A RheuMetric physician checklist to quantitate levels of inflammation, damage and distress on 0–10 visual analogue scales

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Competing interests: T. Pincus is president of Medical History Services, LLC, which receives royalties and license fees for a copyright and trademark for MDHAQ and RAPID3. All revenue supports further development of quantitative questionnaire measurement for patients and doctors in clinical care. Dr Pincus is also a consultant for Abbie, Lilly and Pfizer. J.R. Chua and I. Castrejon have declared no competing interests.

ABSTRACT

A physician global assessment of patient status (DOCGL) was designed initially to quantitate inflammatory activity in rheumatoid arthritis (RA) clinical trials, in which patients are selected for high levels of activity. However, in patients seen in routine care with various diagnoses, and even in some RA patients selected for clinical trials, DOCGL also may be affected by joint damage and/ or patient distress. To clarify DOCGL on a 0-10 visual analogue scale (VAS), 3 additional 0-10 VAS have been developed to record physician estimates of inflammation (DOCINF), damage (DOCDAM), and distress (DOCSTR) (such as fibromyalgia (FM)/depression). Results from 3 locales for these 4 VASs are summarised, including 478 initial-visit patients from Tennessee in 1996 to 2007, 197 initial-visit patients from Pennsylvania in 2008 to 2012, and a random visit of 739 patients from Illinois in 2014 to 2015. Highest DOCGL estimates were seen at the 3 sites in FM, followed by RA and osteoarthritis (OA), spondyloarthropathies (SpA), gout, and systemic lupus erythematosus (SLE). Highest DOCINF (inflammation) estimates were seen in RA and SpA, followed by gout, SLE, FM, and OA. Highest DOCDAM (damage) estimates were in OA, followed by RA, SpA, gout, SLE and FM. Highest DOCSTR (distress) estimates were in FM, followed by OA, RA, SpA, SLE, and gout. In the 2 earlier series, DOCDAM was considerably higher than DOCINF only in OA, and lower in the other diagnoses, although within 50% of DOCINF. In more recent patients from Illinois, mean DOCDAM was higher than DOCINF in all 6 diagnoses. The 0-10 physician VASs depict the expertise of a rheumatologist to distinguish between inflammation, damage and distress in an individual patient and rate levels as quantitative data beyond narrative descriptions. These VASs appear informative for rheumatology care, documentation, and research.

Rheumatic symptoms result broadly from one of three underlying aetiologies: inflammatory activity, e.g., rheumatoid arthritis (RA); organ damage, e.g., osteoarthritis (OA); or distress (in which neither inflammation nor organ damage can be identified to explain symptoms), e.g., fibromyalgia (FM). Most quantitative clinical measures used by rheumatologists are designed and thought to assess levels of inflammatory activity, reflecting that control of inflammation has been emphasised as the primary goal of rheumatology care. For example, the 7 core data measures for RA - swollen joint count, tender joint count, physician global assessment, physical function, pain, patient global assessment, and erythrocyte sedimentation rate (ESR) or Creactive protein (CRP) (1, 2), and indices such as the disease activity score 28 (DAS28) (3) and clinical disease activity index (CDAI) (4), are regarded as measures of inflammatory activity and advocated for treat-to-target in routine clinical care (5).

In clinical trials, for which patients are selected for high levels of inflammatory activity, the RA core data set measures, DAS28 and CDAI, meet the goal of assessing inflammation quite effectively (6). In patients seen in routine rheumatology care, who are not selected for inflammatory activity, RA Core Data Set measures may be considerably more sensitive to organ damage or irreversible symptoms, and/ or distress (e.g., fibromyalgia, depression, etc.) in which patients may have high levels of pain, functional disability, and other symptoms not explained by reversible or irreversible symptoms, signs or laboratory values. Even some

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patients who meet inclusion criteria for inflammatory activity in clinical trials may also have damage and/or distress contributing to poor global status (7, 8). One report indicated that joint damage and patient distress accounted for many instances of non-implementation of treat-to-target in routine care (9).

Among the 7 RA Core Data Set measures, physician global assessment (DOCGL) is most often the most efficient of all 7 to distinguish active from control treatments in RA clinical trials of adalimumab (10), abatacept (11), certolizumab (12), infliximab (6), and rituximab (13), although the relative efficiencies of the 7 measures vary among different trials, supporting the rationale for a Core Data Set of seven measures (6). [The abbreviation "DOCGL" rather than "PGA" or "PhGA" is used to avoid confusion as "PGA" appears in the rheumatology literature to represent either (or both) patient and physician estimates of disease activity in different reports. "MDGL" is not used as some rheumatologists may have other degrees, such as DO (doctor of osteopathy).]

