Concise report

Impact of age and comorbidities on the criteria for remission and response in rheumatoid arthritis

Eswar Krishnan, MD M.Phil., 1 Arja Häkkinen, Ph.D., 2 Tuulikki Sokka, MD Ph.D., 2,3 Pekka Hannonen, MD Ph.D. 2

1 Eswar Krishnan MD. M. Phil. 401 Buttonwood West Reading PA 19611 USA,
2Jyväskylä Central Hospital, Keskussairaalanranta 19, Jyväskylä, 40620 Finland, and 3
Vanderbilt University, Nashville TN, USA

Address for correspondence

Eswar Krishnan MD. M. Phil.
Arthritis & Osteoporosis Centre
01 Buttonwood
West Reading PA 19611 USA
Tel: 610-724-8485
Email: eswar_krishnan@hotmail.com (preferred)

Grant support: Supported in part by the Academy of Finland.

Short title: Remission, response and comorbidities

Word count: Text: 1314 Abstract: 218
Abstract

Objective

Self-report of pain, global assessment and functional disability are important components of the definition of remission and clinical response in patients with rheumatoid arthritis. To what extent health status impairment measured by these tools is attributable to age and other comorbid condition as opposed to the disease in question is unknown.

Methods

Pain, global assessment and Health Assessment Questionnaire Disability Index (HAQ-DI) were measured in a random sample of 1530 adults in the Central Finland District, Finland. Median regressions were used for multivariable analyses.

Results

The mean age was 55.4 years and 72% were women. A large majority of population reported some pain (76%) and less than perfect general health (83%). The overall mean values of pain, HAQ-DI and general health were 20 mm, 0.25 units and 22 mm respectively. The most common self-reported musculoskeletal comorbidities were osteoarthritis (24%) and chronic back pain (25%). Age and number of comorbidities were the only statistically significant correlates of pain and general health in multivariable analyses.
Conclusions

Self-reported disability, pain and poor health were widely prevalent in general population and are related to age and comorbid conditions. This need to be taken into account while interpreting remission and response rates using current criteria and for future development of definitions for these end points in rheumatoid arthritis and other rheumatic diseases.

Key words: Health Assessment Questionnaire, normative, population, percentile, rheumatoid, low disease activity, remission.
Introduction

Remission is unusual among patients with rheumatoid arthritis, regardless of the definition used. Self-report of pain, global assessment of disease activity and functional disability are important health related quality of life (HRQOL) components of remission as well as clinical response in randomized controlled trials of rheumatoid arthritis(1). These metrics have also been proposed as potential tools to define low disease activity in rheumatoid arthritis. However, their population characteristics and correlates are unknown. Understanding the general population characteristics will help us design better clinical trials and cohort studies while lending a practical perspective to the data from these studies. The present study reports the population characteristics of these measures and assesses the implication on interpreting criteria for remission, response and low disease activity.

Methods

Subjects and sampling

A sample of 2000 people who were at least 30 years old and living in the Central Finland District was drawn from the Finnish Population Registry in June 2000. Details of sampling have been published (2).
Outcomes measured:

The wording of global assessment of disease activity (such as the one by the ACR) is not applicable to general population. We therefore used global assessment of general health as the corresponding measure in our group of general population. The pain and global assessment scale consists of a doubly anchored, horizontal Visual Analog Scale scored from zero (best) to 100 (worst). The Health Assessment Questionnaire Disability Index (HAQ-DI) is a measure of functional disability commonly used in the ACR response criteria(3, 4). By convention, the disability index is expressed on a scale from zero (no disability) to 3 (maximum functional disability) units, representing an average score (see url: http://aramis.stanford.edu). Data on date of birth, height and weight for calculating the body mass index (weight in kilograms divided by the square of height in meters), years of education, and self-report of comorbidities were also collected in the questionnaire.

