Quality of Life and Disability in Patients with Treatment-Failure Gout

MICHAEL A. BECKER, H. RALPH SCHUMACHER, KATY L. BENJAMIN, PETER GOREVIC, MARIA GREENWALD, JEFFREY FESSEL, LAWRENCE EDWARDS, ARIANE K. KAWATA, LORI FRANK, ROYCE WALTRIP, ALLAN MAROLI, BILL HUANG, The Gout Natural History Study Group, and JOHN S. SUNDY

ABSTRACT. ***Objective.*** The relationship between self-reported quality of life and disability and disease severity was evaluated in subjects with treatment-failure gout (n = 110) in a prospective, 52-week, observational study.

Methods. Subjects had symptomatic crystal-proven gout of at least 2 years' duration and intolerance or refractoriness to conventional urate-lowering therapy. Serum uric acid (sUA) concentration, swollen and tender joint counts, frequency and severity of gout flares, tophus assessments, comorbidities, and patient-reported outcomes data [Medical Outcomes Study Short Form-36 (SF-36), Health Assessment Questionnaire-Damage Index] were collected. Analyses included correlations of patient-reported outcomes with clinical variables and changes in clinical status.

Results. Mean age of study subjects was 59 years. Mean scores on SF-36 physical functioning subscales were 34.2–46.8, analogous to persons aged ≥ 75 years in the general population. Subjects with more severe gout at baseline had worse health-related quality of life (HRQOL) in all areas ($p < 0.02$ for all measures), compared to patients with mild-moderate disease. Number of flares reported in past year, number of tender joints, swollen joints, and tophi correlated significantly with some or all HRQOL and disability measures. sUA was not significantly correlated with any HRQOL or disability measure. Subjects with comorbidities experienced worse physical, but not mental, functioning.

Conclusion. Severe gout is associated with poor HRQOL and disability, especially for patients who experience more gout flares and have a greater number of involved joints. Subject perceptions of gout-related functioning and pain severity appear to be highly sensitive indicators of HRQOL and disability. (J Rheumatol First Releaase April 1 2009; doi:10.3899/jrheum.071229)

Key Indexing Terms:
GOUT QUALITY OF LIFE HEALTH-RELATED QUALITY OF LIFE
PATIENT-REPORTED OUTCOMES DISABILITY

From the Division of Biological Sciences, Rheumatology Section, University of Chicago, Chicago, IL; Rheumatology Division, University of Pennsylvania School of Medicine, Philadelphia, PA; United BioSource Corporation, Bethesda, MD; Division of Rheumatology, Mount Sinai School of Medicine, New York, NY; Desert Medical Advances, Palm Desert, CA; Kaiser Permanente Medical Group, San Francisco, CA; Rheumatology and Clinical Immunology, University of Florida, Gainesville, FL; Savient Pharmaceuticals, East Brunswick, NJ; and Duke University Medical Center, Durham, NC, USA.

Supported by Savient Pharmaceuticals, Inc.

M.A. Becker, MD, Division of Biological Sciences, Rheumatology Section, University of Chicago; H.R. Schumacher, MD, Rheumatology Division, University of Pennsylvania School of Medicine; K.L. Benjamin, MSW, SM, PhD, United BioSource Corporation; P. Gorevic, MD, Division of Rheumatology, Mount Sinai School of Medicine; M. Greenwald, MD, Desert Medical Advances; J. Fessel, MD, Kaiser Permanente Medical Group; L. Edwards, MD, Rheumatology and Clinical Immunology, University of Florida; A.K. Kawata, PhD; L. Frank, PhD, United BioSource Corporation; R. Waltrip, MD; A. Maroli, PhD; B. Huang, PhD, Savient Pharmaceuticals; J.S. Sundy, MD, PhD, Duke University Medical Center.

Address reprint requests to Dr. J. Sundy, Duke University Medical Center 3278, Room 7066, North Pavilion Building, Durham, NC 27710. E-mail: sundy001@mc.duke.edu

Accepted for publication October 27, 2008.

Gout is estimated to affect 3 to 6 million persons in the United States. Worldwide, gout is one of the most prevalent rheumatic conditions and it is the most common inflammatory arthritis in men[1]. Hyperuricemia or serum urate (sUA) concentration exceeding the solubility of urate in extracellular fluids (6.8 mg/dl) is a cardinal pathogenetic factor in gout[2]. Management of recurrent or progressive gout aims at reducing and maintaining sUA in a subsaturating range, usually < 6.0 mg/dl, a goal frequently requiring a urate-lowering agent, such as allopurinol or probenecid. Longterm maintenance of sUA in this range demonstrably reduces the frequency of gout flares and the size and number of tophi[3].