The high relative efficiency of DOCGL to distinguish active from control treatments may appear unexpected, in part as fewer instructions and criteria for completion of this measure are available than for any of the other 6 Core Data Set measures. Indeed, different physicians may approach assessment of possible damage and/or distress differently in assigning DOCGL. Some physicians restrict DOCGL estimates to the level of inflammation, ignoring possible organ damage and/or patient distress. Other physicians may incorporate damage and distress into their DOCGL estimates, in addition to inflammation (14, 15). This matter complicates interpretation of DOCGL in routine clinical care, and possibly in clinical trials, affecting a treat-to-target strategy in RA (9) and other goals of treatment in many rheumatic diseases.

These considerations have led to development of a RheuMetric (formerly called RHEUMDOC, but name changed to avoid possible confusion with an electronic medical record of the same name) checklist to record quantitative physician estimates beyond

PHYSICIAN GLOBAL ASSE	SSMENT (DOCGL) at this visit:	
EXCELLENT	0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0	VERY POOR
DISEASE ACTIVITY, DAMA Degree of inflammation or	GE and DISTRESS: reversible disease (DOCINF) <u>at this visit</u> :	
NONE	000000000000000000000000000000000000000	MOST SEVERE
Degree of joint or organ st	tructural damage or irreversible disease (DOCDAM) at this v	<u>visit</u> :
NONE	000000000000000000000000000000000000000	MOST SEVERE
Degree of distress (symptot	oms due to neither inflammation nor damage, e.g. fibromya	Igia)(DOCDIS) at this visit
NONE	000000000000000000000000000000000000000	MOST SEVERE

Fig. 1. RheuMetric physician checklist for 4 physician estimates of overall global status (DOCGL), inflammation (DOCINF), damage (DOCDAM), and Distress (DOCSTR) (formerely DOCDIS).

DOCGL (14, 15). RheuMetric (Fig. 1) includes a 0–10 visual analogue scale (VAS) DOCGL estimate, supplemented by 3 separate physician (0–10) VAS subscales for inflammation or reversible findings (DOCINF), damage or irreversible findings (DOCDAM), and distress (DOCSTR) (previously termed DOCNON or DOCDIS) (15). The RheuMetric checklist is completed in 15–20 seconds by the treating rheumatologist.

This report summarises data from published reports which present RheuMetric estimates for DOCGL, DOCINF, DOCDAM, and DOCSTR, in patients with various rheumatic diagnoses, including RA, OA, FM, systemic lupus erythematosus (SLE), spondyloarthropathies (SpA), and gout. The data reviewed from previous reports of data from the initial visit of 478 new patients seen by Dr Pincus in Nashville, TN between 1996 and 2007 (15), the initial visit of 197 new patients seen by Dr Bergman in Ridley Park, a suburb of Philadelphia, PA between 2008 and 2012 (15, 16), and a random (rather than initial) visit of 739 patients seen by 7 rheumatologists in Chicago, IL in 2014 and 2015, updating a previous report of 205 patients (17).

Patients from Nashville, TN at initial visit between 1996 and 2007

In a report of RheuMetric estimates from an initial visit of 478 new patients seen in Nashville, TN between 1996 and 2007 (Table I) (17), mean DOCGL was 6.3 in patients with four different diagnoses, including 174 with RA, 32 with OA, 196 with FM, 30 with spondyloarthropathies (SpA), and 5.0 in both SLE and gout. Mean DOCINF was highest in SpA, *i.e.*, 7.7, second highest in RA, *i.e.*, 7.0, and lowest in FM, *i.e.*, 2.3. Mean DOCDAM was highest in OA, *i.e.*, 6.0, but 5.0 in RA, and 4.3 in SpA, lowest in FM, *i.e.*, 1.7. Mean DOCSTR was highest in FM, *i.e.*, 9.0, 6.3 in SLE, 4.0 in RA, 3.7 in OA, and lowest, *i.e.*, 2.3 in gout (Table I).

