Editorial



Documenting the Value of Care for Rheumatoid Arthritis, Analogous to Hypertension, Diabetes, and Hyperlipidemia: Is Control of Individual Patient Self-Report Measures of Global Estimate and Physical Function More Valuable Than Laboratory Tests, Radiographs, Indices, or Remission Criteria?

Recent recommendations for treatment of rheumatoid arthritis (RA) include "treat-to-target" with a "primary target…a state of clinical remission"[1]. Remission is now a realistic target in RA, because patient status is substantially better than in previous decades in most developed countries[2]. Capacity to induce remission may be an effective rationale for support of aggressive treatment with expensive therapies to insurance company and government payers.

The concept of "treat-to-target" was developed over the years in other chronic diseases, notably hypertension[3,4], diabetes[5], and hyperlipidemia[6]. The basis of treat-to-target was not "remission," a state that may often be possible, but as in RA, usually requires continued lifelong medication. The target, in other diseases, involves "tight control" of a "gold standard" biomarker of dysregulation — elevated blood pressure, serum glucose, or serum cholesterol — to a lower level that results in improved quality of life and reduction of premature mortality rates. Such a target – not a state of remission – provides a strong rationale for aggressive treatment.

RA differs substantially from hypertension, diabetes, or hyperlipidemia in that there is no single, gold standard biomarker (or any other measure) for diagnosis, management, or prognosis in all individual patients. Biomarkers are of unquestioned importance in RA to understand pathogenesis and develop new therapies: Biological agents would not be available without them. However, biomarkers are limited in clinical application to diagnosis, management, and prognosis of RA:

Diagnosis. Forty percent of new patients have normal erythrocyte sedimentation rate (ESR) or C-reactive protein (CRP)[7,8], and > 30% test negative for rheumatoid factor or anti-citrullinated protein antibodies (ACPA)[9].

Management. Clinical decisions in RA are based more on a patient history and physical examination than on biomarkers; in contrast, biomarkers dominate clinical decisions in many chronic diseases, and may include vital signs (e.g., blood pressure in hypertension); laboratory tests (e.g., hemoglobin A1c in diabetes); imaging (e.g., computed tomographic scan in pulmonary fibrosis), or other ancillary studies (e.g., endoscopy in inflammatory bowel disease)[10].

Prognosis. The most significant markers for future quality of life and premature mortality in RA are not laboratory tests, radiographs, indices, or remission criteria, but individual patient self-report measures of patient global estimate of status or physical function[11].

In the absence of a single gold standard biomarker (or any measure) applicable to each individual patient with RA[12], pooled indices[13] are needed to assess and monitor clinical status quantitatively, and to provide quantitative remission criteria. These indices are based on a core data set for RA[14] of 7 measures: 3 from patient self-report, 3 from physical examination, but only 1 laboratory test — ESR or CRP — reflecting limitations of biomarkers and the promin-ence of patient history and physical examination in

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RA[10]. Remission according to Disease Activity Score with 28 joint count (DAS28)[15], Simplified Disease Activity Index (SDAI)[16], Clinical Disease Activity Index (CDAI)[16], and Routine Assessment of Patient Index Data (RAPID3)[17] has been described. More recently, more stringent "Boolean" criteria, as well as SDAI score ≤ 3.3, have been advocated by a committee of the American College of Rheumatology/European League Against Rheumatism (ACR/EULAR)[18,19].

The highest levels of remission reported in RA are seen in clinical trials of a treat-to-target strategy[20,21,22,23,24,25] (Table 1). However, in most series from usual clinical care, only 6–33% of patients met even the least stringent DAS28 remission criteria[17,26,27,28,29,30,31,32] (Table 1). Therefore, an important, if not critical, task for the rheumatology community is to document effective rheumatology care although only a minority of patients reach the stated goal of clinical remission. This goal might be met more effectively by analyzing efforts to control the most significant individual core data set measures to achieve improved quality of life and reversal of premature mortality — patient global estimate and physical function on a patient questionnaire — rather than by focusing on indices or remission.

A report by Linde, *et al*[33] in this issue of *The Journal* documents the value of a patient global estimate of status to explain improvement in quality of life associated with treatment of RA. Among the 4 measures of the DAS28, swollen and tender joint counts were less significant, CRP was not at all significant, while patient global estimate was most significant to explain improvement in quality of life during treatment with biological therapies. Their report extends impressive contributions from the Danish community to international rheumatology, including much information about biological therapies in usual care from the comprehensive DANBIO registry[34], and the Ciclosporine, Methotrexate, Steroid in RA (CIMESTRA) trial[24], in which

Table 1. Prevalence of remission in selected published reports of rheumatoid arthritis (RA) clinical trials following a tight control strategy and RA clinical cohorts, 1999–2013+.

