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

T. Pincus¹, I. Castrejón¹, M.J. Bergman², Y. Yazici¹

**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

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recognition of 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 (RADAII) (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 patients, as reviewed below.

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

<table>
<thead>
<tr>
<th>Study, year (ref.)</th>
<th>Location</th>
<th>n</th>
<th>Strategy</th>
<th>Treatments</th>
</tr>
</thead>
<tbody>
<tr>
<td>FIN-RACo 1999, 2005 (3,4)</td>
<td>Finland</td>
<td>195</td>
<td>Aim for remission</td>
<td>• SSZ + MTX + HCQ</td>
</tr>
<tr>
<td>TICORA 2004 (5)</td>
<td>Scotland</td>
<td>111</td>
<td>DAS28 to change Rx</td>
<td>• Triple RX, q mo, inj</td>
</tr>
<tr>
<td>BeSt Netherlands 2005, 2007 (9)</td>
<td>Netherlands</td>
<td>508</td>
<td>DAS28 to change Rx</td>
<td>• DMARD monotherapy</td>
</tr>
<tr>
<td>CAMERA 2007 (6)</td>
<td>Netherlands</td>
<td>299</td>
<td>Computer-assisted management by pre-defined response criteria</td>
<td>• MTX-visit q month + CyA with computer decision model</td>
</tr>
<tr>
<td>CIMESTRA Denmark 2008, 2009 (7,8)</td>
<td>Denmark</td>
<td>160</td>
<td>DAS28 to change Rx</td>
<td>• Step-up MTX + CyA</td>
</tr>
</tbody>
</table>


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 comorbidities, 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.
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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.

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).

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

*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.
radiographic progression, and premature mortality – are usually greater than the risks of therapy.

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. Furthermore, many healthy individuals in the general population over age 50 would not meet criteria for RA remission or even low disease activity. 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) 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
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Strongly and weakly correlated measures to assess rheumatoid arthritis – measures on right far more significant to predict work disability, premature death

- Rheumatoid factor
- ACPA, ESR, CRP
- Shared epitope
- Joint swelling
- Radiographic damage
- Joint deformity
- Duration of disease
- Functional disability
- Pain
- Patient global
- Fatigue
- Age

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.

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. 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.

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).
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-naive 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 with...
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.
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” (SPEERA) (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 “bio-psychosocial 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.

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