Progression of gout to a chronic deforming and/or disabling disease is often a consequence of treatment refractoriness or treatment failure, such as may occur among patients intolerant of currently available urate-lowering agents or with medical comorbidities limiting the extent of their use; patients who do not or cannot adhere to prescribed urate-lowering therapy (ULT), or receive inadequate ULT; or organ transplant recipients whose therapy to prevent graft

rejection promotes hyperuricemia and limits the safety of urate-lowering agents. Elderly persons, especially women, are also at high risk for chronic progressive gout because the diagnosis is often not considered until late in the course of the disease[4]. A patient is considered to have treatment-failure gout when the disease is active and uric acid cannot be controlled by conventional urate-lowering agents either because of allergy or because the patient's medically maximally tolerated dosage is insufficiently effective. The renal compromise that is frequently seen late in uncontrolled gout is a common dose-limiting factor undermining effective ULT[5].

To date, there has been no evaluation of the health-related quality of life (HROQL) or disability of patients with treatment-failure gout. In part, the paucity of data in this area may be explained by the high frequency of comorbidities among gout patients, particularly cardiovascular and chronic kidney diseases and the components of the metabolic syndrome. In the face of other significant disorders, it is often difficult to attribute disability or diminished lifestyle to gout. However, severe chronic gout may have a major influence on patient health-related quality of life due to the frequency and severity of episodes, the recurrent pain, and the disfigurement associated with this condition. These symptoms may affect the patient's emotional and social as well as physical functioning, and result in significant disability. Factors that contribute to overall HRQOL can include not only those directly related to gout symptoms, but also those related to disease complications and adverse effects of gout treatment.

Our objectives, therefore, were to assess quality of life and disability in a group of subjects with treatment-failure gout and to evaluate the relationship between patient perceptions of their quality of life and disability and gout severity or manifestations over time. The analyses conducted for this study were intended to be exploratory, in order to determine how treatment-failure gout affects patient functioning, and to identify specific factors that may be used to assess efficacy of treatment for these patients in future clinical studies.

MATERIALS AND METHODS

Study design. Subjects were evaluated in a multicenter prospective observational study conducted at academic and private rheumatology practices in the United States. Symptomatic gout was defined by any of the following characteristics: multiple (> 3 per year), recurrent self-reported flares; chronic synovitis or arthropathy; presence of tophi (confirmed by examination or the presence of typical erosions on radiograph); or uric acid nephrolithiasis or nephropathy. All eligible subjects were aged 18 years or older and had treatment-failure gout, as defined by the following criteria: (1) symptomatic crystal-proven gout of at least 2 years' duration; and (2) intolerance or refractoriness to conventional ULT, indicated by sUA > 6.0 mg/dl[6,7]. Study entry also required confirmation of the diagnosis of gout by demonstration of monosodium urate crystals by polarized light microscopy of joint or tophus aspirates prior to or at the time of enrollment; subjects were to be evaluated every 2 months over the course of 1 year from enrollment. Between followup visits, subjects completed and returned gout symptom diaries, which were reviewed by the investigators at the succeeding visit.

Measures. A physical examination was performed at each visit, and subjects completed 2 questionnaires, the Medical Outcomes Study Short Form-36 (SF-36; Version 1)[8] and the Health Assessment Questionnaire-Disability Index (HAQ-DI) survey[9]. The SF-36 consists of 8 subscales evaluating bodily pain (BP), general health (GH), mental health (MH), physical functioning (PF), role-emotional functioning (RE), role-physical functioning (RP), social functioning (SF), and vitality (VT). Additionally, 2 summary measures of physical (physical component score; PCS) and mental (MCS) functioning can be calculated using weighted averages of the 8 subscales. The HAQ-DI consists of 20 questions in 8 areas of functioning, including activities of daily living, usual activities, and mobility. Subjects also performed a global assessment of gout impact, using disease-specific modifications of the HAQ pain and patient global health 10-cm visual analog scale (VAS) measures, where 0 = best outcome and 10 = worst outcome. Examining physicians also performed a global assessment of gout impact, using the latter measure and metric.

The instruments employed have been evaluated in this study population for internal consistency, test-retest reliability, and validity (unpublished data). The internal consistency reliability for both instruments was good: alpha scores ranged from 0.75 to 0.97 for the SF-36 subscales, and 0.95–0.97 for the HAQ-DI. Spearman correlations and intraclass correlation coefficients (ICC) were used to estimate test-retest reliability for the SF-36 subscales and summary scores, and ranged from 0.40 to 0.90. HAQ-DI scores were also strongly associated across time, with correlations and ICC ranging from 0.83 and 0.84. Construct and discriminant validity, assessed by correlating SF-36 subscales and the HAQ-DI scores with various clinical indicators, showed all correlations to be in the expected direction, with expected strength of associations between measures. The HAQ-DI has also recently been independently validated for use in Mexican patients with gout using methods similar to those employed for this US study population[10], with comparable results.

Subjects completed diaries of their gout-related health covering the period between each bimonthly visit. Information contained in the diaries included incidence, dates, duration, and severity of flares; joint(s) affected; medications (both prescribed and over the counter); and whether the gout attack necessitated a medical office contact or visit.

