Patient Acceptable symptom state in scleroderma: Results from the tocilizumab compared to placebo trial in active diffuse cutaneous systemic sclerosis

Authors: Michael B. Arnold, MD,[1] Dinesh Khanna, MD,[2] Christopher P. Denton, MD,[3] Celia J.F. Lin MD,[4] Jacob M. van Laar, MD,[5] Tracy M. Frech, MD,[6] Marina E. Anderson, FRCP,[7] Murray Baron, MD,[8] Lorinda Chung, MD,[9] Gerhard Fierlbeck, MD,[10] Santhanam Lakshminarayanan, MD,[11] Yannick Allanore, PhD,[12] Gabriela Riemekasten, PhD,[13] Virginia Steen, MD,[14] Ulf Müller-Ladner, MD,[15] Helen Spotswood, PhD,[16] Laura Burke, BSc (Hons),[16] Jeffrey Siegel, MD,[4] Angelika Jahreis, MD[4], Daniel E. Furst, MD,[17] Janet E. Pope, MD.[1]

Affiliations: [1]Schulich School of Medicine and Dentistry, Western University, London, Canada [2]University of Michigan Scleroderma Program, Ann Arbor, MI, United States; [3]University College London Medical School, London, United Kingdom; [4]Genentech, South San Francisco, CA, United States; [5]University of Utrecht, Utrecht, Netherlands; [6]University of Utah, Veterans Affairs Medical Center, Salt Lake City, UT, United States; [7]University of Liverpool and Aintree University Hospital, Liverpool, United Kingdom; [8]Jewish General Hospital, Montreal, QC, Canada; [9]Stanford University School of Medicine and Palo Alto VA Health Care System, Palo Alto, CA, United States; [10]University of Tubingen, Tubingen, Germany; [11]University of Connecticut Health Center, Farmington, CT, United States; [12]Paris Descartes University, Paris, France; [13]Charité University Hospital, German Rheumatism Research Center, Berlin, Germany; [14]Georgetown University, Washington, DC, United States; [15]Justus-Liebig University Giessen, Kerckhoff Clinic, Bad Nauheim, Germany; [16]Roche Products Ltd., Welwyn Garden City, United Kingdom; [17]University of California, Los Angeles, CA, United States

Corresponding Author: Dr. Janet Pope, MD
Professor of Medicine, Western University, Division of Rheumatology
St Joseph's Health Care, London, ON, Canada
Address: 268 Grosvenor St., London, ON N6A 4V2
Phone: 519-646-6332
Fax: 519-646-6334
Email: janet.pope@sjhc.london.on.ca

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Abstract

Objectives: Patient Acceptable Symptom State (PASS) as an absolute state of well-being has shown promise as an outcome measure in many rheumatologic conditions. We assessed whether PASS may be effective in active diffuse cutaneous SSc.

Methods: Data from the Phase 2 faSScinate trial were used, which compared tocilizumab vs. placebo over 48 weeks followed by an open-label tocilizumab period to 96 weeks. Three different types of PASS questions were evaluated at weeks 8, 24, 48 and 96, including would a current state be acceptable over time as yes vs. no response, and Likert scales about how acceptable a current state is if remaining over time. Additional outcomes assessed included mRSS, HAQ-DI, MD and Pt global VAS, CRP and ESR.

Results: The placebo group consisted of 44 patients, and the tocilizumab group had 43 patients. At baseline, 33% achieved PASS for all three PASS questions, with the proportion increasing to 69%, 71% and 78%, respectively at 96 weeks. Changes in PASS scores showed a moderately negative correlation with HAQ-DI, Pt and MD global VAS, which indicates expected improvements as PASS improved. PASS asking 'Considering all of the ways your scleroderma has affected you how acceptable would you rate your level of symptoms?' showed significant correlations with patient-reported outcomes and differentiating placebo vs. tocilizumab at 48 weeks (P=0.023).

Conclusions: PASS may be used as patient-centered outcome in SSc especially as a 7-point Likert scale. Further validation is required to determine the utility as an outcome measure in trials and clinical practice.

Trial registration number: ClinicalTrials.gov, number NCT01532869.