Author, Year, (Reference)	Patients	Prevalence of Remission; Criteria
Treatment strategy clinical trials		
Möttönen, 1999[20]	Finnish RA Combination Therapy (FIN-RACo) trial	25% combination therapy; ACR 1981; 11% single-drug therapy; ACR 1981
Grigor, 2004[21]	Tight Control for Rheumatoid Arthritis (TICORA) trial; single-blind RCT	65% intensive group; DAS; 16% usual care group; DAS
Verstappen, 2007[22]	Computer Assisted Management in Early Rheumatoid Arthritis (CAMERA) study; open-label strategy trial	50% intensive group; Utrecht criteria*; 37% conventional group Utrecht criteria*
Klarenbeek, 2011[23]	BehandelStrategien (BeSt) or "treatment strategies" trial	23% drug-free remission
Hetland, 2012[24]	Ciclosporine, Methotrexate, Steroid in RA (CIMESTRA)	56%; Boolean; 78%; DAS28
Wevers-de Boer, 2012[25]	Induction therapy with MTX and Prednisone in Rheumatoid Or Very Early arthritic Disease (IMPROVED) trial; 2-step treatment strategy study in Dutch early arthritis patients	60%; Boolean
Clinical cohorts		
van der Woude, 2009[26]	Leiden Early Arthritis Clinic (EAC) and British Early Rheumatoid Arthritis Study (ERAS)	21.4% Leiden EAC; modified ACR 15%; Leiden EAC; DMARD-free; 9.4% ERAS; DMARD-free
Shahouri, 2011[27]	US Department of Veterans Affairs RA (VARA) registry Arthritis and Rheumatology Clinics of Kansas (ARCK)	24.0% VARA; DAS28; 7.0% VARA; Boolean; 28.3% ARCK; DAS28; 6.9% ARCK; CDAI
de Punder, 2012[28]	Dutch Rheumatoid Arthritis Monitoring (DREAM) biologic registry	6%; DAS28
Prince, 2012[29]	Brigham and Women's Rheumatoid Arthritis Sequential Study (BRASS)	31%; DAS28 < 2.6; 10%; Boolean
Castrejón, 2013[17]	Etude et Suivi des Polyarthrites Indifférenciées Récentes (ESPOIR) French early arthritis cohort	32.5%; DAS28; 12.9%; Boolean
Navarro-Millan, 2013[30]	Consortium of Rheumatology Researchers of North America (CORRONA), 2001–2011	8%; Boolean
Thiele, 2013[31]	German Collaborative Centers, 2007–2009	28%; DAS28; 7%; Boolean

+ Where a study reported remission according to multiple criteria, the criteria with the highest and lowest percentages of patients in remission are presented. * Utrecht criteria for remission = no swollen joint, and at least 2 of the following: TJC ≤ 3, erythrocyte sedimentation rate ≤ 20 mm/h and visual analog scale general well being ≤ 20 mm[22]. DAS28: Disease Activity Score 28 joint; MTX: methotrexate; ACR: American College of Rheumatology; DMARD: disease-modifying antirheumatic drugs; CDAI: Clinical Disease Activity Index.

56% of patients met Boolean and 78% DAS28 remission criteria after 5 years[24] (Table 1).

A measure of quality of life is a criterion used by insurance companies and government payers to estimate the potential value of biological therapies for a patient with RA. Control of patient global estimate, rather than joint counts, radiographic scores, or laboratory tests, could be more valuable to justify expensive RA treatments. Remission might become a valuable surrogate in the future if it was commonly achieved, say, in two-thirds of patients in usual care, rather than in one-third (the maximum reported rate today).

Another important possible target for control using an individual RA patient questionnaire measure involves physical function and longterm mortality. The natural history of RA involves the shortening of lifespan by about a decade, comparable to hypertension and diabetes[35,36]. Further, diseases such as systemic lupus erythematosus (SLE)[37], polymyositis[38], vasculitis, and systemic sclerosis are associated with increased mortality rates, comparable to or greater than most forms of cardiovascular and neoplastic diseases[39,40]. RA and other inflammatory rheumatic diseases should be monitored routinely for 5-year survival and other mortality outcomes, as is the case for cardiovascular and neoplastic diseases.

