EXTENDED REPORT

Evaluation of clinically relevant states in patient reported outcomes in knee and hip osteoarthritis: the patient acceptable symptom state

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Background: The patient acceptable symptom state (PASS) is the value beyond which patients can consider themselves well. This concept can help in interpreting results of clinical trials.
Objective: To determine the PASS estimate for patients with knee and hip osteoarthritis (OA) by assessing pain, patient's global assessment of disease activity, and functional impairment.
Methods: A 4 week prospective multicentre cohort study of 1362 outpatients with knee or hip OA was carried out. Data on assessment of pain and patient's global assessment of disease, measured on visual analogue scales, and functional impairment, measured on the Western Ontario McMaster Universities Osteoarthritis Index (WOMAC) function subscale, were collected at baseline and final visits. The patients assessed their satisfaction with their current state at the final visit. An anchoring method based on the patient's opinion was used.
Results: For patients with knee and hip OA, the estimates of PASS were, respectively, 32.3 and 35.0 mm for pain, 32.0 and 34.6 mm for patient global assessment of disease activity, and 31.0 and 34.4 points for WOMAC function score. The PASS varied moderately across the tertiles of baseline scores but not across age, disease duration, or sex.
Conclusion: The use of PASS in clinical trials would provide more meaningful results expressed as a proportion of patients in an acceptable symptom state.

In clinical trials, at the group level, results are usually reported as mean and standard deviation of the change in score, which is not meaningful for most readers. The importance of incorporating patient perspectives in research into rheumatic diseases and defining outcomes that are comprehensive and influence clinical decision making was emphasised during the OMERACT 6 meeting.[1] Previous studies have dealt with the concept of the minimal clinically important difference (MCID)[2–4] or minimal clinically important improvement (MCII)[5] that could help in interpreting changes in scores in individual patients, by expressing the results as a proportion of improved patients. Another potentially clinically relevant concept is the patient acceptable symptom state (PASS), defined as the value beyond which patients consider themselves well. The MCID deals with the concept of improvement (feeling better) and the PASS the concept of wellbeing or remission of symptoms (feeling good). Thus, the PASS is undoubtedly a clinically relevant outcome for the patient.

The MCID and PASS concepts are complementary. If a patient with a high level of pain (90 mm on a 0–100 mm visual analogue scale (VAS)) experiences a decrease in pain of 40 mm, thus reaching 50 mm on the VAS, one can probably recognise a clinically relevant improvement (concept of MCID) but not a satisfactory state (concept of PASS). Results could be expressed both as a proportion of improved patients and of patients in a satisfactory state.

This prospective cohort study aimed at determining the PASS estimates for three main patient reported outcomes used in osteoarthritis (OA) trials[6]: pain, patient's global assessment of disease activity, and functional impairment.

MATERIALS AND METHODS

Study design

We conducted a 4 week prospective cohort study.

Study population

This study involved 1362 outpatients with knee and hip OA, as defined by the American College of Rheumatology,[7 8] included by 399 rheumatologists in France. Each rheumatologist had to include four patients, three with knee OA and one with hip OA. To be included in the study, patients had to experience pain from OA (≥30 mm on a VAS varying from 0 to 100), require treatment with a non-steroidal anti-inflammatory drug (NSAID), and be able to complete questionnaires in French. Inclusion could begin with the onset of treatment or a switch from one NSAID to another. Patients were excluded if they had a prosthesis on the assessed joint or if they had been treated by intra-articular injection in the 4 weeks before the study began. All patients initially visited the rheumatologist in charge of the patient, and an NSAID was prescribed (the drug and its dosage were chosen by the physician). A final visit to the same rheumatologist was scheduled 4 weeks later.

Table 1 shows the descriptive statistics on clinical and demographics variables.

