS T, CALLAHAN LF, SALE WG, BROOKS AL, PAYNE LE, VAUGHN WK: Severe functional declines, work disability, and increased mortality in seventy-five rheumatoid arthritis patients studied over nine years. *Arthritis Rheum* 1984; 27: 864-72.
36. PINCUS T, CALLAHAN LF: The 'side effects' of rheumatoid arthritis: Joint destruction, disability and early mortality. *Br J Rheumatol* 1993; 32: (Suppl. 1): 28-37.
37. MIERAU M, SCHOELS M, GONDA G, FUCHS J, ALETAHA D, SMOLEN JS: Assessing remission in clinical practice. *Rheumatology* (Oxford) 2007; 46: 975-9.
38. SHAHOURI SH, MICHAUD K, MIKULS TR *et al*.: Remission of rheumatoid arthritis in clinical practice: application of the American College of Rheumatology/European League Against Rheumatism 2011 remission criteria. *Arthritis Rheum* 2011; 63: 3204-15.
39. WOLFE F, CATHEY MA, KLEINHEKSEL SM: Fibrositis (fibromyalgia) in rheumatoid arthritis. *J Rheumatol* 1984; 11: 814-8.
40. CLAUW DJ, KATZ P: The overlap between fibromyalgia and inflammatory rheumatic disease: When and why does it occur? *J Clin Rheumatol* 1995; 1: 335-41.
41. PINCUS T, WOLFE F, CALLAHAN LF: Updating a reassessment of traditional paradigms concerning rheumatoid arthritis. *In*: WOLFE F, PINCUS T, editors. Rheumatoid Arthritis: Pathogenesis, Assessment, Outcome, and Treatment. New York: Marcel Dekker, Inc.; 1994. 1-74.
42. BERKANOVIC E, HURWICZ ML: Rheumatoid arthritis and comorbidity. *J Rheumatol* 1990; 17: 888-92.
43. BOERS M, DIJKMANS B, GABRIEL S, MARADIT-KREMERS H, O'DELL J, PINCUS T: Making an impact on mortality in rheumatoid arthritis: targeting cardiovascular comorbidity. *Arthritis Rheum* 2004; 50: 1734-9.
44. MICHAUD K, WOLFE F: Comorbidities in rheumatoid arthritis. *Best Pract Res Clin Rheumatol* 2007; 21: 885-906.
45. PINCUS T, YAZICI Y, SOKKA T: Complexities in assessment of rheumatoid arthritis: absence of a single gold standard measure. *Rheum Dis Clin North Am* 2009; 35: 687-97.
46. PREVOO MLL, VAN'T HOF MA, KUPER HH, VAN LEEUWEN MA, VAN DE PUTTE LBA, VAN RIEL PLCM: Modified disease activity scores that include twenty-eight-joint counts: Development and validation in a prospective longitudinal study of patients with rheumatoid arthritis. *Arthritis Rheum* 1995; 38:44-8
47. ALETAHA D, SMOLEN J: The simplified disease activity index (SDAI) and the clinical disease activity index (CDAI): a review of their usefulness and validity in rheumatoid arthritis. *Clin Exp Rheumatol* 2005; 23: S100-S108.
48. PINCUS T, SWEARINGEN CJ, BERGMAN M, YAZICI Y: RAPID3 (routine assessment of patient index data 3), a rheumatoid arthritis index without formal joint counts for routine care: Proposed severity categories compared to DAS and CDAI categories. *J Rheumatol* 2008; 35:2136-47.
49. SOKKA T, HETLAND ML, MAKINEN H *et al*.: Remission and rheumatoid arthritis: Data on patients receiving usual care in twenty-four countries. *Arthritis Rheum* 2008; 58: 2642-51.
50. OLSEN NJ, CALLAHAN LF, BROOKS RH *et al*.: Associations of HLA-DR4 with rheumatoid factor and radiographic severity in rheumatoid arthritis. *Am J Med* 1988; 84: 257-64.
51. PINCUS T, YAZICI Y, SOKKA T: Quantitative measures of rheumatic diseases for clinical research versus standard clinical care: differences, advantages and limitations. *Best Pract Res Clin Rheumatol* 2007; 21: 601-28.
52. CALLAHAN LF, BLOCH DA, PINCUS T: Identification of work disability in rheumatoid arthritis: Physical, radiographic and laboratory variables do not add explanatory power to demographic and functional variables. *J Clin Epidemiol* 1992; 45: 127-38.