Analysis. While descriptive information is provided for the entire study population (n = 110), the inferential analysis is restricted to subjects (n = 95) whose outcomes were obtained during the first 4 months (baseline through followup Visit 2) due to significant attrition of subjects after this time. Descriptive data included the mean, SD, and range values, as well as frequencies and distributions for all patient clinical and demographic characteristics. The association of clinical variables and changes in clinical status to patient HRQOL was evaluated using Spearman correlations and ANOVA, with Scheffe post-hoc comparisons. SAS statistical software, version 9.1 (SAS Institute Inc., Cary, NC, USA), was used to conduct all analyses. All statistical tests used a significance alpha level of 0.05.

RESULTS

Overall, 110 subjects were enrolled. Fifty-two subjects (47.3%) completed all followup assessments. Of those subjects who discontinued, 9 (8.2%) withdrew their consent, 6 (5.5%) were noncompliant, 5 (4.6%) were lost to followup, and 4 (3.6%) died. Another 23 (21%) did not complete all intended visits because the study was discontinued prematurely by the sponsor for cost reasons, and 10 subjects (9%) were excluded due to a high percentage of missing data. Ninety-five patients (86% of all enrollees) completed the 4-month assessment.

No significant demographic differences between study completers and noncompleters were observed, nor were there any significant differences between these groups regarding duration of disease, baseline mean sUA level, number of flares reported in the year prior to study entry, or number of subjects reporting tophi in the year preceding study entry.

The mean interval between confirmation of the diagnosis and study entry was 6.9 years (SD 8.2), indicating that most patients had experienced a prolonged period of time since crystal diagnosis. Review of prestudy use of gout-related therapies indicated that most patients had received multiple gout medications over time and more than one ULT. Most subjects (75%) had been or were being treated with colchicine or colchicine and allopurinol (68%). Another 10% of subjects had been or were treated with probenecid or sulfinpyrazone. Use of antiinflammatory medications was also common: 21% of subjects were treated with indomethacin, 19% ibuprofen, and 28% cyclooxygenase-2 selective inhibitors. Twenty-seven percent of subjects reported use of a variety of other nonsteroidal antiinflammatory drugs. It was not possible to discriminate between prophylactic and nonprophylactic medication use.

Subjects not completing the study reported more baseline joint pain and swelling than subjects remaining on-study. Mean number of swollen joints was 9.9 (SD 10.3) and 5.4 (SD 6.7) for study noncompleters and completers, respectively ($p < 0.02$). Mean number of tender joints was 8.7 (SD 9.6) for noncompleters and 4.8 (SD 7.1) for study completers ($p < 0.03$).

Subjects' demographic and clinical characteristics for the entire sample are presented in Table 1. The great majority of subjects were male (90%), and almost 70% were non-Hispanic whites. Subjects ranged in age from just under 28 to almost 90 years (mean 59). Mean baseline sUA was 7.8 mg/dl, but several subjects had sUA levels < 6.0. While all participants were considered to have treatment-failure gout, a wide range of clinical expression was observed. For example, although clinicians reported that almost all subjects (98%) had experienced an acute gout attack in the year prior to the study, the self-reported average monthly rate of flares over this time varied widely, between none and 2.9.

Almost all subjects (87%) had other comorbid conditions, typically metabolic and cardiovascular disorders. The most common comorbidities included hypertension (71%), osteoarthritis (42%), and kidney disease (44%). Most subjects (75%) had more than one comorbid condition; exclusive of gout, the average number of comorbid illnesses was 3.

Quality of life. Overall, physical function in these subjects with gout with treatment failure was more impaired than mental health or social activities. Compared with the general US adult population[8], the mean SF-36 subscale scores were considerably lower, except for the mental health and MCS summary scales (Figure 1).

Table 1. Baseline demographic and clinical characteristics of patients with treatment-failure gout (n = 110).

Characteristic	
Age, mean (SD) yrs	59 (13.2)
Male, n (%)	90 (81.8)
Race, n (%)	
White, non-Hispanic	75 (68.2)
Black, non-Hispanic	22 (20.0)
Other	13 (11.8)
Duration of disease > 5 yrs, n (%)	38 (34.5)
Mean serum uric level, mg/dl (SD)	7.81 (2.0)
Mean creatinine level, mg/dl (SD)	1.56 (0.8)
Mean rate of gout attacks (flares) per month, past year (SD)	0.6 (0.65)
No. of patients with tophi, past year, n (%)	77 (70.0)
No. of patients with joint pain, past year, n (%)	79 (71.8)
Mean no. of painful joints, past year (SD)	8.87 (8.6)
No. of patients with swollen joints, past year, n (%)	93 (84.6)
Mean no. of swollen joints, past year (SD)	8.6 (8.7)
No. of patients with comorbid conditions, n (%)	
Hypertension	78 (71.0)
Renal disorders, defined by estimated creatinine clearance	48 (43.6)
Osteoarthritis	46 (41.8)
Cardiovascular disorders	17 (15.0)
Diabetes	15 (14.0)
Liver disorders	8 (7.3)
Neoplasms	3 (2.7)
Other conditions	43 (3.9)

The mean score of subjects on the physical function subscale was 46.8 (SD 30.2); the mean role-physical score was 35.0 (SD 41.1) and the mean score on the summary PCS measure was 34.2 (SD 11). Despite the relative youth of the study population (over half were under age 60 yrs), subject scores were much lower than those of the general US adult male population of similar age (ages 55–64) and are more comparable to scores in the US population for people 75 years of age and over (Figure 1). Within the study population, significant age-related differences in SF-36 mental health (MH and MCS scores) were observed, with the oldest subjects (ages ≥ 70 yrs) reporting better mental health functioning ($F = 1.68$, $p < 0.02$). Older subjects also reported significantly better vitality than younger subjects ($F = 3.04$, $p < 0.04$). No other significant age-related differences in HRQOL or disability were observed.