Abbreviations: LDA, low disease activity; MCID, minimal clinically important difference; MCII, minimal clinically important improvement; NSAID, non-steroidal anti-inflammatory drug; OA, osteoarthritis; PASS, patient acceptable symptom state; VAS, visual analogue scale; WOMAC, Western Ontario McMaster Universities Osteoarthritis Index

Table 1 Baseline characteristics of patients

	Knee OA (n = 914)		Hip OA (n = 310)	
	Mean	SD	Mean	SD
Age (years)	67.8	10.2	65.7	10.8
Weight (kg)	75.2	14.2	72.2	14.0
Height (cm)	163.6	8.7	164.8	8.2
Body mass index (kg/m^2)	28.1	4.7	26.5	4.1
Disease duration (years)	4.8	5.8	3.4	4.8
Pain score (0–100 mm VAS)				
Week 0	58.3	16.9	56.7	17.4
Change (week 0–week 4)	−24.5	22.1	−18.7	21.8
Patient global assessment (0–100 mm VAS)				
Week 0	58.7	19.1	58.6	16.5
Change (week 0–week 4)	−24.0	24.6	−19.5	23.5
WOMAC function score (0–100)				
Week 0	42.9	16.6	45.9	17.1
Change (week 0–week 4)	−11.6	14.4	−10.8	14.1
	No	**(%)**	**No**	**(%)**
Female sex	637	(69.7)	189	(61.0)
Kellgren and Lawrence grade				
II	178	(19.5)	57	(18.5)
III	394	(43.1)	145	(46.9)
IV	342	(37.4)	107	(34.6)
NSAID* intake during past 4 weeks	262	(28.8)	97	(31.3)
Analgesic intake†	513	(56.3)	209	(67.9)
Symptomatic slow acting drugs intake‡	311	(34.1)	123	(39.8)

*Non-steroidal anti-inflammatory drugs (before the start of the study); †other than NSAIDs (before the start of the study); ‡chondroitin sulphate, diacerhein, or avocado soybean unsaponifiables.

Measurements

The design of the trial included a baseline visit to the rheumatologist, a 4 week NSAID treatment phase, and a final visit at week 4. At the baseline visit, demographic and disease data (in particular, disease duration) were collected. Patients assessed their OA status at baseline and final visit. They assessed the following patient reported outcomes: (*a*) pain on movement during the 48 hours before the visit, measured on a 0–100 mm VAS; (*b*) global assessment of disease activity, measured on a 0–100 mm VAS; and (*c*) physical function, measured on the Western Ontario McMaster Universities Osteoarthritis Index (WOMAC) function subscale (17 items, five point Likert scale for each item; high scores indicate high degree of functional impairment; total score normalised to a 0–100 score).

At the final visit, patients' opinions of their state was also recorded by their answering ''Yes'' or ''No'' to ''Taking into account all the activities you have during your daily life, your level of pain, and also your functional impairment, do you consider that your current state is satisfactory?''.

Statistical analysis

All the analyses considered patients with knee and hip OA separately.

We used an anchoring method based on patient satisfaction with the current state. The same methods as for the MCII study (see companion paper in this issue[5]) were used, and the PASS was estimated by constructing a curve of cumulative percentages of patients as a function of the score of interest at the final visit among patients who considered their state satisfactory. Logistic regression was used to model the observations (fig 1). We targeted the point at the flattening of the curve at which most subjects stated they had a satisfactory status. This point corresponds to the 78.9th centile of the final score, and thus we propose to define the PASS as the 75th centile of the final score (at week 4), because it is very close to the point defined above and easier to derive. The model permitted us to determine that the target point was correctly approached by the 75th centile and to estimate the 95% confidence intervals. We also modelled the data from patients who considered their state unsatisfactory (fig 1).