53. WOLFE F, HAWLEY DJ: The longterm outcomes of rheumatoid arthritis: Work disability: A prospective 18 year study of 823 patients. *J Rheumatol* 1998; 25: 2108-17.
54. FEX E, LARSSON B, NIVED K, EBERHARDT K: Effect of rheumatoid arthritis on work status and social and leisure time activities in patients followed 8 years from onset. *J Rheumatol* 1998; 25: 44-50.
55. SOKKA T, KAUTIAINEN H, MÖTTÖNEN T, HANNONEN P: Work disability in rheumatoid arthritis 10 years after the diagnosis. *J Rheumatol* 1999; 26: 1681-5.
56. BARRETT EM, SCOTT DGI, WILES NJ, SYMMONS DPM: The impact of rheumatoid arthritis on employment status in the early years of disease: a UK community-based study. *Rheumatology* 2000; 39: 1403-9.
57. LUBECK DP, SPITZ PW, FRIES JF, WOLFE F, MITCHELL DM, ROTH SH: A multicenter study of annual health service utilization and costs in rheumatoid arthritis. *Arthritis Rheum* 1986; 29: 488-93.
58. WOLFE F, KLEINHEKSEL SM, CATHEY MA, HAWLEY DJ, SPITZ PW, FRIES JF: The clinical value of the Stanford health assessment questionnaire functional disability Index in patients with rheumatoid arthritis. *J Rheumatol* 1988; 15: 1480-8.
59. LEIGH JP, FRIES JF: Mortality predictors among 263 patients with rheumatoid arthritis. *J Rheumatol* 1991; 18: 1307-12.
60. CALLAHAN LF, PINCUS T, HUSTON JW, III, BROOKS RH, NANCE EP, JR., KAYE JJ: Measures of activity and damage in rheumatoid arthritis: Depiction of changes and prediction of mortality over five years. *Arthritis Care Res* 1997; 10: 381-94.
61. MAIDEN N, CAPELL HA, MADHOK R, HAMPSON R, THOMSON EA: Does social disadvantage contribute to the excess mortality in rheumatoid arthritis patients? *Ann Rheum Dis* 1999; 58: 525-9.
62. PINCUS T, KEYSOR J, SOKKA T, KRISHNAN E, CALLAHAN LF: Patient questionnaires and formal education level as prospective predictors of mortality over 10 years in 97% of 1416 patients with rheumatoid arthritis from 15 United States private practices. *J Rheumatol* 2004; 31: 229-34.
63. SOKKA T, HAKKINEN A, KRISHNAN E, HANNONEN P: Similar prediction of mortality by the health assessment questionnaire in patients with rheumatoid arthritis and the general population. *Ann Rheum Dis* 2004; 63: 494-7.
64. SOKKA T, ABELSON B, PINCUS T: Mortality in rheumatoid arthritis: 2008 update. *Clin Exp Rheumatol* 2008; 26 (Suppl. 51): S35-S61.
65. VETERANS ADMINISTRATION COOPERATIVE STUDY ON ANTIHYPERTENSIVE AGENT: Effects of treatment on morbidity in hypertension: II. Results in patients with diastolic blood pressure averaging 90 through 114 mm Hg. *JAMA* 1970; 213: 1143-50.
66. The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. The Diabetes Control and Complications Trial Research Group. *N Engl J Med* 1993; 329: 977-86.
67. KRAUSE D, SCHLEUSSER B, HERBORN G, RAU R: Response to methotrexate treatment is associated with reduced mortality in patients with severe rheumatoid arthritis. *Arthritis Rheum* 2000; 43: 14-21.
68. CHOI HK, HERNÁN MA, SEEGER JD, ROBINS JM, WOLFE F: Methotrexate and mortality in patients with rheumatoid arthritis: a prospective study. *Lancet* 2002; 359: 1173-7.
69. JACOBSSON LTH, TURESSON C, NILSSON JA *et al*.: Treatment with TNF blockers and mortality risk in patients with rheumatoid arthritis. *Ann Rheum Dis* 2007; 66: 670-5.
