Complexities in Assessment of Rheumatoid Arthritis: Absence of a Single Gold Standard Measure

Theodore Pincus, MDa,*, Yusuf Yazici, MDa, Tuulikki Sokka, MD, PhDb

The clinical approach to rheumatic diseases differs considerably from the approach to typical chronic diseases in several important respects (Box 1). Further recognition of these differences may be informative in efforts to advance quantitative scientific patient assessment and management in rheumatic diseases, leading to improved patient outcomes.

ABSENCE OF A GOLD STANDARD IN RHEUMATIC DISEASES

Quantitative assessment and monitoring of typical chronic diseases, such as hypertension, diabetes, and osteoporosis, is characterized by a gold standard measure, such as blood pressure, hemoglobin A1c, and bone density, to provide the primary information for diagnosis, assessment, prognosis, and monitoring for clinical decisions. Tight control according to this gold standard measure has been documented to result in better patient outcomes, including improved survival, largely, in many diseases. A patient history and physical examination are limited and often irrelevant.

KEYWORDS
- Laboratory tests
- Patient questionnaires
- Classification criteria
- Assessment indices
to management decisions, which are based largely, if not entirely, on the gold standard measure.

Rheumatologists have attempted to implement a similar approach to patients with inflammatory rheumatic diseases for more than half a century. The discovery in the 1940s of rheumatoid factor\textsuperscript{1,2} in rheumatoid arthritis (RA), and antinuclear antibodies (ANA)\textsuperscript{3} in systemic lupus erythematosus (SLE), led to hopes that laboratory tests could be used effectively for diagnosis and management of all individuals with RA, SLE, and other rheumatic diseases. Indeed, laboratory tests are included in assessment of virtually every patient suspected of having an inflammatory rheumatic disease by both primary care physicians and rheumatologists. As of 2009, however, no laboratory test or any other quantitative measure can serve as a gold standard for all individual patients with any rheumatic disease.

### SENSITIVITY AND SPECIFICITY OF LABORATORY TESTS IN INFLAMMATORY RHEUMATIC DISEASES

Laboratory tests are abnormal in most patients who have RA or SLE, and are helpful in many patients. More than one third of patients with RA have at presentation, however, a normal erythrocyte sedimentation rate, C-reactive protein, rheumatoid factor, and anti–cyclic citrullinated peptide antibodies (Table 1). More than one third of patients with SLE have normal levels of anti-DNA antibodies, and ANA subset tests anti-Smith (anti-Smith) and antiribonucleoprotein (anti-RNP) (Table 2, Fig. 1). In addition to these false-negative results, ANA subsets indicate relatively little specificity for particular rheumatic diagnoses. For example, among a group of 150 patients with anti-Smith or anti-RNP antibodies, 64% of patients with anti-Smith and 51% of those with anti-RNP had a diagnosis of SLE (see Table 2). The percentages of patients with various other rheumatic and nonrheumatic diagnoses ranged from 1% to 12%, with little specificity (see Table 2).

Information concerning autoantibodies and other biomarkers is invaluable in laboratory research to further characterize the pathogenesis, course, and outcomes of diseases, and to develop new therapies. Anti–tumor necrosis factor and other biologic
agents emerged from efforts to characterize rheumatoid factor alpha (TNFa) and immunologic dysregulation in patients with RA. Furthermore, strong associations of clinical status with variation in biomarkers have been observed in some patients and reported by many rheumatologists, including the senior author. For example, treatment of a patient with SLE nephritis was reported in 1969 to result in a decline in anti-DNA antibodies and erythrocyte sedimentation rate, with a rise in serum

<table>
<thead>
<tr>
<th>Table 2</th>
<th>Diagnoses in 150 patients with antibodies to Sm or RNP</th>
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</thead>
<tbody>
<tr>
<td>Diagnosis</td>
<td>Anti-Sm: 42 Patients N (%)</td>
</tr>
<tr>
<td>Systemic lupus erythematosus</td>
<td>27 (64)</td>
</tr>
<tr>
<td>Cutaneous lupus</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Drug-induced lupus</td>
<td>4 (10)</td>
</tr>
<tr>
<td>Rheumatoid arthritis</td>
<td>4 (10)</td>
</tr>
<tr>
<td>Juvenile arthritis</td>
<td>1 (2)</td>
</tr>
<tr>
<td>Mixed connective tissue disease</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Raynaud disease</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Progressive systemic sclerosis</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Miscellaneous rheumatic disease</td>
<td>1 (2)</td>
</tr>
<tr>
<td>Undifferentiated connective tissue disease</td>
<td>4 (10)</td>
</tr>
<tr>
<td>Miscellaneous nonrheumatic disease</td>
<td>1 (2)</td>
</tr>
</tbody>
</table>

