Quality of life measurement in asthma

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In chronic disease, such as asthma, cure is not possible and death, though of great importance, is rare. The majority of adult asthmatics lead lives that are characterized neither by good health nor by severe impairment. To assess disease severity, monitor progression, and quantify treatment effects, this impairment of health must be measured. How is this to be done?

Asthma is a disease that is characterized, in part, by variations in airways obstruction. Measurements of airways function, such as peak flow and forced expiratory volume in one second (FEV1) were the first parameters to be used for assessing disease severity. These have been invaluable tools with which to show that treatment for asthma improved airways function. It has proved a little more difficult to translate such measurements into an understanding of whether the improvement was clinically worthwhile, however. Furthermore, measurements of airways function do not fully reflect all the disease processes that occur in asthma, such as overinflation and airways plugging. Evidence from clinical trials suggests that airflow measurements may not always follow other markers of disease activity. For example, in very mild asthmatics treated with budesonide over one year, asthma symptoms and bronchodilator use improved in steroid treated patients, but not in those receiving placebo. These improvements occurred in the absence of a change in FEV1 [1]. In another study, that compared budesonide and terbutaline, at the end of a one year treatment period, the initial improvement in peak flow on starting steroids had been sustained, but asthma symptoms were returning towards pretreatment levels [2]. Clearly, in mild-moderate asthmatics, who constitute the bulk of patients with this disease, standard physiological measurements do not tell the whole story.

What additional measures are required to supplement airflow measurements? Two have already been mentioned, bronchodilator use and asthma symptoms. One frequently cited treatment objective is the avoidance of acute exacerbations, but these are difficult to define. Other measures may include the use of health resources, such as visits to the physician or hospital admissions, but these may depend on a range of factors, including local medical practice. In most circumstances, these different variables are used as surrogate markers for the patient's state of health. There is little need for the use of such surrogates, however. Health can be measured directly using specifically designed questionnaires. These quantify the effects of disease on the patient's daily life and well-being in a formal and standardized manner. Unfortunately, the term "quality of life" has become attached to these instruments, which has led to certain misunderstandings about them. This has been compounded by the widespread use of this phrase, by politicians and journalists, to convey sweeping concepts about life without the inconvenience of providing specific details that may be open to scrutiny. The science of measuring health is very rigorous, but unfortunately the jargon term with all its nebulous associations has stuck very firmly.

A critical part of the validation of a health questionnaire is the demonstration that its scores are related to disease severity. Despite the availability of such evidence, one criticism of these measures is that it may be possible for patients with asthma "to die with a good quality of life". This is unlikely. An examination of disease-specific quality of life questionnaires reveals that they look rather like clinical check lists albeit far more comprehensive than the histories that most of us take in routine practice. It might be reasonable, therefore, to rephrase the anonymous quote and express a concern about patients "who die despite appearing to have well-controlled asthma as assessed by a comprehensive clinical history". Whilst such patients do appear to exist (although they have rarely been assessed using a comprehensive disease-specific questionnaire), their existence does not constitute a valid argument against either clinical history-taking or health measurement.

The concerns just discussed may arise partly through a failure to distinguish between the processes, requirements and purposes of a clinical trial involving populations of patients and those required in the treatment of an individual patient. At present, health-related quality of life questionnaires are used largely in clinical trials to quantify average changes in health. There are few routine therapies for asthma for which there is clear evidence, at a population level, of a dissociation between disease in the airways and the patients' symptoms and health. Indeed, only by carrying out studies which measure both airways function and quality of life will it be possible to test whether this does occur. The possible existence of patients who have bad asthma, yet apparently normal health and no disturbance to daily life, constitutes an argument for the development of tools with which to test this hypothesis, not an argument against them.

The process of validating any new method of measurement in medicine is long and multifaceted. How many of us can detail the history of the development and

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validation of the spirometric and airflow measurements in use for asthma today? We all have an idea of what is "airways obstruction", yet this is rather an abstract concept; Which part(s) of the airways? Which phase of the respiratory cycle? Homo- or inhomogeneity of obstruction? Despite these detailed considerations, the overall concept has acquired clinical value through the accumulation of many small pieces of evidence that build the complete picture. This process is still continuing, even for airways function measurements. In the absence of an absolute "gold standard", the validation of any method of measurement is open-ended.

