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Research paper

Development of a harmonized patient-reported outcome questionnaire to assess myelofibrosis symptoms in clinical trials

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ABSTRACT

Along with reducing spleen size, relieving symptom severity is a key objective of the treatment of myelofibrosis (MF). Several questionnaires have been developed for patient self-report of MF symptoms in clinical trials and each includes unique instructions, items, and/or response scales. This variability in questionnaire content increases uncertainty; it is unclear which questionnaire is the most appropriate for assessing MF symptoms and it makes comparisons across trials difficult. The Patient-Reported Outcome (PRO) Consortium's MF Working Group (WG) was established to review existing MF symptom questionnaires and to develop a harmonized, consensus-based PRO questionnaire for use in future MF trials. The WG focused on the seven core symptoms of MF: fatigue, night sweats, pruritus, abdominal discomfort, pain under the ribs on the left side, early satiety, and bone pain. The resulting Myelofibrosis Symptom Assessment Form version 4.0 (MFSAF v4.0) asks respondents to report symptom severity at its worst for each of the seven items on a 0 (Absent) to 10 (Worst Imaginable) numeric rating scale. The MFSAF v4.0, for which there are 24-h and 7-day recall formats, will be maintained and licensed by the Critical Path Institute and made publicly available for use in future clinical trials.

1. Introduction

Myelofibrosis (MF) is a chronic Philadelphia chromosome-negative myeloproliferative neoplasm that primarily affects older individuals and is characterized by progressive bone marrow fibrosis and ineffective hematopoiesis. Dysregulation of the Janus kinase (JAK) −STAT pathway resulting from mutations that lead to constitutively active JAK2 [1,2] or increased proinflammatory cytokines that signal through JAK1 and JAK2 [3] are believed to underlie splenomegaly and symptoms associated with MF. This understanding of the underlying pathophysiology of MF has led to the development of new treatments; Ruxolitinib is approved for the treatment of MF, and other JAK inhibitors [4–7] and non-JAK inhibitor compounds [8] are under investigation.

MF is associated with significant, debilitating symptoms including early satiety, abdominal discomfort, and pain under the ribs on the left side of the body due to splenomegaly and fatigue, night sweats, bone pain, fever, and weight loss due to inflammation and hypercatabolic state [9–15]. Although some of these symptoms, such as fatigue, are not specific to MF, their prevalence and severity are substantially higher among patients with myeloproliferative neoplasms than in matched controls [16]. Demonstrating an improvement in MF symptoms is an important goal in clinical trials. This improvement may be manifested as a reduction in symptom burden from baseline, a delay in worsening of symptoms, or both. Ruxolitinib substantially reduced symptoms in the COMFORT-I trial; a reduction in symptoms of 50% or more was observed in 45.9% of patients assigned to ruxolitinib compared to 5.3% of patients assigned to placebo [14]. Symptom reductions were also

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observed in an open-label, dose-ranging study of fedratinib [17] and in a randomized clinical trial of pacritinib [18].

Several questionnaire variants for patient self-report of MF symptoms have been used in clinical trials and observational research. These variants include different symptoms, recall periods, descriptions of symptoms, and/or response scales. This variability increases uncertainty associated with assessing symptoms in trials. In the drug development context, lack of a harmonized questionnaire may lead to regulatory uncertainty as well as unnecessary expenditure of substantial time and money to develop new questionnaires, which further compounds the problem. Stakeholders reviewing MF trials, including regulatory bodies, are required to evaluate each MF symptom questionnaire variant, which increases complexity and may make it difficult to interpret observed effects on symptoms. Additionally, the use of multiple MF symptom questionnaires makes it difficult to compare the efficacy of different treatments across trials. The development of a harmonized MF symptom questionnaire that can be used across clinical trials is needed to address these limitations.

The MF Working Group was established by the Critical Path Institute's Patient-Reported Outcome (PRO) Consortium [19] to create a publicly available, consensus-based, harmonized version of an MF symptom questionnaire that can be used across MF treatment trials. Another goal of the Working Group is to facilitate adoption of the harmonized MF symptom questionnaire by the biopharmaceutical industry and academic investigators. The Working Group focused on seven symptoms of MF identified through existing patient- and clinician-based evidence to be the most relevant: fatigue, night sweats, pruritus, abdominal discomfort, pain under the ribs on the left side of the body, early satiety, and bone pain. After a significant amount of preparatory work was completed and the existing evidence was assembled, the MF Working Group held a meeting on March 2, 2016, to gain consensus around a harmonized MF symptom questionnaire. The harmonization panel included an MF patient, representatives from the Critical Path Institute, US Food and Drug Administration (FDA), and pharmaceutical companies, as well as clinical experts and individuals with expertise in the development of PRO questionnaires for use in clinical trials. This article describes the efforts of the MF Working Group and the outcome of the harmonization meeting.