Keywords: scleroderma, systemic sclerosis, diffuse systemic sclerosis, patient acceptable symptom state, PASS, patient-reported outcomes, tocilizumab, outcome measure.

•**Key Messages:**PASS may be used as an effective patient-centered outcome in active diffuse cutaneous SSc.

•PASS is not the same as patient global assessment and may have added value in scleroderma.

•PASS is best assessed by level of symptom acceptability on a 7-point Likert scale.

Introduction

Systemic sclerosis (SSc) is a rare connective tissue disease that is characterized by fibrosis, inflammation and vascular damage. Clinical presentations are heterogeneous in nature, affecting the skin as well as pulmonary, cardiac, renal and gastrointestinal systems. Diffuse cutaneous SSc (dcSSc) has a high mortality (1). Clinical trials are ongoing to search for more effective treatment options, with the faSScinate trial assessing the effectiveness of tocilizumab, a novel IL-6 antibody in a randomized placebo controlled trial in dcSSc (2).

Designing effective clinical trials in SSc has many challenges, which is in part due to the paucity of previous positive studies in SSc (2). The heterogeneity of the disease along with its varying clinical presentation makes it difficult to identify what outcome measures to assess. Often the modified Rodnan skin score (mRSS) is a primary endpoint (3). Patient reported outcomes have been used as a means of understanding what patients' view as a satisfactory response to therapy. The concept of minimal clinically important difference (MCID) has been seen as a helpful way to provide complementary and more meaningful information to the endpoints of a trial (4, 5). However, Tubach et al. (6) have shown that patients care more about feeling good than they do about feeling better. For instance, if there is a large change in status but a patient is still in a moderate state of activity, this is not preferred, as the goal is likely to feel good, not to benchmark as feeling better than a previous state.

Patient acceptable symptom state (PASS) is an outcome measure that allows for assessing either when patients feel good or when patients feel better. The OMERACT (Outcome Measures in Rheumatology) meeting in 2007 established the concept of PASS, however there has been no standardized question across diseases (5). Achieving a PASS is dependent on how this question is asked, but generally is used to describe the point beyond which patients consider themselves well (7). The aim of introducing PASS is to provide a

means to translate a holistic look at patients' symptoms into more clinically meaningful information.

PASS has been demonstrated to be an effective assessment and robust marker in many rheumatologic diseases (8-11), although it is yet to be evaluated in SSc. Our aim was to assess the effectiveness of PASS as an outcome marker for SSc using patients from the faSScinate trial including relationships to other outcomes and if and when it could differentiate active treatment from placebo.

Methods

Study Population

This study uses data collected from patients enrolled in the faSScinate trial, which is outlined in detail by Khanna et al. (2). To summarize, this was a 48 week randomized control trial with another 48 weeks of open label extension, that enrolled 87 patients who had a diagnosis of SSc according to the 1980 American College of Rheumatology Criteria and demonstrated signs of active disease (12) and active dcSSc subset. Patients were randomized to tocilizumab (TCZ) 162 mg sc weekly or placebo (PBO) and were assessed at regular intervals. The primary outcome was modified Rodnan Skin Score (mRSS) assessed at 24 weeks. At 24 weeks, the treating physician could place patients on rescue medication as deemed necessary, while all patients could be transitioned to TCZ at 48 weeks. While the results for the primary outcome resulted in a negative study, there was a clinically meaningful decline in mRSS over 48 weeks in the tocilizumab group compared with the placebo group as determined by MCID.

Patient Acceptable Symptom State

There has been no standardized question as to the best way to ask a patient whether they are in an acceptable symptom state (13). Previous studies have evaluated dichotomous and scaled patient reported outcomes as well as statistical approaches to define PASS (5, 8-10). We evaluated three questions that considered dichotomous vs. scaled outcomes as well as the acceptability of symptoms vs. changes to baseline.

PASS #1 was aimed at assessing level of acceptability of symptoms based on a scale. "Considering all of the ways your scleroderma has affected you over the last week, how acceptable would you rate your level of symptoms?" Responses were reported on a 7-point Likert scale with choices ranging from -3 (highly unacceptable) to 3 (highly acceptable).