In RA, the most significant predictor of mortality is a patient questionnaire measure of physical function — not a laboratory test or other biomarker — documented initially almost 30 years ago[35,41], confirmed in a second cohort observed from 1985–1990[42], and in 15 of 16 reported RA cohorts[43] (Figure 1). Further, a measure of physical function on a patient questionnaire is more significant than any laboratory test or radiographic score to predict costs, work disability, or even joint replacement surgery[11]. The only outcome predicted most significantly by radiographs or laboratory tests is radiographic progression[44], which appears less relevant to the other longterm outcomes noted than patient questionnaire scores. Even if premature mortality is falling, the relative importance of physical function likely remains; in a study in Finland, physical function on Health Assessment Questionnaire (HAQ) predicted 5-year mortality at higher levels than smoking in

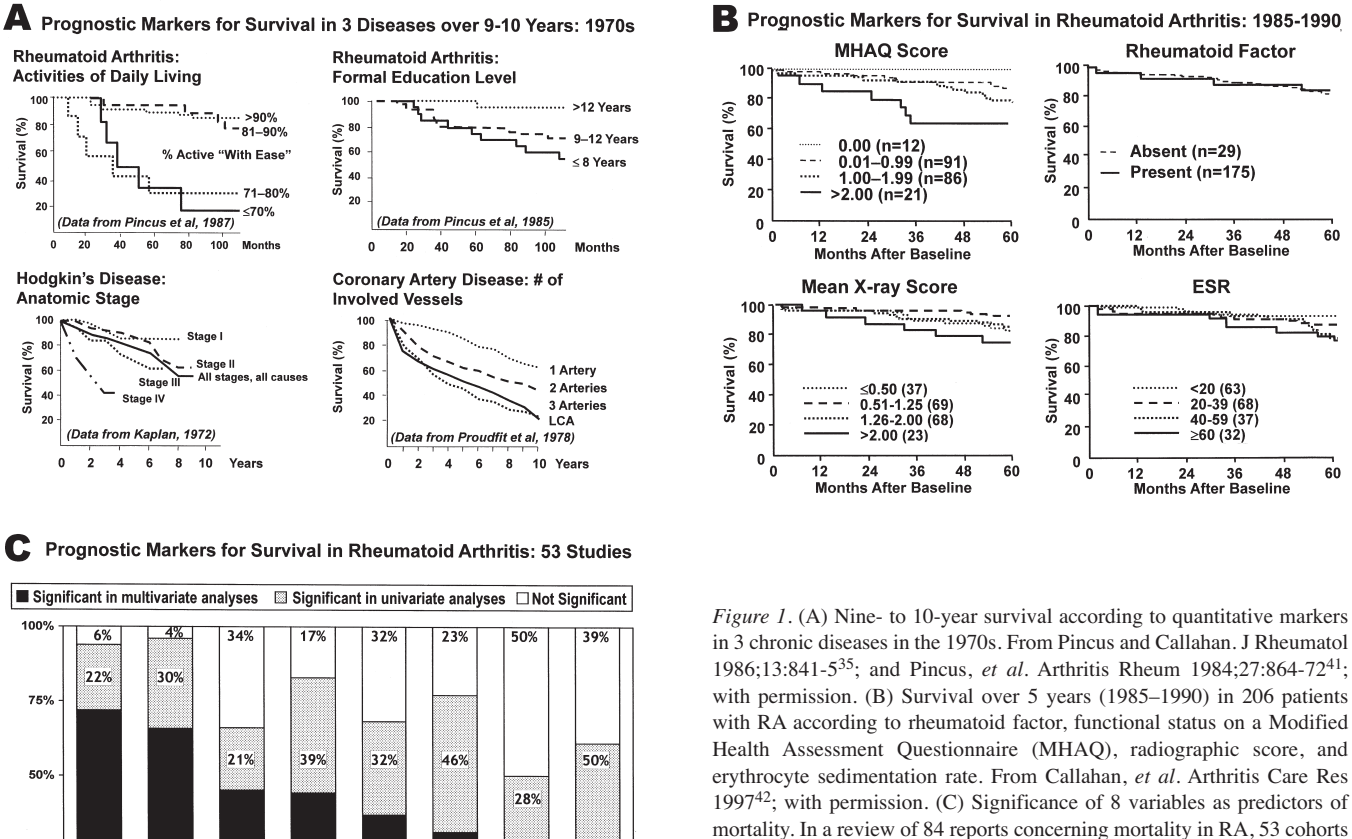

Figure 1. (A) Nine- to 10-year survival according to quantitative markers in 3 chronic diseases in the 1970s. From Pincus and Callahan. J Rheumatol 1986;13:841-5[35]; and Pincus, *et al*. Arthritis Rheum 1984;27:864-72[41]; with permission. (B) Survival over 5 years (1985–1990) in 206 patients with RA according to rheumatoid factor, functional status on a Modified Health Assessment Questionnaire (MHAQ), radiographic score, and erythrocyte sedimentation rate. From Callahan, *et al*. Arthritis Care Res 1997[42]; with permission. (C) Significance of 8 variables as predictors of mortality. In a review of 84 reports concerning mortality in RA, 53 cohorts presented predictors of mortality[43]. 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). From Sokka, *et al*. Clin Exp Rheumatol 2008;26 Suppl 51;S35-S61; with permission.