Mean HAQ-DI score at baseline was 1.0, indicating moderate physical disability (possible score range 0–3, 3 indicating most disabled). Item-level responses to the HAQ-DI ranged from a mean of 0.7 for eating to a mean of 1.2 for ability to walk and to perform basic hygiene tasks (data not shown). There was no significant difference between age groups in HAQ-DI scores overall.

Relationship of demographic, biochemical, and clinical indicators to HRQOL and disability. Associations of several baseline laboratory and clinical indicators to HRQOL and disability were evaluated. Serum uric acid level was not significantly correlated with any SF-36 subscale, or with the

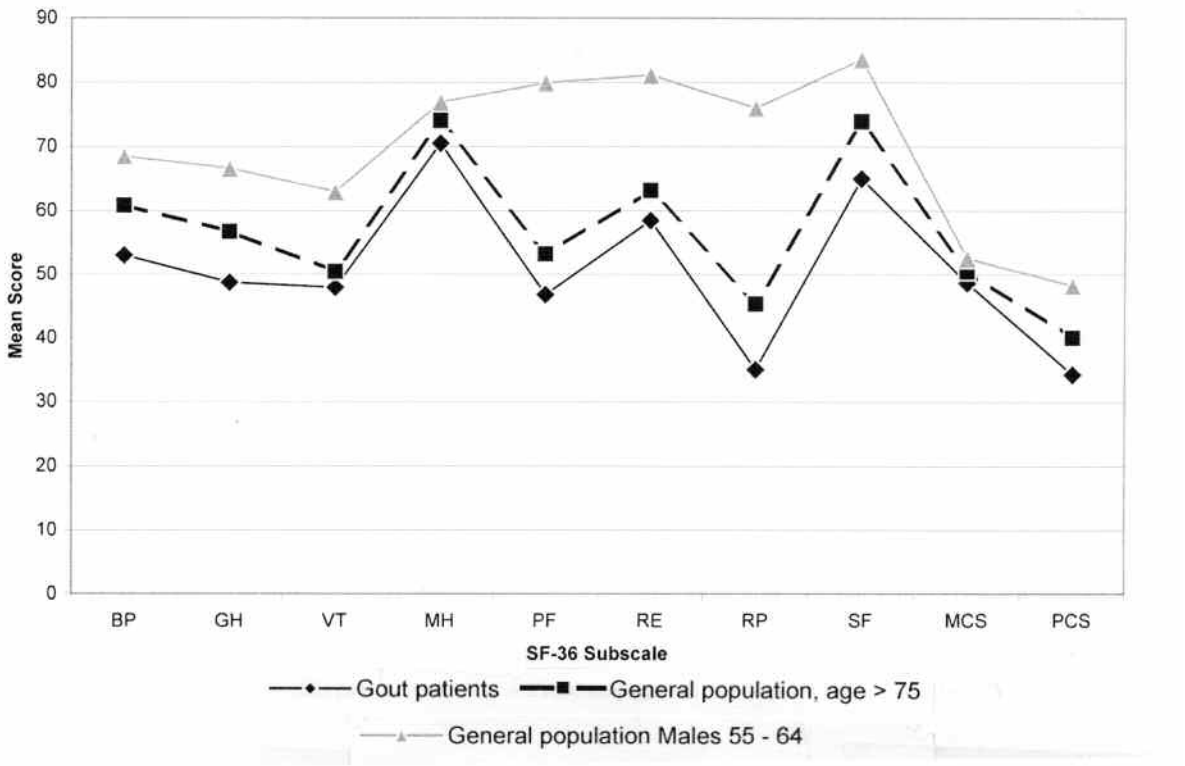

Figure 1. Comparison of mean SF-36 scores for the general US population aged ≥ 75 years, the US male population aged 55–64, and patients with treatment-failure gout (mean age 59 yrs, n = 110).

HAQ-DI. The number of acute attacks per year was significantly associated with all HRQOL and disability measures, however, indicating worse functioning with higher flare rates. The number of tender joints was also significantly correlated with all HRQOL and disability measures. Number of swollen joints at baseline was significantly associated with the SF-36 bodily pain score, as well as the physical functioning, role-physical, social functioning, and PCS scores. This variable was also significantly related to the HAQ-DI score. Presence of tophi at baseline was significantly associated with worse SF-36 bodily pain, general health, role-physical, social functioning, vitality, and PCS subscales, but was not highly correlated with the HAQ-DI. Table 2 summarizes correlations between clinical measures, HRQOL, and disability.

