Complexities in the quantitative assessment of patients with rheumatic diseases in clinical trials and clinical care

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ABSTRACT

Quantitative measurement has led to major advances in the diagnosis, prognosis and management of chronic diseases. Quantitative measures in rheumatic diseases differ from measures in many chronic diseases in several respects. There is no single "gold standard," such as blood pressure or cholesterol, in the diagnosis, management, and prognosis of any rheumatic disease. Laboratory tests are limited; for example, in rheumatoid arthritis >40% of patients or more have a normal erythrocyte sedimentation rate (ESR). Formal joint counts have poor reliability and are not performed at most visits of most patients. Radiographs are rarely read quantitatively, except in formal clinical trials. The optimal quantitative measures to monitor status and assess long-term prognosis are often derived from patient self-report questionnaires. Quantitative measures may reflect disease activity, e.g., swollen joint counts or C-reactive protein (CRP), long-term damage, e.g., radiographic damage, or poor outcomes, e.g., work disability and premature death. Disease activity measures used in clinical trials are primarily surrogates for long-term outcomes. As there is no single "gold standard" measure, indices of multiple measures are used in patient assessment. Indices used in rheumatoid arthritis assess primarily disease activity, but separate indices have been developed to assess disease activity versus damage in patients with ankylosing spondylitis, systemic lupus erythematosus, and vasculitis.

Introduction

Quantitative measurement has provided major advances in medical care. As noted by Buchanan and Smythe quoting Lord Kelvin, "When you can measure what you are speaking about and express it in numbers, you know something about it; but when you cannot measure it, when you cannot express it in numbers, your knowledge is of a meager and unsatisfactory kind." (1). This quote reflects the advantages of translating qualitative clinical impressions into quantitative measures for diagnosis, prognosis and treatment in any disease.

Measurement in patients with rheumatic diseases differs from measurement in most clinical conditions in several respects:

1. There does not exist a single "gold standard" measure for patient assessment, such as blood pressure or serum cholesterol, which can be used to assess all individual patients in clinical trials, clinical research and clinical care.
2. Objective laboratory tests may be very helpful, but are limited in both diagnosis and treatment. For example, among patients with rheumatoid arthritis, 20-30% do not have a positive test for rheumatoid factor and > 40% have a normal erythrocyte sedimentation rate (ESR) (2,3), while many people with a positive antinuclear antibody (ANA) test or elevated uric acid do not have a disease.
3. Patient questionnaires to assess physical function, pain, fatigue, global status and psychological status are often the optimal quantitative measures to assess and monitor patient status and describe a long-term prognosis (4).
4. Quantitative measures may reflect disease activity, e.g., swollen joint counts, ESR or C-reactive protein (CRP); long-term damage, e.g., radiographic damage; or poor outcomes, e.g., work disability and premature death. Disease activity measures used in clinical trials are only surrogates for long-term outcomes (5).
5. Pooled indices of multiple measures

Table I. Advantages and disadvantages of various types of measures in rheumatic diseases.

Method	Advantages	Disadvantages
Laboratory Tests	Physiologic basis of disease; regarded as best measure to predict control to slow long term damage.	Normal in ≥ 40% of patients, perhaps even more as efforts are made to intervene in early disease. Results often not available to clinician at time of visit to add to clinical decisions.
Radiographs and Imaging	Give permanent record of structural image for comparison over time.	Changes generally require at least 6 months in individuals; hence cannot be used to assess results of acute intervention. MRI scanning generally is too expensive for use, other than in research studies. Ideally damage should be prevented, rather than assessed.
Joint Counts	Assess the primary clinical problem in RA. Results available to clinician at time of visit.	Reproducibility poor in formal studies, although improves with training. This measure is more likely to improve with placebo than other types of measures. Time consuming and tedious
Physical Measures of Functional Status	Can be performed in clinic at time of visit. More reproducible than any other clinical measures in rheumatology care. Do not include issues of language and culture found in patient questionnaires.	Time consuming and tedious
Patient Questionnaires	Patient does most of the work in providing data. Validated questionnaires are available for functional status, pain, fatigue, psychological distress and global status. Reproducible. Available best measure to predict long term outcomes of functional status, work disability and premature death.	Cultural differences in interpretation of data. Some patients have difficulty completing questionnaires questionnaires because of issues of literacy. Motivation. Open to possibility of manipulation by patient, though this is infrequently seen.
Global Measures	Simple and easily completed.	Do not change sufficiently over time to be useful to monitor changes in clinical status.

add considerable power to patient assessment, particularly in the absence of a single "gold standard" measure (6); clinical indices in rheumatoid arthritis are sensitive to changes in disease activity, while separate indices have been developed to assess disease activity versus damage in patients with systemic lupus erythematosus (SLE), vasculitis, and ankylosing spondylitis.