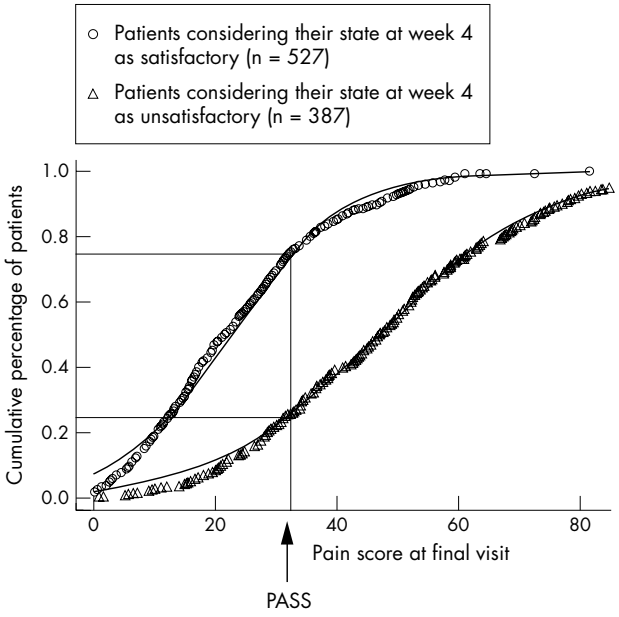

Figure 1 Aspects of the cumulative distribution function used to determine the PASS (pain scores in patients with knee OA). Among patients considering their state as satisfactory, 75% assessed their pain score at final visit below 32.3 mm on a 0–100 mm VAS (which is the PASS limit). Among patients considering their state as unsatisfactory, only 25% assessed their pain score at final visit below 32.3 on a 0–100 mm VAS.

In a second step, we stratified the analysis on the baseline score of interest (divided into tertiles) to assess whether the baseline scores for level of pain, patient's assessment of disease activity, and functional impairment affected the PASS estimates. That is we stratified (*a*) on the baseline pain score to estimate the PASS for pain; (*b*) on the baseline patient's assessment of disease activity score to estimate the

Table 2 Patient acceptable symptom state (PASS) scores according to location of OA

	Knee OA		Hip OA	
Patient reported outcomes	**PASS**	**(95% CI)**	**PASS**	**(95% CI)**
Pain (0–100 mm VAS), mm	32.3	(30.1 to 34.7)	35.0	(32.8 to 37.4)
Patient global assessment (0–100 mm VAS), mm	32.0	(29.5 to 34.8)	34.6	(32.3 to 37.1)
WOMAC function score (0–100)	31.0	(29.4 to 32.9)	34.4	(31.9 to 37.3)

PASS for patient's assessment of disease activity; and (*c*) on the baseline WOMAC function score to estimate the PASS for functional impairment.

In a third step, to investigate the effect of covariates (other than location of OA) on the PASS, we stratified the analysis successively by age, disease duration (both divided into tertiles), and sex.

Statistical analyses was performed with the SAS Release 8.2 statistical software package and the S plus 4.5 statistical software package.

Compliance with research ethics standards

This study was conducted in compliance with the protocol, good clinical practices, and the Declaration of Helsinki principles.

RESULTS

A total of 1362 patients were enrolled in the study: 1019 (75%) had knee and 343 (25%) hip OA; 913 (67%) were female; and the mean (SD) age was 67.2 (10.5) years. A total of 914 (90%) patients with knee and 310 (90%) with hip OA completed the final visit. Patients lost to follow up were excluded from the analysis and did not differ from completers in their baseline characteristics.

Among the completers, 527/914 (57.7%) patients with knee and 156/310 (50.2%) with hip OA considered their functional state at week 4 as satisfactory.

Table 2 lists the PASS estimates for the three patient reported outcomes and gives their 95% confidence intervals. For instance, patients with knee OA considered their state satisfactory if their pain score was less than 32.3 mm on the 0–100 mm VAS. The PASS estimates are similar (scores of approximately 33) across location of OA, whatever the patient reported outcome. These values are very close to those calculated for the 25th centile of the cumulative distribution function for the final score among patients with knee (fig 1) and hip (data not shown) OA who considered their functional state unsatisfactory.

Table 3 shows the estimates of the PASS stratified on the baseline score of interest. For instance, patients with knee OA with severe pain (high tertile of baseline pain score) considered their state satisfactory if their pain score was <27 mm on the 0–100 mm VAS. The PASS estimate varied moderately across tertiles of baseline scores (the higher the baseline score, the higher the PASS), but this trend is clearer for functional impairment.

The PASS estimates did not vary across age or disease duration tertiles or sex (data not shown).

DISCUSSION

In this prospective study we estimated the PASS for the three main patient reported outcomes used in clinical trials in knee and hip OA.