PASS #2 used the level of acceptability as a dichotomous outcome. "Think about all the ways that your scleroderma has affected you during the last week. If you were to remain for the next few months as you were in the last week, would this be acceptable to you?" Responses were reported as either Yes or No.

PASS #3 asked for a change of symptoms "Has there been a change in how you would describe your level of functional impairment since you started the study?" Responses were reported on a 5-pont Likert scale with choices ranging from -2 (much worse) to 0 (no change) to 2 (much better).

Outcomes assessed

Khanna *et al*. (14) recently provided suggestions as to the most relevant disease outcome markers to consider in trials on SSc. These included mRSS, percent predicted of forced vital capacity (%pFVC), physician global assessment (MD global VAS), patient global assessment (Pt global VAS), and health assessment questionnaire-disability index (HAQ-DI). We considered all of these outcomes with the exception of %pFVC, as successful treatment is expected to slow progression of lung disease rather than lead to improvement in

symptoms. Additionally, we included C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) to assess systemic inflammation. Patients were evaluated at weeks 8, 24, 48 and 96.

Statistical Analysis

Normality for each of the outcome markers was assessed using the Shapiro–Wilk test. Patient characteristics were analyzed using independent samples *t*-tests with two-tailed P values. The proportion of patients achieving PASS #1 and #3 was considered as a 1-point increase from their baseline visit score, whereas PASS #2 was having a response of "Yes." Correlations were assessed using Goodman and Kruskal's gamma value due to the many tied ranks with respect to the PASS questions and other outcomes at weeks 8, 24, 48 and 96. Determining significance of PASS in differentiating patients on tocilizumab vs. placebo was done using Pearson Chi-square value. P-values < 0.05 were considered significant. All analysis was carried out using SPSS version 24.

Results

Patient characteristics comparing placebo vs. tocilizumab are presented in Table 1. There were 44 patients at baseline in the placebo group and 43 patients in the tocilizumab group. At baseline, PASS #1 had 32 (73%) and 35 (81%) patients scoring a 0 or less, respectively for placebo and tocilizumab. PASS #2 had 28 (63.6%) and 29 (69%) responding with a "No," respectively. PASS #3 was designed to have a baseline of 0 suggesting no change, however only 36 (82%) and 32 (74%) responded with a baseline score of 0, respectively. There were no reports of patients refusing to answer PASS.

All outcomes were non-normally distributed with the exception of age and mRSS. A greater number of patients were discontinued from the trial in the placebo group (n = 20) vs.

the tocilizumab group (n = 16), but with no statistical significance identified. Similarly, 9 (28%) patients required rescue meds in the placebo group compared to 3 (10%) in the tocilizumab group between 24 to 48 weeks, but without statistical significance. Baseline characteristics were similar between active and placebo (refer also to Table 1 and Figure 1 of the faSScinate paper) (2).

The three PASS questions are evaluated and compared in Table 2. The proportion of patients achieving PASS increased for all three questions as the trial progressed, with the proportions being similar across all three questionnaires at each visit. The majority of patients had achieved PASS by the end of the trial (69%, 71% and 78% for PASS #1, #2 and #3, respectively).

PASS #1 at 48 weeks showed statistical significance in being able to differentiate those patients on placebo vs. tocilizumab (P value = 0.023) where a greater than or equal to one-point change on the Likert scale could differentiate tocilizumab from placebo. Pt global VAS and HAQ-DI score showed a moderately negative correlation across all three PASS questions. MD Global VAS also showed a moderately negative correlation that was statistically significant for PASS #2 and #3. Total mRSS, CRP and ESR did not show a correlation with any of the PASS questions.

Discussion

This paper is the first to assess the usefulness of PASS in a RCT in SSc. We found that the majority of patients in the faSScinate study had achieved PASS by the end of the trial. Given the clinically meaningful changes identified with tocilizumab (2), PASS was able to differentiate between placebo and tocilizumab.