It was of interest that mean DOCGL was identical (6.3) in RA, SpA, OA, and FM, but highest mean DOCINF was seen in SpA (7.7) and RA (7.0), highest DOCDAM in OA (6.0), and highest DOCSTR in FM (9.0). Furthermore, although the mean DOCINF was 7.7 in SpA and 7.0 in RA, DOCDAM estimates were 4.3 in SpA and 5.0, in RA, but at least 50% of the DOCINF value, and 7.0 for DOCDAM in OA.

Patients from Philadelphia (Ridley Park), PA at initial visit between 2008 and 2012

In a report of estimates from the initial visit of 197 new patients seen in Philadelphia (Ridley Park), PA between 2008 and 2012, (Table II) (17), median (rather than mean) DOCGL was 3.90 in 48 patients with RA, 3.28 in 67 with OA, 4.53 in 15 with FM, 2.23 in 13 with SLE, 3.61 in 23 with SpA, and 2.36 in 31 with gout. Median DOCINF was highest in SpA and RA, *i.e.*, 4.35, and lowest in OA, *i.e.*, 0.79. Median DOCDAM was highest in OA, *i.e.*, 3.56, but 2.18 in RA, 1.65 in FM

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Table I. Mean physician VAS estimates in 478 new patients seen by Dr Pincus in Nashville between 1996 and 2007 in 6 diagnostic categories: rheumatoid arthritis, osteoarthritis, fibro-myalgia, systemic lupus erythematosus, spondyloarthropathy, and gout.

Diagnosis	Physician Global Estimate (PATGL) (0-10)	Inflammation (DOCINF) (0-10)	Damage (DOCDAM) (0-10)	Distress (DOCSTR) (0-10)
Rheumatoid arthritis, n=174	6.3	7.0	5.0	4.0
Osteoarthritis, n=32	6.3	3.3	6.0	3.7
Fibromyalgia, n=196	6.3	2.3	1.7	9.0
Systemic lupus erythematosus, n=3-	4 5.0	3.6	2.3	6.3
Spondyloarthropathies, n=30	6.3	7.7	4.3	4.0
Gout, n=12	5.0	6.0	3.0	2.3

Table II. Median physician VAS estimates and interquartile ranges in 197 new patients seen by Dr Bergman in Philadelphia PA, between 200 and 2012 in 6 diagnostic categories: rheumatoid arthritis, osteoarthritis, fibromyalgia, systemic lupus erythematosus, spondyloarthropathy, and gout.

Diagnosis	Physician Global Estimate (PATGL) (0-10)	Inflammation (DOCINF) (0-10)	Damage (DOCDAM) (0-10)	Distress (DOCSTR) (0-10)
Rheumatoid arthritis, n=48	3.90 (0-8)	4.35 (0-10)	2.18 (0-10)	0.91 (0-10)
Osteoarthritis, n=67	3.28 (0-8)	0.79 (0-6.6)	3.56 (0-10)	0.97 (0-10)
Fibromyalgia, n=15	4.53 (2-8)	0.94 (0-6.6)	1.65 (0-6.6)	6.13 (0-10)
Systemic lupus erythematosus, n=13	2.23 (0-4)	2.28 (0-6.6)	0.76 (0-6.6)	1.02 (0-3.3)
Spondyloarthropathies, n=23	3.61 (1-9)	4.35 (0-10)	1.65 (0-6.6)	1.35 (0-6.6)
Gout, n=31	2.36 (0-6)	2.64 (0-10)	0.44 (0-3.3)	0.77 (0-10)

Table III. Mean (SD) RheuMetric Physician physician VAS estimates and standard deviation in one random visit of 739 patients with different rheumatic diseases seen at Rush University Medical Center seen by 7 rheumatologists in Chicago, IL, between 2014 and 2015, in 6 diagnostic categories: rheumatoid arthritis, osteoarthritis, fibromyalgia, systemic lupus erythematosus, spondyloarthropathy, and gout.