The PASS is the value beyond which patients consider themselves well. Thus, it can be considered a clinically relevant treatment target. It is an absolute value, not a change. Describing the number of patients achieving and maintaining such a state for a specified period of time will add useful information for daily practice and aid in the interpretation of trial and longitudinal results.[9]

This concept is very close to the low disease activity (LDA)[10 11] but applies only to patient reported outcomes (that is, symptoms). The LDA reflects an intermediate state between high disease activity and remission that could be called LDA or partial remission. An OMERACT 6 workshop focused on this concept for rheumatoid arthritis.[11] LDA was defined as a disease activity state deemed a useful treatment target by both physicians and patients. The definition of the PASS is anchored to the personal experience of the patient (satisfaction and adaptation to symptoms), although the LDA is anchored to both the patient's experience and the physician's clinical experience (treatment decision and prognosis). In a symptomatic disease such as OA, PASS and LDA are joined. In a disease such as rheumatoid arthritis, the PASS deals only with patient reported outcomes, although

Table 3 Patient acceptable symptom state (PASS) in patients with knee or hip OA, by baseline score of interest divided into tertiles

	Knee OA			Hip OA		
	Baseline score tertile			**Baseline score tertile**		
	Low	**Intermediate**	**High**	**Low**	**Intermediate**	**High**
Pain (0–100 mm VAS)	27.0 (24.6 to 29.9) {30 to 51.0}	34.5 (32.3 to 37.0) {51.1 to 66.2}	36.4 (33.2 to 40.0) {>66.2}	29.4 (26.0 to 33.7) {30 to 49.3}	35.2 (32.8 to 37.9) {49.4 to 65.4}	43.6 (38.9 to 49.6) {>65.4}
Patient's global assessment (0–100 mm VAS)	28.3 (25.5 to 31.6) {⩽50.4}	34.3 (32.1 to 36.7) {50.5 to 68.7}	34.4 (32.1 to 36.7) {>68.7}	30.3 (26.6 to 34.9) {⩽49.9}	33.5 (31.0 to 36.5) {50.0 to 69.9}	41.2 (37.2 to 45.9) {>69.9}
WOMAC function score (0–100)	20.4 (19.1 to 21.8) {⩽35.3}	33.0 (31.3 to 34.9) {35.4 to 51.5}	43.1 (40.8 to 45.7) {>51.5}	20.6 (19.1 to 22.3) {⩽38.2}	34.4 (31.9 to 37.4) {38.3 to 52.9}	44.2 (41.0 to 48.2) {>52.9}

Results are shown as the PASS (95% confidence interval) {tertile}.

the LDA also encompasses factors such as biological signs of inflammation.

The concept of PASS is based on patient opinion as an external anchor, according to the OMERACT LDA module recommendation (the opinion based rather than data based approach seems more appropriate in deriving the LDA definition). The large sample of patients used as experts to determine remission in symptoms in our study is a good indicator of the representativeness.

The PASS was defined as the 75th centile of the final score in patients who considered their state satisfactory. This threshold relies on the data modelling and was chosen with the help of experts (NB, CB, DF, MH, DvdH, MD). However, these values are very close to those calculated for the 25th centile of the cumulative distribution function for the final score among patients who considered their functional state unsatisfactory. Thus, beyond the PASS limit were 75% of the patients who considered their current state satisfactory and only 25% of those who did not. Otherwise, the estimates of the PASS range from approximately 30 to 33 on a 0–100 point scale, whatever the patient reported outcome. The relevance of these results is reinforced by results which showed, in a study of patients who used intravenous patient controlled analgesia to self administer morphine sulfate after intra-abdominal surgery, that only 4% who rated their pain <30 mm on the 0–100 mm VAS requested additional analgesia, compared with 43–80% of those with pain scores of 31–70 or higher.[12] Thus, a pain score of <31 mm seems acceptable in this context as well.

In our study we investigated the effect of several covariates on the PASS estimates. The PASS varied moderately across the tertiles of baseline scores but less markedly than the MCII.[5] Thus, the PASS seems to be more robust than the MCII, which is affected by the initial level of symptoms, so the PASS is the recommended choice. However, the other factors investigated (age, sex, OA location, and disease duration) did not consistently modify the PASS estimates.

In conclusion, this study, dealing with a concept of emerging use, provides preliminary information facilitating the presentation and interpretation of results obtained in clinical trials. Further studies involving different datasets, clinical environments, languages, and countries, are necessary to validate these observations.

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