Evaluating PASS in trials involving SSc appears to be a reliable means of complementing primary endpoints of studies by weighing up the benefits or harms that

patients may experience from therapy. As a result, PASS has the benefit of being able to translate results from large trials to an individual level, thus providing further guidance for patient decisions (7). No patients refused to answer PASS, which along with previous studies suggests its acceptability (8).

The PASS questions were moderately correlated with HAQ-DI score, Pt global VAS and MD global VAS. This means that as these disease outcomes improve, patients are more likely to enter into an acceptable symptom state. When assessing active dcSSc and drugs to improve skin and overall disease, it is not likely that most treatments will improve the GI involvement, Raynaud's and other symptoms when softening skin and/or targeting lung function. Asking a PASS question is a holistic way to determine if the treatment is improving their quality of life overall. Patients likely consider the benefit of treatment, the side effects and their SSc symptoms altogether. The moderate correlation identifies that PASS is sufficiently different from these outcomes, suggesting that it may consider additional aspects of a patient's disease state that our current outcome markers do not evaluate. Despite mRSS being the primary endpoint in many SSc trials (3), including the faSScinate trial (2), there was no correlation seen with PASS. This suggests that mRSS complements patient-reported outcome measures and may actually play a smaller role in affecting the patient's symptom state than previously expected, at least for the degree of skin improvement that occurs during a RCT where the change is modest. An example of this is that hand function is often still quite impaired, as skin tends to soften more in proximal areas first.

Our findings support the use of PASS #1 in future clinical trials. Although an improvement of 1-point does not indicate whether patients have reached an absolute acceptable symptom state, it does serve to distinguish tocilizumab vs. placebo, which can be used as an endpoint in future clinical trials. Whereas PASS #2 only showed a trend towards statistical significance, it could serve as a reasonable alternative given its validation in

previous trials (8, 16). The simple dichotomous outcome does indicate whether patients have reached an absolute acceptable symptom state, but concerns arise due to loss of statistical power in what is already a rare disease (5). We would advise against using PASS #3 given lack of statistical significance and patients misinterpreting the question.

Although achieving PASS suggests a state of wellbeing, it is not synonymous with achieving perfect health (15). PASS #1 helps to instruct clinicians as to when their patients feel better from treatment. Conversely, PASS #2 gives clinicians a sense of when patients feel good and reach a level of contentment with their current symptoms. PASS #1 and #2 ask the current state acceptability whereas #3 is a change in state. The first two are an absolute state. It is difficult to interpret what it means to "achieve a PASS" to a patient with SSc and to their treating physician.

There are inherent limitations in an exploratory analysis. When evaluating patients at 48 weeks, a disproportionate number of patients between the placebo and tocilizumab groups received rescue medication, possibly limiting the ability of PASS to differentiate placebo vs. tocilizumab. For the patients remaining in the study up to 96 weeks (in the open label extension between 48 and 96 weeks), more patients entered into an acceptable symptom state, so a longer duration of placebo vs. tocilizumab could have provided more power to differentiate the two groups. Raynaud's and gastrointestinal symptoms are examples of symptoms that may be strongly correlated with patients achieving PASS or not, which this study did not evaluate.

Conclusion

In summary, PASS may be used as an effective outcome marker in SSc. PASS is likely to be most effective when evaluating the acceptability of symptoms based on a 7-point

Likert scale. Further validation of PASS in clinical trials and practice in SSc are required to

determine if the findings of this study are consistent.

End notes

Abbreviations:
    SSc – Systemic sclerosis
    PASS – Patient acceptable symptom state
    MCID – Minimal clinically important difference
    PBO – Placebo
    TCZ – Tocilizumab
    mRSS – Modified rodnan skin score
    HAQ-DI – Health assessment score-disability index
    MD global VAS– Physician global assessment
    Pt global VAS – Patient global assessment
    VAS – Visual analog scale
    CRP – C-reactive protein
    ESR – Erythrocyte sedimentation rate
    %pFVC – Percent predicted force vital capacity
    OMERACT - Outcome measures in rheumatology

collected and interpreted data. VS designed the study and collected data. UM-L analysed and interpreted data. GS designed the study and collected, analysed, and interpreted data. HS designed the study and analysed and interpreted data. HC-H collected and analysed data. SD designed the study and collected data. AM and TS collected, analysed, and interpreted data. DEF designed the study, collected and analysed data. All authors revised the report and approved the final draft for publication. JEP designed the study, collected, analysed and interpreted data, and wrote the report.