Abbreviations: Anti-CCP, anticyclic citrullinated peptide; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate.


bData from Sokka T, Pincus T. Erythrocyte sedimentation rate, C-reactive protein, or rheumatoid factor are normal at presentation in 35%–45% of patients with rheumatoid arthritis seen between 1980 and 2004: analyses from Finland and the United States. J Rheumatol 2009;36:1387–90.

complement levels and creatinine clearance (Fig. 2). This type of analysis is intellectually satisfying, apparently related to the pathogenesis of disease, and introducing the scientific method into standard rheumatology clinical care.

At the same time, rheumatologists, including the senior author, have conveniently ignored that laboratory biomarkers are not informative in all patients. For example, in the previously mentioned report concerning DNA antibodies, although 50% of SLE patients and no control patient had binding to DNA greater than 50%, 25% of SLE patients were in the normal range of less than 20% binding (see Fig. 1). No biomarker is positive in 100% of patients with any rheumatic disease.

A further complexity in interpretation of laboratory test results in rheumatic diseases involves false-positive results, in which a test is abnormal in people who do not have a disease. Indeed, results of most tests that are regarded as important in the diagnosis of specific rheumatic diseases, such as rheumatoid factor, ANA, HLA B-27, and serum uric acid, are abnormal more frequently in the general population in individuals who do not have the associated disease than those who have this disease, sometimes 100-fold more likely in the case of an ANA. Laboratory tests cannot provide a single gold standard measure for diagnosis, prognosis, monitoring, and outcomes assessment in every individual patient with a rheumatic disease.

DIAGNOSIS, CLASSIFICATION, AND MANAGEMENT OF RHEUMATIC DISEASES

In the absence of a single gold standard measure, the clinical approach to patients with inflammatory rheumatic diseases is guided by patterns of the four types of information used in standard clinical assessment: (1) patient history, (2) physical examination, (3) laboratory tests, and (4) imaging studies. These four types of measures are incorporated into formal classification criteria established to standardize patient enrollment in clinical trials and other clinical research studies for RA, ankylosing spondylitis, rheumatic fever, osteoarthritis, gout, SLE, systemic sclerosis, polymyositis and dermatomyositis, Sjögren syndrome, vasculitis, etc.
Behçet disease,24 and antiphospholipid syndrome.25 American College of Rheumatology (ACR) 1987 classification criteria for RA12 include seven features (Table 3):

- Morning stiffness
- Arthritis of three or more joint areas
- Arthritis of hand joints
- Symmetric arthritis
- Rheumatoid nodules
- Serum rheumatoid factor
- Radiographic changes

A patient is considered to have RA if four of these seven criteria are met over at least six weeks. New criteria were presented at the 2009 ACR meeting, and may have been published by the time this article is published.

The tetrad of patient symptoms, physical examination, laboratory tests, and imaging studies also is recognized in formal indices to describe clinical status in RA,26–31 SLE,32–39 vasculitis,40–45 psoriatic arthritis,46–48 ankylosing spondylitis,49–53 and other rheumatic diseases. Indices for RA are based on a Core Data Set54 of seven measures (Table 4): three from a physician (swollen joint count, tender joint count, physician global estimate of status); one laboratory test of an acute-phase reactant (erythrocyte sedimentation rate or C-reactive protein); and three from a patient self-report questionnaire (physical function, pain, and patient global estimate of status).

The most widely used index, the disease activity score 28 (DAS28),26,27 includes measures from physical examination, laboratory, and patient self-report (see Table 4). The clinical disease activity index (CDAI)28 (see Table 4) includes a physician global estimate in lieu of a laboratory test. Routine assessment of patient index data 3 (RAPID3)30,31 (see Table 4) excludes both laboratory tests, on the basis of frequently normal values and unavailability, and a formal joint count, on the basis of many limitations55 (see “Joint Counts to Assess Rheumatoid Arthritis” by Sokka T, Pincus T, in...