Compared with subjects who experienced no gout attacks between visits or to those whose rate of flares was unchanged, subjects experiencing an increase in flare rates

Table 2. Correlations between baseline clinical measures of gout severity, SF-36 subscales, and the HAQ-DI[†].

Subscale	Presence of Tophi	No. of Swollen Joints	No. of Painful Joints	No. of Flares, Past year	Serum Uric Acid Level	Disease Duration
	Correlation	Correlation	Correlation	Correlation	Correlation	Correlation
Bodily pain	0.190*	–0.348***	–0.624***	–0.547***	–0.027	–0.009
General health	0.402***	–0.192	–0.393**	–0.302**	–0.116	–0.023
Mental health	0.118	–0.188	–0.457***	–0.296**	0.019	0.140
Physical functioning	0.163	–0.286**	0.483***	–0.239*	–0.060	0.005
Role-emotional	0.084	–0.160	–0.413***	–0.353***	0.073	0.015
Role-physical	0.202*	–0.325**	–0.562***	–0.444***	–0.027	0.003
Social functioning	0.196*	–0.304**	–0.591***	–0.379***	0.078	0.015
Vitality	0.191*	–0.197	–0.480***	–0.295**	–0.132	0.141
PCS	0.277**	–0.334**	–0.544***	–0.369**	–0.105	–0.015
MCS	0.077	–0.139	–0.436***	–0.321**	–0.001	0.087
HAQ-DI	–0.178	0.443***	0.650**	0.278	0.125	–0.014

[†] SF-36 subscale score range 0–100, higher score = better functioning. HAQ-DI score range: 0–3, higher score = worse functioning. * $p \leq 0.05$, ** $p < 0.01$, *** $p \leq 0.001$. PCS: physical component summary score; MCS: mental component summary score.

during these intervals reported considerably worse functioning and disability over time. As indicated by mean SF-36 summary or subscale scores (Figure 2), over the 4-month period between the first and third followup visits, the SF-36 scores of subjects who experienced an increase in flare rates decreased in all domains except physical functioning and general health. There were no substantial changes to HAQ-DI scores associated with change in flares, however (data not shown). Subjects who experienced no flares or no change in flare rate over the time period did not report any substantive difference in HRQOL.

Subjects with cardiovascular conditions reported worse physical functioning than subjects without cardiovascular problems [mean 32.7 (SD 24.1) vs mean 48.6 (SD 30.7); $p < 0.03$]. Hypertensive subjects did not differ from those without hypertension, except with regard to mental health, where they had significantly better mean functioning levels than nonhypertensive subjects [mean SF-36 MH score 73.2 (SD 20.1) vs mean 61.2 (SD 22.4); $p < 0.04$]. There were no significant differences in HRQOL or disability outcomes for diabetics, subjects with renal conditions, or those with osteoarthritis, compared to subjects without this condition.

The contribution of comorbid conditions to HRQOL and disability was also evaluated by comparing the SF-36 and HAQ-DI scores for patients with one or more comorbid conditions to the SF-36 and HAQ-DI scores for subjects with gout only. Patients were grouped by number of comorbid conditions (none, 1–2, 3–4, and ≥ 5 comorbidities). Subjects with comorbid conditions experienced worse HRQOL in terms of PF, RP, BP, and SF scores compared to those with no comorbid conditions, although no significant differences between subgroups based upon number of comorbidities was observed. Compared to subjects with gout only, those with one or more comorbid conditions also experienced greater disability, as measured by mean HAQ-DI score. This relationship was not linear; subjects with 3–4 comorbidities in addition to gout reported the highest level of disability, those with ≥ 5 comorbidities had the next-highest mean HAQ-DI scores. There were no significant differences in HAQ-DI score by number of comorbid conditions, however.

Subjects' gout-related pain and global assessment scores ranged from 0 to 10, and the physician gout-related global assessment ranged from 0 to 9.75 at baseline. Subjects were categorized according to their reported levels of pain or functional difficulty as mild (0–3.25), moderate (3.5–6.5), or severe (6.75–10). Overall, at baseline, 50 subjects rated their pain as mild, 32 as moderate, and 24 as severe. Scores were similar for subject global assessment (n = 56 mild, 30 moderate, and 20 severe) and physician global assessment (n = 57 mild, 30 moderate, and 21 very poor). One-way ANOVA comparisons of mean SF-36 subscale and HAQ-DI scores by severity groups revealed significant differences between these groups, with more severe decrements in gout-related functioning and higher gout pain levels corresponding to worse HRQOL and disability on all measures. Differences between groups were significant for both subject-reported pain and subject global assessment. However, differences in physician global assessment were not significant for any of the mental or emotional function measures (Table 3).