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Table 1 – Patient characteristics of placebo vs. tocilizumab

Baseline	Placebo (n = 44)	Tocilizumab (n = 43)
PASS #1, # selecting "Score of -3 to 0" (%)[a]	32 (73)	35 (81)
PASS #2, # selecting "No" (%)[a]	28 (64)	29 (69)
PASS #3, # selecting "Score of 0" (%)[a]	36 (82)	32 (74)
Age	48 (12.9)	51 (11.7)
Female, # (%)	35 (80)	32 (74)
White, # (%)	40 (91)	38 (88)
Duration of SSc, days	595 (517)	537 (418)
Total mRSS[b]	25.6 (5.9)	26.5 (7.2)
HAQ-DI score[b]	1.36 (0.74)	1.31 (0.61)
MD Global VAS, mm[b]	60.1 (15.2)	64.1 (15.1)
Pt Global VAS, mm[b]	61.9 (21.0)	60.0 (18.3)
CRP, mg/L[b]	10.5 (13.6)	10.5 (13.7)
ESR, mm/h[b]	26.2 (21.2)	31.0 (18.8)
Follow up during the trial		
Discontinued from trial, # (%)	20 (45)	16 (37)
Rescue Medication		
By Week 48, #yes (% of n)	9 (28)	9 (38)
By Week 96, #yes (% of n)	3 (10)	6 (22)

All values are mean (SD) unless stated otherwise.
[a]Possible scores are: PASS #1, -3 (highly unacceptable) to 3 (highly acceptable); PASS #2, yes/no; PASS #3, -2 (much worse) to 0 (no change) to 2 (much better).
[b]Possible scores are: mRSS, 0-51; HAQ-DI, 0-3; Global VAS, 0-100; upper limit of normal for CRP is 3 mg/L; ESR is dependent on age and gender.
PASS – Patient Acceptable Symptom State; mRSS – modified Rodnan Skin Score; HAQ-DI – Health Assessment Score-Disability Index; MD – physician; Pt – patient; VAS – Visual Analog Scale; CRP – C-Reactive Protein; ESR – Erythrocyte Sedimentation Rate.

Table 2 – Evaluation of PASS Questions

	PASS #1	PASS #2	PASS #3
Proportion achieving PASS [a]			
Week 8, # (%)	26 (33)	26 (33)	26 (33)
Week 24, # (%)	27 (39)	28 (41)	34 (48)
Week 48, # (%)	28 (45)	34 (55)	31 (50)
Week 96, # (%)	35 (69)	36 (71)	40 (78)
Placebo vs. Tocilizumab (P value) [b]			
Week 8			0.877
Week 24			0.156
Week 48			0.023*
			0.747

0.280

0.070

0.230

0.287

0.611**Correlations with outcome markers at Week 96 (Gamma value)**[c]

MD Global VAS

Pt Global VAS

HAQ-DI score

Total mRSS

CRP

ESR

-0.208

-0.430**

-0.264*

-0.106

0.022

-0.162

-0.395*

-0.453**

-0.494**

0.013

0.061

0.154

-0.396**

-0.480**

-0.530**

-0.193

-0.092

-0.064

For Proportion achieving PASS and Tocilizumab vs. Placebo sections, PASS #1 and #3 considered those patients with a 1-point increase from baseline. PASS #2 considered patients with a response of "Yes."
[a]Percentages were calculated based on available data for each time period.
[b]p-values were calculated using Chi-square analysis.
[c]Values were calculated using Goodman and Kruskal's gamma. Negative value indicates a negative correlation, in which a decrease in relative relates with improvement in PASS score.
* indicates P value <0.05, ** indicates P value <0.01

ion to the 2 tables in Results.
In order to fit the requirements of a concise report, only 2 tables are permitted. The last two rows of this table do provide some valuable information to what is referenced in the Results section. They were simplified in this table in hopes of making it easier for the reader to understand and digest.