These matters are discussed briefly in this report, and in greater detail in essays in this supplement.

No single "gold standard"

A single "gold standard" for patient assessment, such as blood pressure or serum cholesterol, which can be used to assess all individual patients in clinical trials, clinical research and clinical care, is not available in any rheumatic disease, as noted above. Therefore, different types of measures are used in assessment of patients with rheumatic diseases. Measures used in assessment of rheumatoid arthritis include formal joint counts, radiographic scores, laboratory tests, physical measures of physical function, and patient self-report questionnaire measures of physical function, pain, global status, fatigue, and others. Each of these measures appears effective to document changes of status with treatment in groups of patients, but no single measure can serve as a "gold standard" to document changes in every individual patient.

A brief summary of some of the advantages and disadvantages of each type of measure is presented in Table I. Laboratory tests such as ESR and CRP assess the physiologic basis of disease and traditionally were regarded as the best measure to predict outcomes. However, the ESR is normal in >40% of patients (2,3), as noted above, and results often are not available to the clinician at the time of the visit to affect clinical decisions.

Radiographs (7) and other imaging procedures provide a permanent record of structural damage, and magnetic resonance imaging (MRI) and ultrasonography may indicate inflammatory changes when radiographs are normal (8). However, quantitative scoring methods for radiographs devised by Sharp (9-11), Larsen (12-14), van der Heijde (7,15), and Rau (16) while extensively used in clinical trials and research, are complex and rarely used in clinical care. MRI scanning is generally too expensive for clinical use, and ultrasonography may not be easily available in the U.S. and other locales. Furthermore, radiographic damage ideally should be prevented rather than assessed, i.e., many rheumatologists suggest that patients should be treated aggressively toward a goal of remission prior to any radiographic damage (17-20).

Joint counts (21) assess the primary clinical problem in RA and results are available to the clinician at the time of visit, so a joint count ideally should be assessed at each visit. However, formal joint counts are time-consuming and tedious in clinical practice and reproducibility is poor. Although they are regarded by clinicians as the most impor-

tant measure (22), formal joint counts are generally not performed in the clinical care of most patients in the US and elsewhere.

Physical measures such as grip strength, walk time and button tests (23,24), can be performed at the time of visit and are quite reproducible, and also do not involve issues of language and culture seen with patient questionnaires. However, these measures are time-consuming as well.

Patient questionnaires (25-33) are quite reproducible and the patient does almost all of the work. However, many physicians continue to regard a patient questionnaire as a "subjective" measure, not as useful as an "objective" measure, and there are cultural differences in collection and interpretation of the data. Global measures are easily assessed and correlated significantly with most other measures to be effective representations of patient status. However, traditional global measures, such as Steinbrocker Functional Class (34) do not change sufficiently over time to monitor patients effectively.

Limitations of laboratory tests

Laboratory tests may be quite helpful in diagnosis and management of patients with rheumatic diseases. A positive rheumatoid factor will enable a physician to be more comfortable with the diagnosis of rheumatoid arthritis, as might be the case with identification of HLA-B27 in a patient with ankylosing spondylitis. An ESR or CRP confirms the likelihood of significant inflammation. A positive antinuclear antibody, elevated uric acid or positive Lyme borreliosis titer will help confirm a diagnosis of SLE, gout or Lyme disease. Tests for anti-phospholipid antibody and anti-cytoplasmic antibodies can be diagnostic.

However, laboratory tests in rheumatic diseases have significant limitations, which have not been discussed at great length. In rheumatoid arthritis, 20-30% of patients are negative for rheumatoid factor. Although the presence of rheumatoid factor is associated with a higher likelihood of premature mortality over 5 years in early arthritis (35), in which rheumatoid factor can be a marker for sustained (rather than self-limited) disease, long term work disability and premature mortality differ only marginally in patients who have or do not have rheumatoid factor (36). Rheumatoid factor may be positive in people who have no evidence of rheumatoid arthritis, often in conditions of immunologic stimulation such as hepatitis, tuberculosis or pulmonary fibrosis (37).