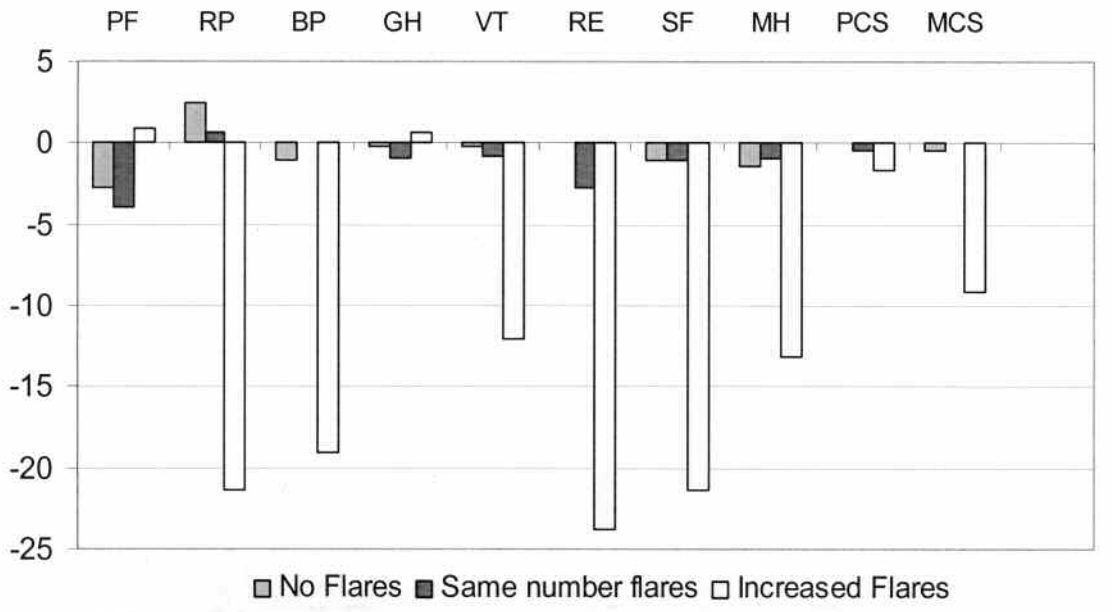

Figure 2. Mean change in SF-36 subscale scores by gout flare status over a 4-month time period (followup visits 2–4). PF: physical functioning, RP: role-physical functioning, BP: bodily pain, GH:general health, VT: vitality, RE: role-emotional functioning, SF: social functioning, MH: mental health, PCS: physical component score, MCS: mental component score.

Table 3. Differences in mean baseline SF-36 and HAQ-DI scores by severity of pain and functional status, as evaluated by gout subjects and physicians*.

Severity Group	BP	GH	MH	PF	RE	RP	SF	VT	MCS	PCS	HAQ-DI
Gout-related pain											
Mild	57.8	55.4	73.9	58.3	75.7	59.2	77.0	5.9	51.4	39.2	0.58
Moderate	42.8	49.6	75.3	42.1	57.0	22.7	65.6	49.6	51.3	30.5	1.1
Severe	22.1	35.1	58.2	29.8	27.8	4.2	38.5	37.4	41.2	25.1	1.57
p	< 0.0001	< 0.002	0.003	0.0002	< 0.0001	< 0.0001	< 0.0001	< 0.02	0.0008	< 0.0001	< 0.0001
Patient-assessed gout-related functioning											
Mild	53.8	56.0	74.0	56.6	73.3	53.6	75.0	51.8	51.3	37.6	0.67
Moderate	44.4	50.3	75.7	47.0	58.3	22.5	65.4	49.1	50.7	32.0	1.02
Severe	22.1	28.0	54.2	20.0	20.0	5.0	35.6	35.4	39.4	23.4	1.7
p	< 0.0001	< 0.0001	0.0003	< 0.0001	< 0.0001	< 0.0001	< 0.0001	0.009	0.0002	< 0.0001	< 0.0001
Physician-assessed gout-related functioning											
Mild	52.1	57.2	72.2	55.9	65.4	48.2	73.9	51.9	50.1	37.7	0.66
Moderate	43.0	45.4	73.5	41.1	57.1	26.7	62.9	47.1	50.1	30.5	1.04
Severe	27.1	29.1	61.8	29.8	41.7	12.5	40.6	37.0	43.4	24.3	1.72
p	0.0003	< 0.0001	0.11	0.001	0.13	0.001	< 0.0001	0.02	0.08	< 0.0001	< 0.0001

* Severity categories are based upon responses to 10-cm visual analog scale (VAS) for gout-related pain (0 = no pain, 10 = worst possible pain), patient-assessed gout-related functioning (0 = very well, 10 = very poor), and physician assessed gout-related functioning (0 = very good, 10 = very bad). For each measure, VAS scores were categorized into mild = 0–3.25, moderate = 3.5–6.5, and severe = 6.75–10. BP: bodily pain, GH: general health, MH: mental health, PF: physical functioning, RE: role-emotional functioning, RP: role-physical functioning, SF: social functioning, VT: vitality, MCS: mental component summary score, PCS: physical component summary score.