Diagnosis	Physician Global Estimate (PATGL) (0-10)	Inflammation (DOCINF) (0-10)	Damage (DOCDAM) (0-10)	Distress (DOCSTR) (0-10)
Rheumatoid arthritis, n=193	3.8 (2.2)	2.3 (2.3)	3.0 (2.2)	2.0 (2.0)
Osteoarthritis, n=204	3.9 (1.8)	0.9 (1.3)	4.0 (1.8)	1.7 (2.7)
Fibromyalgia, n=125	5.1 (1.6)	0.7 (1.1)	1.8 (1.9)	5.7 (2.3)
Systemic lupus erythematosus, n=120	2.8 (1.9)	1.7 (1.6)	1.9 (1.8	1.3 (2.4)
Spondyloarthropathies and psoriation arthritis, n=44		2.3 (2.0)	2.4 (2.0)	1.2 (2.0)
Gout, n=53	2.9 (2.4)	1.7 (2.2)	2.1 (1.9)	0.5 (1.3)

and SpA and lowest in gout, *i.e.*, 0.44. Median DOCSTR was highest in FM, *i.e.*, 6.13, 1.35 in SpA, 1.02 in SLE, and lowest, *i.e.*, 0.7 in gout (Table II).

The patterns were similar to those seen in Nashville, although many VAS estimates were 1–3 units higher in Nashville *versus* Philadelphia (Ridley Park), albeit comparing mean to median values. These differences may reflect in part an older patient population with longer duration of disease in Nashville, greater disease severity at an earlier period, a tendency for one rheumatologist to rate patients as more severe than another, as well as other possible explanations.

A random visit of 739 patients from Chicago, IL 2014–2105

An updated analysis of a previous compilation of 205 patients from Rush University rheumatology clinic in Chicago, IL (17) includes RheuMetric VAS estimates in 739 patients seen over the same period (Table III). This database differs from the two previously-described databases, in that ratings were made by 8 rheumatologists, rather than a single rheumatologist, and the data were estimated at a random, rather than an initial visit. The mean (not median) DOCGL was 3.8 in 193 patients with RA, 3.9 in 204 with OA, 5.1 in 125 with FM, 2.8 in 120 with SLE, 3.4 in 44 with SpA, and 2.9 in 53 with gout (Table III). Mean DOCINF was highest in RA, *i.e.*, 2.4, and lowest in FM, *i.e.*, 0.8. Mean DOCDAM was highest in OA, *i.e.*, 4.0, but 3.0 in RA, 2.4 in SpA, 2.1 in gout, 1.9 in SLE, and 1.8 in FM. Mean DOCSTR was highest in FM, *i.e.*, 5.7, 2.0 in RA, 1.7 in OA, 1.3 in SLE, 1.2 in SpA and 0.5 in gout (Table III).

Most of the 24 estimates (4 VASs in patients with 6 diagnoses) were within 1 unit of those from Philadelphia (Ridley Park) in Table II, other than 4/24 comparisons, albeit again comparing mean and median values. Two involved DOCINF both RA and SpA as 4.35 in Philadelphia 2008-2012 versus 2.3 in Chicago in 2014–1015, a difference of 2.05 units. These differences may reflect that data from Philadelphia were median values at an initial visit, versus mean values at a random visit in Chicago, and that therapy in these prototypic inflammatory diseases had advanced over 6-7 years. Also, DOCSTR in RA was lower in Philadelphia versus Chicago, 1.1 units in RA and 1.7 units in OA, perhaps reflecting a trend to recognise FM over time. Nonetheless, the overall similarity of median and mean VAS estimates in the two analyses suggest considerable face validity for the VAS estimates.

A striking finding in the Chicago data was that VAS estimates for damage were higher than for inflammation in patients with all diagnoses (Table III). Again, these data are from a random visit and many of the patients had good control of the inflammatory activity of their disease. Nonetheless, the data suggest that clinical decisions in "inflammatory" diseases such as RA, SpA, and SLE appear to be based as much on findings reflecting damage as inflammation at this time, at least at one site. Although estimates at the TN site were generally 2-3 units higher than the other sites, in ranking the 6 diagnoses from highest to lowest estimates (24 comparisons), no ranks differed by more than 3: 10 were identical, e.g., highest DOCGL for FM, lowest for SLE, highest DOCINF for SpA (tied with RA at 2 sites), highest DOCDAM in OA followed by RA, and highest DOCSTR in FM, lowest in gout), within 1 rank in 4, 2 ranks in 6, and 3 ranks in 4.