Statistical methods

Differences in mean measures between groups were tested using the Student’s t-test. Relationships between HAQ-DI, pain and global health were measured using Pearson’s product moment correlation coefficient (r). We defined values greater than 95th percentile values of pain (72mm), HAQ-DI (1.5 units) and global health assessment (66mm) as abnormal/severe and calculated the proportions of the individuals with one or more abnormal values.
To visualize the non-linear relationship between HAQ-DI and comorbidities, we used fractional polynomial modification ordinary least squares regression(5). Median regression was used to examine the relationship between pain and global general health in one hand and age, sex, BMI and number of comorbidities on the other. This regression is similar to ordinary least squares regression but differs from it in the fact that the median of the dependent variable is the modelled metric and the sum of deviations as opposed to least sum of squares is the minimized entity when the regression line is fitted minimizing the effect of outliers.

Results

Descriptive characteristics of the sample

Of the 2000 subjects, 1,530 returned the completed questionnaire, representing a 77% response rate. Women constituted 72% of the responders. The mean age of the sample was 55.4 years (standard deviation [SD] =14.9) and the mean education level was 10.8 years (SD=4.1). All respondents were Caucasian residents of the Central Finland District. The mean number of comorbidities in our sample was 1.6 (SD 1.6, range 0-8).

Normative data

Overall, the estimated average population pain level was 20 (95% confidence interval 19-21). Overall, 76% (n=1038) of the respondents reported some pain (pain score>0). The
estimated population mean (95% confidence interval) pain for men and women were not different at 19(16-21) and 20 (19-22), respectively. Percentile normative data on pain is shown in Appendix Table 1.

A large majority (83%) of the population rated their health less than perfect (i.e. >0). The overall mean (95% confidence interval) global general health score was 21 (20-23). There was no significant difference between mean scores for men (20, [18-22]) and women (22 [20-23]). The percentile values are shown in Appendix Table 2.

The normative data on HAQ-DI in this population has been published and is reproduced in Appendix Table 3 for easy reference(6).

**HRQOLs and comorbidities**

Seventy two percent of the survey respondents admitted to at least one medical condition. The most common were hypertension (30%), back pain (25%), osteoarthritis (24%) and post-traumatic injuries (12%). Four percent of the responders reported fibromyalgia. As expected the outcomes worsened steadily with increasing number of comorbidities (Figure 1). The three HRQOLS were correlated with each other with correlation coefficients 0.82 (pain and global), 0.59 (pain and HAQ-DI) and 0.62(HAQ-DI and global) (Appendix Figure 1)
Table 1 shows that as the number of comorbidities increase, the number of individuals with high levels of pain, global health assessment and HAQ-DI increase. When there are three or more comorbidities, one in five (20%) of general population have two or more clearly abnormal measurements. In median regressions, the only independent predictors of pain and global general health were age and comorbidities (Table 2).

Discussion

Patient reported HRQOL is an important outcome in real-life clinical practice. Our study has demonstrated the prevalence of ACR HRQOL deficits in general population. These were prominent in older age groups age and those with multiple comorbidities. Thus, in research studies such as clinical trials where these data are formally collected (using tools such as the Health Assessment Questionnaire as well as pain and global general health visual analog scales), interpreting HRQOL data pose several problems:

First, a HRQOL indicator such as pain or disability does not only reflect the disease in question but also other comorbidities (7, 8). The interpretation of self-reported HRQOL data is relatively easy in clinical practice where the physician can parse them in the context of the rheumatologic and non-rheumatologic comorbidities, age and psychosocial background. In research studies, where one can ask the patient for pain or disability attributable to a specific disease (such as rheumatoid arthritis) it is unlikely to solve the problem. For example, re-wording the question to query pain attributed to rheumatoid arthritis is unlikely to solve this problem since knee and hand osteoarthritis pain, an
important concurrent source of pain, is indistinguishable from rheumatoid arthritis pain. Global self assessment question can be re-worded to ask how well the rheumatoid arthritis is doing. This approach assumes that the patient is able to neatly and reliably apportion symptoms between the arthritis and other comorbidities according to the underlying disease- a sweeping and un-validated assumption.