DISCUSSION

Our results provide evidence that symptomatic treatment-failure gout has a significant effect on patient HRQOL and disability, especially in the realm of physical functioning. The average age of subjects in our study was under 60 years, but these subjects had mean SF-36 scores that were analogous to those of healthy individuals age 75 years and older. While comorbid conditions contributed to these results, HRQOL scores were substantially lower than for the normative US adult male population, even for subjects who did not have any other illness. While normative age data are not available for the HAQ-DI, the consensus is that scores < 1 indicate mild disability, scores 1–2 denote moderate disability, and scores ≥ 2 signify severe disability[11]. The mean baseline HAQ-DI of 1.0 thus indicated that subjects experienced a moderate degree of disability overall. However, HAQ scores were higher (indicating more disability) for patients with greater disease severity, as indicated by an increase in flares over time, as well as baseline number of painful or swollen joints, presence of tophi, and number of flares in the year prior to enrollment into the study. These findings suggest that, even in a population defined as suffering from severe gout, there are significant differences in physical disability. It is interesting that a recent study[12] of patients with gout (not defined as having treatment-failure gout) found similar associations with clinical variables, although average HAQ-DI scores were lower than those observed in our study; such a finding of less disability might be expected if the patients studied had less severe disease or fewer chronic symptoms than the patients studied here.

Our results also show differences in the strength of association between various clinical severity measures and HRQOL. Some clinical characteristics, such as number of recent flares and number of painful or swollen joints, were significantly correlated with all or most of the SF-36 subscales and the HAQ-DI. A worsening of flare activity over time was also clearly associated with worsening on all but 2 indices of the SF-36 measure (physical functioning and general health), including decrements in mental health functioning.

While hyperuricemia is regarded as a primary risk factor in the pathogenesis of gout[1], there is little to suggest that sUA is a direct clinical severity indicator, and, indeed, sUA was not significantly related to any HRQOL or disability measure. This is not a unique finding; similar results were observed in a validation study of a gout-specific HRQOL measure, where no differences in SF-36 scores by sUA measures were noted[12]. Any relationship between sUA and HRQOL is likely to be mediated by clinical indicators of severe disease, such as presence of tophi, flare frequency, or number of tender, swollen joints. Mediated relationships are defined as those where one variable explains how or why another variable affects an outcome[13]. In such relationships, the mediated variable (in this case, sUA) precedes and is significantly related to the mediator variable (e.g., tophi, flare frequency, etc.). While the relationship between the mediator and the outcome is significant, the association between the mediated and outcome variables is not. This does, indeed, appear to be the case here; sUA was correlated strongly with other clinical outcomes (data not shown), but no significant direct association was observed between sUA and the HRQOL outcomes. Presence of tophi, number of flares, and swollen or tender joints, however, were all significantly associated with HRQOL. As Kraemer and col-

leagues observed, "All causal factors are risk factors, but not all risk factors are causal"[13]. In our study, it appears that, while sUA is a risk factor for gout and thereby changes in HRQOL, it is not a causal factor for these outcomes.

Subjects' perceptions of their overall gout-related pain and functioning were highly correlated to HRQOL and disability. Our results showed a clear relationship between subject-rated level of severity on these measures and all HRQOL and disability indices. While physician global assessment was also correlated with HRQOL and disability, the associations were not as strong or consistent as those observed for subject assessments. This is a compelling argument for the inclusion of subject-reported outcomes measures in treatment-effectiveness research.

While the number of comorbid conditions had an influence on HRQOL, especially on dimensions of physical functioning, there were no statistically significant differences between SF-36 and HAQ-DI scores for patients with and without comorbid conditions, or for those with multiple comorbid conditions. This result was based upon a simple count of other conditions, however, and did not take severity of comorbid illnesses into account; the strength of the observed associations might well have been stronger had this parameter been factored into the analysis[14]. Age had less of an effect on HRQOL and disability. The only areas where significant associations were found between HRQOL and age were in the mental health, MCS, and vitality subscales, where older patients reported better functioning than younger participants. Age has often been observed to be positively correlated to SF-36 mental health subscales, in both condition-specific populations[15] and general populations[16].

The major strength of our study was the ability to correlate HRQOL and disability measures with a variety of clinical indicators as well as with patient and clinician perceptions of overall pain and functioning related to gout. This enabled the evaluation of SF-36 and HAQ-DI results within a rich context of clinical and patient information. Such data will be useful in designing clinical trials and other studies of treatment effectiveness now that the variables most likely to yield significant differences between treatment groups are better understood. However, the small sample size and significant study attrition limited the types of analyses that could be performed and shortened the followup period that could be evaluated.

It may be argued that the compromised quality of life and level of disability displayed by these subjects with treatment-failure gout was largely, or in part, due to the comorbidities common in these subjects. Although this may be the case, the correlations of HRQOL and disability measures with a variety of clinical gout indicators suggest a substantial role for gout in these functional impairments. Moreover, establishment of such correlations offers the opportunity to assess the functional benefits that may occur when additional urate-lowering agents, now in development, are approved for treatment-failure gout. That is, if the improved clinical outcomes (flare reduction, tophus resolution, reduction in tender and swollen joint counts) associated with longterm urate-lowering by these agents are paralleled by improved HRQOL and reduced disability, it follows that gout is a significant contributor to functional impairment, even in the presence of comorbidities. Such a finding would justify and even mandate aggressive management of gout.