The HLA-B27 test is as specific as any laboratory test in rheumatic diseases in the diagnosis of ankylosing spondylitis. Nonetheless, 10% of patients with ankylosing spondylitis are negative for HLA-B27. HLA-B27 is positive in about 7% of the general population (up to 14% in Scandinavia), reducing its possible specificity as a potential “diagnostic test.” Although sophisticated mathematical analyses suggest possible circumstances in which an HLA-B27 can add to the diagnosis (38, 39), the critical diagnostic maneuver for ankylosing spondylitis involves a radiograph showing sacroilitis or more recently an MRI scan which has greater sensitivity (39). It has been calculated that an individual in the population with back pain and a positive HLA-B27 has only a 1 in 3 chance of having ankylosing spondylitis (40).

The problem of “false positive” tests for rheumatoid factor or HLA-B27 is dwarfed by the “false positive” rate for positive antinuclear antibody (ANA). ANA is positive in 100% of patients with lupus (“ANA negative lupus” is described, although some might refer to such patients as having “vasculitis”). However, at least 5% of blood bank specimens of healthy adults are found to have a positive ANA. Since the prevalence of SLE is estimated at 1 in 2,000, and a positive ANA would be seen in 100 in 2,000 individuals, a positive ANA in the general population would indicate a 1 in 100 chance of having SLE. The odds are 20 times greater to have SLE than in patients with a negative ANA, but the ANA is hardly a specific test. Even if one restricted the ANA to patients with musculoskeletal symptoms, which are seen in 15% of the population, a positive ANA would signify only a 1 in 16 risk of SLE (41, 42).

An elevated uric acid is seen most often in people who do not have gout, and an elevated Lyme borreliosis titer is seen in 5% of the population, most of whom do not have Lyme disease. Indeed, in the authors’ experience in the U.S., many if not most people who believe they have diagnosis of SLE, gout or Lyme disease do not have these diseases at all, but rather an incorrect diagnosis based on an inappropriate understanding of a laboratory test.

Further evidence of limitations of laboratory testing in rheumatology may be seen in subsets of antinuclear antibodies, which have been described in inflammatory rheumatic diseases. These autoantibodies, such as anti-SSA (anti-Ro), anti-SSB, anti-LA, anti-Sm, anti-RNP, anti-centromere, may have great value in research settings, but may add minimally to decisions in clinical settings. Published data concerning these tests indicate no specificity for particular syndromes – the differences of probability of 30% versus 70% or even 10% versus 70% remains limited in an individual patient. Although there exists unquestioned value for rheumatology research into the nature and function of these autoantibodies, each of these serologic tests cost more than a visit to a rheumatologist in the US. The rheumatology community might examine critically their use in clinical care.

Patient questionnaires

Since most decisions in clinical rheumatology are made on the basis of clinical phenomena, it is not surprising that patient self-report questionnaires in which data are derived from patients rather than images or laboratory tests, have become more prominent in rheumatology assessment. Anumber of generic, disease-specific, and utilities questionnaires have been used in rheumatology clinical research. The SF-36 (43) is a “generic,” non-disease specific questionnaire, which has been used in patients with many diseases, and can be used to compare the impact of RA on daily life with the impact of other rheumatic and non-rheumatic chronic diseases such as congestive heart failure or lymphoma.

Table II. Measures of activity, damage, function, and long-term outcomes in rheumatoid arthritis.

Type of prognostic or outcome measure	Activity	Damage	Function	Outcomes
Joint count physical examination	Swelling* Tenderness* Pain on motion Limited motion Deformity	Deformity	Pain on motion Limited motion	Joint surgery
Radiographic and imaging data	MRI and ultrasound Evidence of swelling Tissue inflammation	Joint space narrowing Erosion Malalignment		Joint replacement surgery
Laboratory data	Acute phase reactant: (ESR or CRP)* Rheumatoid factor			
Functional measures			Grip strength Walking time Button test	
Questionnaire measures			Functional disability (HAQ) Pain score	Functional disability
Global measures			Physician assessment of global status Patient assessment of global status* ARAFunctional Class Comorbidity Extraarticular disease	Work disability Premature death Costs Comorbidity

Underlined measures are included in the American College of Rheumatology (ACR) Core Data Set (90-92).
*Measures denoted by asterisks are also included in Disease Activity Score (DAS) (93, 94).

Two important questionnaires were published in the April 1980 issue of *Arthritis and Rheumatism* – the Health Assessment Questionnaire (HAQ) (44) and the Arthritis Impact Measurement Scales (AIMS) (45) – which were developed as "arthritis specific" questionnaires. The AIMS has excellent psychometric validity and reliability but is not as easily completed by patients as the HAQ. Although the HAQ was developed for use in patients with rheumatic diseases, it (and other "arthritis specific" questionnaires) appears to be useful and relevant to assess patients with all types of diseases, as well as the in general population (46, 47).