2. Review of existing measures

The MF Working Group conducted a comprehensive review of existing MF symptom questionnaires, in order to identify items that had been used to assess the seven core MF symptoms in previous studies. The questionnaires were identified through a review of the published literature and by soliciting information from questionnaire developers. Eight MF symptom questionnaires were identified (Table 1; see also supplemental materials) along with several individual items that were designed to address specific MF symptoms. All of the questionnaires are directly related to the original published questionnaire for MF symptoms – the Myelofibrosis Symptom Assessment Form (MF-SAF) [15]. The MF-SAF includes 20 items that assess six of the seven core MF symptoms, as well as 14 other signs and symptoms that may be related to MF (Table 1). The number of items has generally decreased with subsequent iterations, resulting in an almost exclusive focus on the seven core MF symptoms in more recent questionnaires.

There are notable similarities across the questionnaires. The core symptoms of night sweats, pruritus, abdominal discomfort, and bone pain are captured across all of the questionnaires. All of the items use a 0–10 numeric rating scale (NRS) for responding and, with the exception of early items drawn from the Brief Fatigue Inventory [20], the anchors used at the extremes of the response scale are "Absent" and "Worst Imaginable."

However, there are also notable differences between the versions.

- Early versions assessed signs of MF, most notably fever and weight loss (Table 1).
- Several of the questionnaires also include functional limitations associated with MF, such as inactivity.
- Some of the questionnaires assess the severity of symptoms (e.g., "Select the one number that describes the worst severity you have experienced with each of the following in the past 24 h"), while others assess difficulty associated with the symptom (e.g., "Circle the one number that describes how much difficulty you have had with each of the following symptoms during the past week.").
- Early versions of the symptom questionnaires asked patients to consider the past week when responding to items and were administered at the clinical site, while more recent versions tend to use a 24-h recall period and are administered via electronic diary in the patient's home environment.
- Each individual symptom item used in the ruxolitinib COMFORT-I trial asked patients to attribute their symptoms to MF, while items in other questionnaires do not require this attribution.
- Early questionnaires included up to 10 items drawn from the Brief Fatigue Inventory; later versions include single items assessing fatigue (although this single item is based on an item from the Brief Fatigue Inventory). Notably, fatigue was not assessed at all in the Myelofibrosis Symptom Assessment Form version 2 (MFSAF v2) used in the COMFORT-I trial, but is included in every other questionnaire.
- The core symptom of pain under the ribs on the left side of the body is included across questionnaires less frequently than any other core symptom (Table 1).
- Recent items (not included in a formal questionnaire and, therefore, listed only in the supplemental materials) capture different aspects of fatigue, including "exhaustion," "sleepiness," and "weakness."
- The terms used to capture abdominal discomfort (e.g., abdominal pain, discomfort, pressure, bloating) and early satiety (e.g., feeling of fullness, filling up quickly when you eat, early satiety) vary across questionnaires.

The measurement characteristics of the identified questionnaires were also reviewed, in order to determine if the evidence for the reliability, validity, and sensitivity to change of any questionnaire was particularly compelling. There were no unique data that supported one questionnaire over another. Regardless of the number of items, tests of internal consistency suggested that the symptom items should be aggregated into a single unidimensional symptom score [21]. MF symptom items were moderately correlated with clinician evaluations of the same symptoms [22] and distinguished MPN patients from matched controls [16] and MF patients from essential thrombocythemia and polycythemia vera patients [23]. The MF symptom questionnaires, particularly the MFSAF v2, were associated with changes in spleen volume [21], measures of health-related quality of life [20], and to both treatment effects [14,21] and discontinuation of treatment [24]. Although a responder definition of reduction in symptoms of 50% or more from baseline has been used in clinical trials of ruxolitinib [14], there was no published evidence supporting the clinical appropriateness of this threshold and a different threshold may be appropriate for other contexts of use.

3. Harmonization meeting

The Working Group's harmonization panel meeting was held on March 2, 2016. The panel used the findings from the literature review and the listing of individual items included in the supplemental materials to this article as a foundation in developing the harmonized items. General administration considerations, including recall interval and mode of administration, were discussed. Each symptom item was then considered sequentially and the group considered different wording options for the instructions, item text, and response options until a consensus was achieved. The harmonized instrument was named the