The influence of gout on patient HRQOL and functioning is increasingly recognized[17]. As such, the importance of evaluating these patient-centered outcomes has been noted by clinical and professional groups, and the development or validation of existing instruments for this purpose is now a priority[18,19]. Severe treatment-failure gout is a debilitating condition that affects patient functioning and well-being. Some clinical severity indices appear to be more sensitive to differences or changes in HRQOL than others, and may therefore be important to consider when designing clinical trials or effectiveness studies. The results of our study are limited by a small sample size and require confirmation in larger patient populations.

ACKNOWLEDGMENT

The Gout Natural History Study Group**:** John Sundy, MD, PhD; Michael Becker, MD; H. Ralph Schumacher, MD; Peter Gorevic, MD; Maria Greenwald, MD; Jeffrey Fessel, MD; Michael Weisman, MD; Antonio Reginato, MD; Robert Griffin, DO; Edward Goldberger, MD; Lawrence Edwards, MD; Peter Simkin, MD; John Morgan, MD; Alan Kivitz, MD, CPI; Michael Weitz, MD; H.S. Eugene Fung, MD, FACR, FRCPC; Edward Fudman, MD; Mary Cronin, MD; Jeffrey S. Peller, MD; Richard Lies, MD; Joel Block, MD; Pamela Rosenthal, MD; Joan Merrill, MD; Guy Dewees III, MD.

REFERENCES

1. Saag KG, Choi H. Epidemiology, risk factors, and lifestyle modifications for gout. Arthritis Res Ther 2006;8 Suppl:S2.
2. Kim KY, Schumacher HR, Hunsche E, Wertheimer AI, Kong SX. A literature review of the epidemiology and treatment of acute gout. Clin Ther 2003;25:1593-617.
3. Miller AV, Ranatunga SM, Francis ML. Gout [Internet. Accessed January 6, 2009.]. Available from: http://emedicine.medscape.com/article/329958-overview.
4. Dieppe PA. Investigation and management of gout in the young and the elderly. Ann Rheum Dis 1991;50:263-6.
5. Hande KR, Noone RM, Stone WJ. Severe allopurinol toxicity. Description and guidelines for prevention in patients with renal insufficiency. Am J Med 1984;76:47-56.
6. Sundy JS, Hershfield MS. Uricase and other novel agents for the management of patients with treatment-failure gout. Curr Rheumatol Rep 2007;9:258-64.
7. Sundy JS, Becker MA, Baraf HS, et al. Reduction of plasma urate levels following treatment with multiple doses of pegloticase (polyethylene glycol-conjugated uricase) in patients with treatment-failure gout: Results of a phase II randomized study. Arthritis Rheum 2008;58:2882-91.
8. Ware JE, Snow KK, Kosinski MK, Gandek B. SF-36 health survey: Manual and interpretation guide. Boston: The Health Institute, New England Medical Center; 1993.
9. Bruce B, Fries JF. The Stanford Health Assessment Questionnaire: Dimensions and practical applications. Health Qual Life Outcomes

2003;1:20.
10. Alvarez-Hernandez E, Pelaez-Ballestas I, Vazquez-Mellado J, et al. Validation of the Health Assessment Questionnaire disability index in patients with gout. Arthritis Rheum 2008;59:665-9.
11. Krishnan E, Tugwell P, Fries JF. Percentile benchmarks in patients with rheumatoid arthritis: Health Assessment Questionnaire as a quality indicator (QI). Arthritis Res Ther 2004;6:R505-R513.
12. Colwell HH, Hunt BJ, Pasta DJ, Palo WA, Mathias SD, Joseph-Ridge N. Gout Assessment Questionnaire: Initial results of reliability, validity and responsiveness. Int J Clin Pract 2006;60:1210-7.
13. Kraemer HC, Stice E, Kazdin A, Offord D, Kupfer D. How do risk factors work together? Mediators, moderators, and independent, overlapping, and proxy risk factors. Am J Psychiatry 2001;158:848-56.
14. Fortin M, Lapointe L, Hudon C, Vanasse A, Ntetu AL, Maltais D. Multimorbidity and quality of life in primary care: a systematic review. Health Qual Life Outcomes 2004;2:51.
15. Stolwijk-Swuste JM, Beelen A, Lankhorst G, Nollet F. Impact of age and co-morbidity on the functioning of patients with sequelae of poliomyelitis: a cross-sectional study. J Rehabil Med 2007;39:56-62.
16. Ware JE, Gandek B. The SF-36® Health Survey: Development and use in mental health research and the IQOLA Project. Int J Ment Health 1994;23:49-73.
17. Brixner DI, Ho MJ. Clinical, humanistic, and economic outcomes of gout. Am J Manag Care 2005;11 Suppl) S459-64; quiz S465-8.
18. Schumacher HR Jr, Edwards LN, Perez-Ruiz F, et al. Outcome measures for acute and chronic gout. J Rheumatol 2005;32:2452-5.
19. Schumacher HR, Taylor W, Joseph-Ridge N, et al. Outcome evaluations in gout. J Rheumatol 2007;34:1381-5.