**Fig. 2.** Treatment of a patient with SLE nephritis results in a decline in anti-DNA antibodies, rise in serum complement levels, decline in the erythrocyte sedimentation rate (ESR), and rise in creatinine clearance. (From Pincus T, Schur PH, Rose JA, et al. Measurement of serum DNA-binding activity in systemic lupus erythematosus. N Engl J Med 1969;281:701–5; with permission.)
PATIENT HISTORY IN MANAGEMENT DECISIONS IN RHEUMATIC DISEASES

In most diseases a patient history and symptoms are regarded as “subjective,” “unscientific” information, the primary purpose of which generally is to identify an “objective” gold standard “scientific” measure, which provides the primary information to diagnose, assess, monitor, and guide clinical decisions. By contrast, in rheumatic diseases, information from a patient history is considerably more prominent in management decisions compared with typical chronic diseases.

Table 3
ACR Core Data Seta and ACR classification criteria for RA b

<table>
<thead>
<tr>
<th>Measures in Four Categories</th>
<th>ACR Core Data Set</th>
<th>ACR Classification Criteria</th>
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<tbody>
<tr>
<td>Physical history</td>
<td></td>
<td></td>
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<tr>
<td>Physical function</td>
<td>✓</td>
<td></td>
</tr>
<tr>
<td>Pain</td>
<td>✓</td>
<td></td>
</tr>
<tr>
<td>Global estimate</td>
<td>✓</td>
<td></td>
</tr>
<tr>
<td>Morning stiffness</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Physical Examination</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Formal count of swollen joints</td>
<td>✓</td>
<td></td>
</tr>
<tr>
<td>Formal count of tender joints</td>
<td>✓</td>
<td></td>
</tr>
<tr>
<td>MD/assessor global</td>
<td>✓</td>
<td></td>
</tr>
<tr>
<td>Arthritis of three or more joint areas</td>
<td>✓</td>
<td></td>
</tr>
<tr>
<td>Arthritis of hand joints</td>
<td>✓</td>
<td></td>
</tr>
<tr>
<td>Symmetric arthritis</td>
<td>✓</td>
<td></td>
</tr>
<tr>
<td>Rheumatoid nodules</td>
<td>✓</td>
<td></td>
</tr>
<tr>
<td>Laboratory tests</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Serum rheumatoid factor</td>
<td>✓</td>
<td></td>
</tr>
<tr>
<td>ESR or CRP</td>
<td>✓</td>
<td></td>
</tr>
<tr>
<td>Imaging studies</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Radiograph</td>
<td></td>
<td>If more than 1 year</td>
</tr>
</tbody>
</table>

A patient is considered to have RA if four of the seven classification criteria are met.

**Abbreviations:** ACR, American College of Rheumatology; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; RA, rheumatoid arthritis.


A patient history can be captured as standardized, “scientific” quantitative data, according to validated self-report questionnaires (see “Patient Questionnaires Rheumatoid Arthritis” by Pincus and colleagues, in this issue). Patient questionnaires may be used effectively to guide management, document change in status, assess outcomes, and improve the quality of care, as discussed further in this issue (see “How to Collect an MDHAQ” by Pincus and colleagues; “Flowsheets that include MDHAQ” by Pincus and colleagues). Inclusion of a patient questionnaire at every visit of every patient may be used to record information that has a substantial impact on patient management as quantitative scientific data.

**DIAGNOSIS BASED ON A PHYSICIAN’S JUDGMENT**

A final important difference between rheumatic diseases and typical chronic diseases is that rheumatic disease diagnoses are based on the judgment of an individual physician, rather than a pathognomonic marker from a physical examination, laboratory test, biopsy, imaging study, or other measure, as is the case in most typical chronic diseases. For example, in compiling information concerning the prevalence of various autoantibodies in patients with RA, SLE, and other rheumatic diseases (see Tables 1 and 2; see Fig. 1), the closest thing to a “gold standard” an assignment is the designation of a diagnosis by a physician.

These differences in quantitative assessment of rheumatic diseases compared with typical chronic diseases underlie the complexity of diagnosis, management, prognosis, and documentation of outcomes, as discussed in greater detail in subsequent articles in this issue.

**REFERENCES**

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