70. VAN DER HEIJDE D, LANDEWÉ R, KLARESKOG L, RODRIGUEZ-VALVERDE V, SETTAS L, PEDER *et al*.: Presentation and analysis of data on radiographic outcome in clinical trials: experience from the TEMPO study. *Arthritis Rheum* 2005; 52: 49-60.
71. 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.
72. SCHETT G, STACH C, ZWERINA J, VOLL R, MANGER B: How antirheumatic drugs protect joints from damage in rheumatoid arthritis. *Arthritis Rheum* 2008; 58: 2936-48.
73. EMERY P, MCINNES IB, VAN VOLLENHOVEN R, KRAAN MC: Clinical identification and treatment of a rapidly progressing disease state in patients with rheumatoid arthritis. *Rheumatology* (Oxford) 2008; 47: 392-8.
74. YAZICI Y, YAZICI H: Tumor necrosis factor alpha inhibitors, methotrexate or both? An inquiry into the formal evidence for when they are to be used in rheumatoid arthritis. *Clin Exp Rheumatol* 2008; 26: 449-52.
75. FUCHS HA, PINCUS T: Radiographic damage in rheumatoid arthritis: Description by nonlinear models (editorial). *J Rheumatol* 1992; 19: 1655-8.

76. COMBE B, LANDEWÉ R, LUKAS C *et al*.: EULAR recommendations for the management of early arthritis: report of a task force of the European Standing Committee for International Clinical Studies Including Therapeutics (ESCISIT). *Ann Rheum Dis* 2007; 66: 34-45.
77. SMOLEN JS, FLEISCHMANN RM, EMERY P *et al*.: Treating rheumatoid arthritis to target: outcomes and predictors in early rheumatoid arthritis patients treated with adalimumb plus methotrexate, methotrexate alone, or methotrexate plus subsequent adlimumab. [abstract]. *Arthritis Rheum* 2011; 63 (Suppl.): S665.
78. SMOLEN J, SZUMSKI A, MARSHALL L, KOENIG AS: Baseline predictors of remission with combination etanercept-methotrexate therapy in moderately active rheumatoid arthritis: interim results of the RESERVE Trial. [abstract]. *Arthritis Rheum* 2011; 63 (Suppl.): S474.
79. PINCUS T, SOKKA T, KAUTIAINEN H: Patients seen for standard rheumatoid arthritis care have significantly better articular, radiographic, laboratory, and functional status in 2000 than in 1985. *Arthritis Rheum* 2005; 52: 1009-19.
80. SOKKA T: Assessment of pain in patients with rheumatic diseases. *Best Pract Res Clin Rheumatol* 2003; 17: 427-49.
81. SOKKA T, KAUTIAINEN H, HÄKKINEN K, HANNONEN P: Radiographic progression is getting milder in patients with early rheumatoid arthritis. Results of 3 cohorts over 5 years. *J Rheumatol* 2004; 31: 1073-82.
82. UHLIG T, HEIBERG T, MOWINCKEL P, KVIEN TK: Rheumatoid arthritis is milder in the new millennium: health status in patients with rheumatoid arthritis 1994-2004. *Ann Rheum Dis* 2008; 67: 1710-5.
83. WELSING PMJ, FRANSEN J, VAN RIEL PLCM: Is the disease course of rheumatoid arthritis becoming milder? Time trends since 1985 in an inception cohort of early rheumatoid arthritis. *Arthritis Rheum* 2005; 52: 2616-24.
84. KRISHNAN E, FRIES JF: Rheumatoid arthritis: radiographic progression is getting milder. *J Rheumatol* 2005; 32: 195.
85. FINCKH A, CHOI HK, WOLFE F: Progression of radiographic joint damage in different eras: trends towards milder disease in rheumatoid arthritis are attributable to improved treatment. *Ann Rheum Dis* 2006; 65: 1192-7.
86. KAPRAL T, STAMM T, MACHOLD KP, MONTAG K, SMOLEN JS: Methotrexate in rheumatoid arthritis is frequently effective, even if re-employed after a previous failure. *Arthritis Res Ther* 2006; 8: R46.
87. SOKKA T, PINCUS T: Ascendancy of weekly low-dose methotrexate in usual care of rheumatoid arthritis from 1980 to 2004 at two sites in Finland and the United States. *Rheumatology* (Oxford) 2008; 47: 1543-7.