Second, the changes of the HRQOL metrics in longitudinal observational studies and randomized controlled trials are not entirely due to the disease/drug in question. Longer the study duration, greater will be the impact of age. The high ACR20 response rates seen in many placebo arms might be, in part, due to this problem.

Third, simple statistical adjustments for co-morbid conditions especially musculoskeletal ones are not available. The interactions of the these comorbid conditions with rheumatoid arthritis may be unique and a summary count of these may not be valid(9).

Definitions of rheumatoid arthritis remission and low disease activity state (LDAS) based on arbitrarily fixed numeric cut-off values for pain and other self-reports of HRQOL are likely to be problematic. An alternative might be to use cut-off values (if at all) based on population normative values such as ours.

Our study has implications on the sample size calculation in clinical studies as well. Typically, a priori calculation of study size takes into account baseline prevalence of the outcome metric in question among controls and the anticipated effect size/risk difference
of the intervention. Since the prevalence of worse HRQOL indicators increase with age, one would need to have larger size to have the power to demonstrate the same effect size in an older patient population. In such situations, consideration may be given to using the distribution of metric in question in the comparison group (such as control arm in a clinical trial) to arrive at a more realistic sample size estimation.
Legends

Figure 1. The relationship between pain, global assessment and functional disability with increasing number of disease conditions.
Table 1. Percentage of general population with abnormal values (≥95th percentile) for the self-reported ACR response metrics (pain global assessment and HAQ-DI)

<table>
<thead>
<tr>
<th>Number of comorbid conditions</th>
<th>Number of abnormal metrics</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0</td>
</tr>
<tr>
<td>0</td>
<td>89.7%</td>
</tr>
<tr>
<td>1</td>
<td>90.9%</td>
</tr>
<tr>
<td>2</td>
<td>82.3%</td>
</tr>
<tr>
<td>3</td>
<td>69.2%</td>
</tr>
<tr>
<td>&gt;=4</td>
<td>54.9%</td>
</tr>
<tr>
<td>Overall</td>
<td>82.2%</td>
</tr>
</tbody>
</table>
Table 2. Independent predictors of self-reports of pain and global assessment in general population by median regression

<table>
<thead>
<tr>
<th>Covariate</th>
<th>Coefficient</th>
<th>95% Confidence Interval</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Pain</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (per year)</td>
<td>0.083</td>
<td>0.034 to 0.132</td>
<td>0.001</td>
</tr>
<tr>
<td>Female gender</td>
<td>-0.310</td>
<td>-1.541 to 0.922</td>
<td>0.622</td>
</tr>
<tr>
<td>Education (per year)</td>
<td>-0.177</td>
<td>-0.331 to -0.024</td>
<td>0.024</td>
</tr>
<tr>
<td>Body mass Index (per unit)</td>
<td>-0.003</td>
<td>-0.132 to 0.126</td>
<td>0.963</td>
</tr>
<tr>
<td>Comorbidity (per each condition)</td>
<td>7.509</td>
<td>7.097 to 7.922</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Global</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (per year)</td>
<td>0.208</td>
<td>0.130 to 0.287</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Female gender</td>
<td>-0.556</td>
<td>-2.508 to 1.396</td>
<td>0.576</td>
</tr>
<tr>
<td>Education (per year)</td>
<td>-0.171</td>
<td>-0.422 to 0.081</td>
<td>0.184</td>
</tr>
<tr>
<td>Body mass Index (per unit)</td>
<td>0.078</td>
<td>-0.126 to 0.282</td>
<td>0.454</td>
</tr>
<tr>
<td>Comorbidity (per each condition)</td>
<td>6.834</td>
<td>6.174 to 7.493</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>
Legend

Figure 1. Scatter-plot matrix graph of pain, global assessment and functional disability.

The correlation coefficients were 0.82 (pain-global), 0.62 (global-HAQ-DI) and 0.59 (pain-HAQ-DI).
References