The HAQ (44) includes 20 activities of daily living (ADL) in 8 categories to assess functional disability, with 4 patient response options: "without any difficulty" = 0, "with some difficulty" = 1, "with much difficulty" = 2 and "unable to do" = 3. Several modifications have been developed to provide simplified scoring in routine clinical care and allow the clinician to visualize an ADL score, as well as visual analog scales for pain and global status, on one side of one page. The modified HAQ (MHAQ) (48) included 8 ADL, 1 from the 2 or 3 in the 8 categories of the 20 ADL on the HAQ, and scored simply as the mean of these 8 ADL. Addition of 2 ADL to the 8 included on the MHAQ, as well as 3 psychological items in a HAQ format led to a multidimensional HAQ (MDHAQ) (27, 49, 50). The HAQII questionnaire (26, 51) meets psychometric criteria according to item response theory analyzed in Rasch analysis.

Pain (29) is generally assessed in rheumatic diseases according to a pain visual analog scale, which was developed in rheumatology by Huskisson and colleagues in the late 1970s (52). Fatigue and global status are also measured according to 10 cm VAS. The Western Ontario and McMaster Universities arthritis index (WOMAC) questionnaire (32,53,54) was developed for use in osteoarthritis (OA). The fibromyalgia impact questionnaire (FIQ) (33, 55, 56) was developed for patients with fibromyalgia.

Measures of activity, damage and outcomes in clinical trials and clinical care

Quantitative measures used to assess the status of patients with rheumatic diseases may be classified broadly into four groups: a. measures of disease activity; b. measures of damage to joints and other organs; c. questionnaire, physical, and other measures which are sensitive to both activity and damage; d. long term outcomes (Table II) (57-59). Measures of disease activity, such as joint swelling, are consequences of a dysregulation leading to inappropriate production of cytokines, analogous to elevation of glucose in diabetes and of blood pressure in hypertension. Unchecked disease activity or dysregulation generally leads to long term damage, if no effective therapy is instituted (18, 60).

Measures of damage such as radiographic progression and joint deformity tend to be medically irreversible. Questionnaire and observer-derived measures of physical function, pain and global status reflect both activity and

Table III. Indexes of activity or damage or both used to assess and monitor patients with rheumatic diseases

Disease	Index of activity	Index of damage	Questionnaire or index which assesses both activity and damage
All rheumatic diseases			Health assessment questionnaire (HAQ) (44) Multidimensional HAQ (MDHAQ) (50), HAQII (51)
Rheumatoid arthritis	ACR Core Data Set (90-92) Disease activity score (DAS) (93, 94) Simplified disease activity index (SDAI); clinical DAI (CDAI) (85)	Sharp score (9-11) van der Heijde modified Sharp Score (7, 15) Larsen score (12-14) Rattingen score (16)	"Patient only" indices (115, 116)
Psoriatic arthritis	ACR Core Data Set and Disease Activity Score (DAS) Psoriatic Arthritis Response Criteria (PsARC) (95) Psoriasis Area and Severity Index (PASI) (96)		
Systemic lupus erythematosus	SLE Disease Activity Score (SLEDAI) (97) British Isles Lupus Activity Score (BILAG) (98) Systemic Lupus Activity Measure (SLAM) (99) Lupus Activity Index (LAI) (100) European Consensus Lupus Activity Measurement (ECLAM) (101,102)	SLICC/ACR Damage Index (103)	
Ankylosing spondylitis	Bath Ankylosing Spondylitis Disease Activity index (BASDAI) (104) Modified Stoke Ankylosing Spondylitis Disease Activity Index (mSASSS) (105)	Bath ankylosing spondylitis radiology index (BASRI) (106)	Bath Ankylosing Spondylitis Functional Index (BASFI) (107) Bath Ankylosing Spondylitis Metrology Index (108) Dougados Functional Index (DFI) (109)
Vasculitis	Birmingham Vasculitis Activity Score (BVAS) (57) Vasculitis Activity Index (110)	Birmingham Vasculitis Damage Index (112)	
Wegener's granulomatosis	BVAS-derived Wegener's Granulomatosis Activity Index (111)	Wegener's Granulomasosis Damage Index (113)	
Osteoarthriits			Western Ontario McMaster Osteoarthritis Questionnaire (WOMAC) (53)
Fibromyalgia			Fibromyalgia Impact Questionnaire (FIQ) (56)

damage, as they are affected by both reversible and irreversible phenomena. Self-report of functional status also reflects underlying psychological factors that are not directly a result of disease activity or damage. Nevertheless, patient questionnaires identify and predict the most costly consequence of RA, work disability (61-66), as well as other severe long-term outcomes such as functional declines (67, 68), costs (69), and premature mortality (36,46, 70-73), more effectively than any other measures of activity or damage, including joint counts, radiographs and laboratory tests.