88. PINCUS T, SOKKA T, CASTREJÓN I, FURER V, CUTOLO M: Decline of mean initial prednisone dose to treat patients with rheumatoid arthritis from 10.3 mg/day in 1980-1985 to 3.6 mg/day in 2000-2004, with similar efficacy over 12 subsequent months and few adverse events. submitted 2011.
89. PORTER DR, CAPELL HA, MCINNES I *et al*.: Is rheumatoid arthritis becoming a milder disease? Or are we starting second-line therapy in patients with milder disease? *Br J Rheumatol* 1996; 35: 1305-8.
90. UHLIG T, KVIEN TK: Has rheumatoid arthritis become a milder disease? *Drug Discovery Today* 2005; 2: 331-6.
91. SILMAN AJ: The changing face of rheumatoid arthritis: why the decline in incidence? *Arthritis Rheum* 2002; 46: 579-81.
92. MITCHELL JM, BURKHAUSER RV, PINCUS T: The importance of age, education, and comorbidity in the substantial earnings losses of individuals with symmetric polyarthritis. *Arthritis Rheum* 1988; 31: 348-57.
93. CALLAHAN LF, SMITH WJ, PINCUS T: Self-report questionnaires in five rheumatic diseases: Comparisons of health status constructs and associations with formal education level. *Arthritis Care Res* 1989; 2: 122-31.
94. SOKKA T, MAKINEN H, HETLAND ML *et al*.: A multi-national cross-sectional database to assess clinical status of patients with rheumatoid arthritis (QUEST-RA). *Scand J Rheumatol* 35 (Suppl. 121): 32-3. 2006.
95. PINCUS T, SOKKA T: A three-page Standard Protocol to Evaluate Rheumatoid Arthritis (SPERA) for efficient capture of essential data from patients and health professionals in standard clinical care and clinical research. *Best Pract Res Clin Rheumatol* 2007; 21: 677-85.
96. SOKKA T, KAUTIAINEN H, TOLOZA S *et al*.: QUEST-RA: quantitative clinical assessment of patients with rheumatoid arthritis seen in standard rheumatology care in 15 countries. *Ann Rheum Dis* 2007; 66: 1491-6.
97. SOKKA T, KAUTIAINEN H, PINCUS T *et al*.: Disparities in rheumatoid arthritis disease activity according to gross domestic product in 25 countries in the QUEST-RA database. *Ann Rheum Dis* 2009; 68: 1666-72.
98. SOKKA T, PINCUS T: Most patients receiving routine care for rheumatoid arthritis in 2001 did not meet inclusion criteria for most recent clinical trials or American College of Rheumatology criteria for remission. *J Rheumatol* 2003; 30: 1138-46.
99. GOGUS F, YAZICI Y, YAZICI H: Inclusion criteria as widely used for rheumatoid arthritis clinical trials: patient eligibility in a Turkish cohort. *Clin Exp Rheumatol* 2005; 23: 681-4.
100. ENGEL GL: The need for a new medical model: a challenge for biomedicine. *Science* 1977; 196: 129-36.
101. ENGEL GL: How much longer must medicine's science be bound by a seventeenth century world view? *Psychother Psychosom* 1992; 57: 3-162.
102. MCCOLLUM L, PINCUS T: A biopsychosocial model to complement a biomedical model: patient questionnaire data and socioeconomic status usually are more significant than laboratory tests and imaging studies in prognosis of rheumatoid arthritis. *Rheum Dis Clin North Am* 2009; 35: 699-712.
103. Treatment of Rheumatoid Arthritis. *In*: MCCARTY DJ (Ed.): *Arthritis and Allied Conditions*. 10th ed. Philadelphia: Lea & Febiger; 1985; 668-76.
104. KELLEY WN, HARRIS ED JR, RUDDY S, SLEDGE CB: *Textbook of Rheumatology*. 3rd ed. Philadelphia: W.B.Saunders; 1989.
105. WOLFE F, HAWLEY DJ: Remission in rheumatoid arthritis. *J Rheumatol* 1985; 12: 245-52.
106. WEYAND CM, HICOK KC, CONN DL, GORONZY JJ: The influence of HLA-DRB1 genes on disease severity in rheumatoid arthritis. *Ann Intern Med* 1992; 117: 801-6.
107. OLLIER W, VENABLES PJW, MUMFORD PA *et al*.: HLA antigen associations with extra-articular rheumatoid arthritis. *Tissue Antigens* 1984; 24: 279-91.