Discussion

Information from a medical history and physical examination are far more prominent in diagnosis and management decisions in RA than laboratory tests or ancillary studies, in contrast to 7 other prevalent chronic diseases, including hypertension, diabetes, hyperlipidaemia, ulcerative colitis, pulmonary fibrosis, lymphoma, and congestive heart failure (18). A "gold standard" biomarker such as glucose in diabetes or blood pressure in hypertension, cannot be applied to every patient in diagnosis and management of RA (or any rheumatic disease) (19). Of course, many rheumatology biomarkers such as rheumatoid factor and anti-cyclic citrullinated protein antibodies (ACPA) in RA, DNA antibodies in SLE, and many others are recognised, but they are found in about 70% (not 100%) of patients (20). ESR and CRP are normal at presentation in 40% or more of RA patients (21). Therefore, although these biomarkers have provided important clues to pathogenesis and development of new treatments such as biological agents, and may be helpful in diagnosis, they are negative or normal in a sizeable minority of patients who are clinically largely indistinguishable from patients who meet other criteria for a diagnosis. Since diagnosis and management depend primarily on the patient history and physical examination, an effort appears appropriate to have information from these sources meet more rigorous scientific criteria beyond narrative descriptions as quantitative, standard measures (22). Quantitative measures have provided many advances in clinical medicine, most of which are from a laboratory or other high technology source, based on the scientific method of a standard protocol to assess reproducible quantitative data. A self-report questionnaire provides quantitative, standard measures from a patient history, and meets criteria for the "scientific method." Similarly, a RheuMetric checklist may be viewed as providing quantitative, standard data from a

physical examination and overall impressions of a physician, to meet criteria of the "scientific method."

The data from Nashville and Philadelphia were estimated at an initial visit, and indicate that DOCINF estimates in patients with RA, SpA, SLE, and gout were higher than DOCDAM estimates, as might be anticipated, although a higher level of damage was seen than might be expected. The data from Chicago are from a random visit, and suggest that DOCDAM is higher than DOCINF in patients with these inflammatory conditions. Regardless, on a day-to-day basis, it appears that rheumatologists must address damage in clinical decisions in patients with inflammatory diseases at a level at least comparable to inflammation, which is not necessarily articulated, such as in treat-to-target directives (5, 9, 23).

As noted, most quantitative clinical measures used by rheumatologists are designed and thought to assess levels of inflammatory activity. Some measures to assess damage have been developed, such as the Vasculitis Damage Index (24) and the Systemic Lupus International Collabor807ating Clinics/American College of Rheumatology (SLICC/ACR) Damage Index for Systemic Lupus Erythematosus International Comparison (25), both scored by the physician, and Western Ontario McMaster Osteoarthritis Scale (WOMAC) (26), a self-report questionnaire developed for OA (although it may be informative in RA). Many patient questionnaires are available to assess patient distress, such as the fibromyalgia impact questionnaire (FIQ) (27) and polysomatic widespread pain questionnaire (28). However, these measures are used almost exclusively in research studies or specialised clinics rather than in routine rheumatology care. Measures and indices used in routine care, such as DAS28 (3) and CDAI (4), are designated "activity" measures, as advocated for treat-to-target in RA for routine clinical care (5).

Several important limitations are seen to the studies presented. Two are from an initial visit and the third from a random visit. The data do not consider age, duration of disease, socioeconomic

status, treatment, laboratory tests, comorbidities, and other variables which may affect physician VAS ratings. No analyses are presented concerning inter-rater reliability of the physician ratings. All the data are cross-sectional and possible changes over time would be of interest. One study, from the same site in Philadelphia (Ridley Park) as in this study, indicated that patient scores, including patient global assessment, improved by about 25-35% in RA, SpA and SLE, but only about 10-20% in OA (16), perhaps explaining in part why physician VAS damage estimates were higher than VAS inflammation estimates at a random visit.

Nonetheless, the data illustrate an approach to quantitative recognition of the extent to which a physician global assessment may reflect inflammation, damage, or distress. The expertise of a rheumatologist is not only to recognise the severity of symptoms and signs, but also (perhaps primarily) to interpret whether symptoms and signs are explained by inflammation, damage, or distress, or two or three of these components.

Our findings suggest that many patients with "inflammatory" rheumatic diseases have clinically important levels of damage and/or distress, in addition to signs of inflammation, which may be lesser than damage in many patients. The observation that some patients may have clinically important inflammation, damage, and/or distress indicates complexity in management of many patients seen in rheumatology care not seen in management of diseases characterised by a "gold standard" biomarker such as hypertension and diabetes. Recording this information quantitatively may help clarify clinical decisions to doctors, patients, and payers.

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