The paper by Rutten van Molken et al. [3] in this issue of the Journal provides an important contribution to the process of validating quality of life measurement in asthma. In the context of a clinical trial that compared salmeterol with salbutamol in asthma, these authors analysed the performance of two disease-specific questionnaires: the Asthma Quality of Life Questionnaire [4] and the Living with Asthma Questionnaire [5], and a general health measure; the Sickness Impact Profile [6]. These measures all quantify impaired health on scales that range from no impairment (i.e. perfect health) to a worst possible state. The latter is somewhat arbitrary and depends on the structure and content of the questionnaire. This does not matter greatly when comparing different treatments for the same or closely related diseases, but it becomes very important when trying to compare treatments for different diseases. For this purpose, utility instruments are preferred. These use scales that are anchored at each end by health states that are common to all diseases; perfect health and death (although states worse than death may exist). Utility scales are difficult to validate and use. Two scales of this type were used in this study and both proved to be relatively insensitive to change. These results question the validity of efforts to make comparisons between different diseases. If a measure proves incapable of detecting an apparently worthwhile improvement in health in one disease, it cannot be used with confidence to compare the health gain in different diseases.

Whilst it may not yet be possible to compare treatments for different diseases, comparisons between different therapies for the same disease are possible and must be made. How is this to be done? General health measures have been around for around 15 yrs and disease-specific measures for airways disease for half that time. Their number continues to grow, so how is the trialist to choose which one to use? As pointed out by Rutten van Molken et al. [3], none of the recently developed asthma quality of life instruments can be said to be superior; nevertheless, these authors have provided a valuable comparison of some questionnaires that may be used in asthma. Last year in this Journal, the Sickness Impact Profile was shown to be insensitive to clinically worthwhile improvements in health, in asthma, compared to a disease-specific questionnaire [7]. This new study has confirmed this finding and has gone further and compared two disease-specific questionnaires. Scores from the two instruments were highly correlated at baseline, but the Asthma Quality of Life Questionnaire was clearly more sensitive than the Living with Asthma Questionnaire, when assessing differences in efficacy between salmeterol and salbutamol. This important observation reinforced the point that whilst two quality of life questionnaires may correlate well with each other, this does not mean that all of their properties will be shared. Responsiveness of a questionnaire must be tested, not assumed [8].

This study permits a number of other interesting observations. Firstly, the pattern of associations between the health questionnaires and other measures shows some intriguing variations, best exemplified by the Asthma quality of Life Questionnaire. This measure correlated well with day and night asthma symptoms scores, both at baseline and following treatment, but it did not correlate with baseline peak flow or FEV1. The absence of a correlation with FEV1 in a cross-sectional analysis has been observed with this particular questionnaire previously [9], although significant correlations have been reported in asthma between FEV1 and the St George's Respiratory Questionnaire score (a disease specific measure for asthma and chronic obstructive pulmonary disease (COPD)) [10]. In the study by Rutten van Molken et al. [3] and a previous study by Juniper et al. [4], changes in FEV1 and peak flow correlated well with changes in Asthma Quality of Life Score. The difference between cross-sectional and longitudinal correlations with spirometry seen with this questionnaire may be related to the objectives underlying its design. These were to produce a questionnaire directed largely towards the measurement of change in health. Whilst sensitivity to change is of paramount importance in the context of a clinical trial, the ability to make cross-sectional comparisons is also useful. The St George's Respiratory Questionnaire was designed with this additional property in mind [11], yet this measure also proved to be sufficiently sensitive to detect and quantify health gained from modest treatment effects [7]. Taking an overall view of the data currently available, it appears that disease-specific quality of life questionnaires do correlate with other measures of asthma severity. There is little reason to fear that patients will have good quality of life scores and yet also have deteriorating asthma.

The demonstration by Rutten van Molken et al. [3] that changes in health-related quality of life questionnaires correlated with more traditional measures of asthma severity raises the question of what additional information such questionnaires provide. The answer to this is related to two properties of such questionnaires that have not yet been discussed. The first is that they can produce a composite or global score that may provide an answer to the question: "What is the overall improvement with treatment?" Secondly, they may be used to address the question "Is the improvement worthwhile?" A number of different methodologies have been used to identify scores that may define the threshold for a clinically significant change in health [12–14]. In the salmeterol treated patients in this study, the total, Activities and Symptoms components of the Asthma Quality of Life Questionnaire approached or exceeded this threshold, whilst the Environment and Emotions components
did not. In contrast, in the patients using salbutamol, whilst improvements in all questionnaire components achieved statistical significance, none approached the threshold for clinical significance. These findings are slightly overshadowed by the demonstration that the relative health gain of salmeterol over salbutamol did not achieve the threshold for clinical significance, although it did, achieve statistical significance.

This study provides a useful step forward in the application of health-related quality of life measures to the evaluation of treatment efficacy. Such questionnaires offer the potential to distinguish between clinically and statistically significance changes with therapy. In addition, they may even allow further validation of measures of airways function. One useful observation from this study was that, in a population of patients with moderate asthma, a clinically significant improvement in health was achieved if the therapy produced a 33 L·min⁻¹ improvement in morning peak flow or a 9% predicted improvement in FEV₁.

References