individuals in the general population who had no life-threatening diseases[45].

Possible documentation of control of physical function in RA to achieve a lower level might provide a marker for improved longterm outcomes, including improved survival. This would be analogous to documentation of improved survival based on control of blood pressure in hypertension[3,4], serum glucose in diabetes[5], or serum cholesterol in hyperlipidemia[6]. Reduction of mortality may be regarded as a universal goal of all medical care, usually understood by payers for medical services more easily than any other outcome.

It appears likely that improved physical function would be associated with improved survival, based on pioneering studies of improved mortality outcomes associated with methotrexate treatment by Krause[46] and Choi[47], as well as with biologic agents by Jacobsson[48]. Improvement in physical function scores with these agents is well established. However, it remains to be documented that improvement of HAQ or Multidimensional HAQ (MDHAQ) score in an individual patient will result directly in a significant change in mortality outcomes, analogous to studies in other chronic diseases[23,24].

Another difference between RA and other chronic diseases (in addition to the absence of a gold standard biomarker) is that RA is not associated with acute emergencies and sudden death, as may be seen in hypertension and diabetes. It might therefore be suggested that the absence of possible acute catastrophe in RA might limit support for aggressive treatment, based on control of physical function to improve survival. However, a major activity of contemporary clinical medicine involves treatment, with statins, of apparently normal, usually asymptomatic, individuals who have elevated serum cholesterol. The rationale is almost entirely based on epidemiologic data that control of serum cholesterol is associated with improved survival, rather than based on clinical signs or symptoms[6]; although control of a biomarker is accepted more readily than a patient questionnaire score as an important measure by most physicians (including most rheumatologists).

Patient global estimate and physical function may be assessed easily on HAQ[49] or MDHAQ[50], as 2 of the 7 RA core data set[14] measures. However, quantitative clinical data from a patient history in the form of a patient self-report questionnaire, and even from physical examination in the form of joint counts and physician global estimate, have not been incorporated by most clinical rheumatologists, at least in the United States[51]. Further, most training programs continue to neglect these quantitative clinical measures. Indeed, the only quantitative data in the medical records of most RA patients of most rheumatologists — even today — are laboratory tests, despite their limitations in clinical decision and prognosis. Therefore, current medical records of most rheumatologists could not be used to document improved clinical status for most patients with RA, or even remission; much less to achieve control of the most significant prognostic markers.

Completing the HAQ or MDHAQ creates no extra work for the doctor, nor interference with patient flow, when distributed by the receptionist in a cheerful manner to each patient at each visit and/or completed by patients electronically in the waiting area. An MDHAQ helps the patient prepare for the visit, improves doctor-patient communication, and saves time for the doctor, with a 10–15 second overview of information from a self-report joint count, review of systems, and recent medical history that would otherwise require 10–15 minutes of conversation to elicit[52]. Patient questionnaires do not prevent collection of any additional quantitative data such as joint counts, laboratory tests, or radiographic scores; however, longterm databases concerning RA patients, such as DANBIO[34], are needed to document possible improvements in quality of life according to better control of patient global estimates, and possible improvements in longterm mortality according to better of physical function.

Most rheumatologists may do as much for their patients as other specialists, but rheumatology is underappreciated by the general medical community and the general public; not to mention under-reimbursed. Epidemiologic evidence of improved quality of life and survival after control of the patient global estimate and physical function could facilitate reimbursement by insurance and government payers.

If remission criteria were met by the majority of patients, support for expensive biological therapies in RA might be likely. However, because most people with RA are not in remission, other documentation of the value of treatment is needed. Patient global estimate and physical function are far more informative than laboratory tests, joint counts, radiographs, indices, or remission criteria to recognize improved RA outcomes. Routine collection of these quantitative data on patient questionnaires in the infrastructure of clinical care to document control to achieve more favorable values, rather than simple notation of *gestalt* impressions by the physician, would appear to be an intellectual and ethical responsibility to our patients with RA.

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