Over the last decade, it has been recognized that measures of inflammatory activity are often improved or unchanged over 5-10 years in groups of patients, while measures of damage indicate disease progression (5, 36, 67, 74-82). For example, joint tenderness, swelling, ESR, hemoglobin, morning stiffness, pain, and MHAQ were unchanged or improved in 100 patients over 5 years, while scores for radiographic damage as well as joint deformity, grip strength and walking time indicated disease progression (36). Therefore, control of inflammatory activity which is not complete may be associated with progression of radiographic destruction.

Indices of disease activity and damage

As noted, many measures used to describe patient status in rheumatic diseases may be of great value in groups of patients, but no single measure performs perfectly in all individual patients. The absence of a gold standard measure has led to combining measures into pooled indices for assessment of patients with rheumatic diseases (Table III). These include indices for assessment of rheumatoid arthritis (83-85), osteoarthritis (32), fibromyalgia (33), SLE (86), ankylosing spondylitis (87), vasculitis (88), and psoriatic arthritis (89), all of which include some type of assessment of functional status.

The most prominent indices in rheumatology are the ACR Core Data Set (90-92) and disease activity score (DAS)

(93,94), used in clinical research rheumatoid arthritis, most notably in clinical trials, although the DAS has gained some utility in clinical practice, particularly in Europe. These indices are discussed at greater length in this supplement in chapters on the ACR Core Data Set including "Patient Only" indices derived from the ACR Core Data Set (83), the disease activity score (DAS) (84), simplified disease activity index (SDAI) and clinical disease activity index (CDAI) (85) derived from the DAS. In rheumatoid arthritis, radiographic scores such as those reported by Sharp (9-11), Larsen (12-14), van der Heijde (7, 15), and Rau (16) may be regarded as indices of damage, but no clinical index of damage is accepted by the rheumatology community at this time. Patient questionnaires generally reflect both disease activity and damage. Indices for psoriatic arthritis activity include the Psoriatic Arthritis Response Criteria (PsARC) (95) and Psoriasis Area and Severity Index (PASI) (96), as well as ACR20 and DAS, borrowed from those for rheumatoid arthritis (89).

Specific indices that reflect primarily either activity and damage have been developed for SLE (86), ankylosing spondylitis (87), and vasculitis (57, 88), recognizing the need to distinguish these two aspects of patient problems. SLE activity indices include the SLE disease activity score (SLEDAI) (97), British Isles lupus activity score (BILAG) (98), systemic lupus activity measure (SLAM) (99), lupus activity index (LAI) (100), and European consensus lupus activity measure (ECLAM) (101, 102); the systemic lupus international collaborating clinics/American College of Rheumatology (SLICC/ACR) Damage Index recognizes damage (103). The Bath ankylosing spondylitis disease activity index (BASDAI) (104) and modified Stoke ankylosing spondylitis disease activity index (mSASSS) (105) asssess activity, while the Bath ankylosing spondylitis radiology index (BASRI) (106) assesses damage; the Bath ankylosing spondylitis Functional index (BASFI) (107), the Bath ankylosing spondylitis Metrology index (108), and the Dougados functional index (DFI) (109) assess both activity and damage. Vasculitis disease activity indices include the Birmingham vasculitis activity score (BVAS) (57), Vasculitis activity Index (110), and BVAS-derived Wegener's Granulomatosis Activity Index (111), while damage indices include the Birmingham Vasculitis damage index (112) and Wegener's Granulomasosis Damage Index (113).

Concluding thought

Most rheumatic diseases are characterized by the absence of a single quantitative measure which can serve as a pathognomonic diagnostic test and to assess and monitor clinical status in individual patients. Therefore, an extensive array of disease-specific quantitative measures and indices of these measures have been developed to quantitate patient status for clinical trials, clinical research and clinical care. However, most of these measures remain research tools, and are not applied to assess and monitor patient status in standard clinical care. From a pragmatic perspective, a simple patient questionnaire such as the MDHAQ (49, 50), which has been found useful in patients with all rheumatic diseases (49, 114), may provide a promising approach to introducing quantitative measurement to standard clinical rheumatology care.

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