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Developing a Core Set of Outcome Measures for Behçet Disease: Report from OMERACT 2016

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Abstract

Objective.—The Outcome Measures in Rheumatology (OMERACT) Vasculitis Working Group has been working toward developing a data-driven core set of outcome measures for use in clinical trials of Behçet's syndrome [Behçet disease (BD)]. This paper summarizes the group's work through OMERACT 2016, discussions during the meeting, and the future research agenda.

Methods.—Qualitative patient interviews were conducted among 20 patients with BD who have different types of organ involvement. A 3-round Delphi among BD experts and patients was initiated to identify domains, subdomains, and outcomes to be assessed in clinical trials of BD. The results of these studies were discussed during OMERACT 2016 and next steps were planned.

Results.—Patients' perspectives and priorities were identified through qualitative interviews that identified candidate domains and subdomains for inclusion in the Delphi and characterized some short-comings of the currently used patient-reported outcomes in BD. The first round of the Delphi was completed and several domains or subdomains were endorsed by the experts and/or the patients. Because many more items were endorsed than would be feasible to assess during a clinical trial, rating and ranking of items by physicians and patients was planned as a next critical step. The challenges of assessing specific organ system involvement was also discussed.

Conclusion.—The OMERACT Behçet Syndrome Working Group research program will identify core domains for assessment in BD with the goal of developing a core set of outcome measures for use in all trials of BD with the option to incorporate additional outcomes for specific organ involvement.

Key Indexing Terms:

BEHÇET DISEASE; OUTCOMES; OUTCOME MEASURES; OUTCOME ASSESSMENT; OMERACT

Several outcomes and outcome measures have been used in clinical trials that address different types of organ involvement in Behçet's syndrome [Behçet disease (BD)]. However, the diversity and variability in the outcomes and outcome measures across trials has made it difficult to combine and compare the results of trials[1] and reducing the cumulative effect of the trials on development of management and treatment guidelines[2,3]. Moreover, patient engagement has not been optimal in the development and validation of outcomes and outcome measures in common use in trials of BD. The Outcome Measures in Rheumatology

(OMERACT) Vasculitis Working Group seeks to develop a core set of outcome measures for use in trials of BD. A previous systematic review by our group showed that few measures are either properly validated or widely used, and there is a lack of standardized definitions for frequently used outcomes such as response, relapse, and remission[1]. We conducted a survey among BD experts from different specialties and the majority of the experts agreed that none of the currently available instruments for assessing disease activity in BD were reliable and valid[4]. Input from the Behçet research community in an outcome measures meeting during the 16th International Conference for Behçet's Disease in 2014 helped us further understand the needs in this area. Our paper summarizes the work we have done prior to OMERACT 2016, the discussions during the special interest group (SIG) meeting, and our future research agenda.

The main findings of our work leading to OMERACT 2016 meeting were the following: (1) qualitative patient interviews revealed several themes that are important to patients that help us understand the complex perspectives of patients with BD, (2) several domains and subdomains were endorsed by BD experts during the first round of the Delphi, (3) patients endorsed all domains and subdomains chosen by experts, but the patients endorsed additional outcomes such as fatigue, sleep, and sexual functioning. These are all novel findings that have not been reported in BD before and they will help advance the research toward developing a core set. Next steps will be completing the second and third rounds of Delphi and further analysis of patient interviews.

Qualitative Patient Interviews

We conducted in-depth, semistructured interviews to better understand the perspective and priorities of patients with BD to determine patient-important candidate domains and subdomains for the Delphi questionnaire and help improve and modify already existing patient-reported outcomes (PRO) or develop a new PRO for BD. The interview included 7 different conceptual frameworks (disease onset, diagnostic experience, treatment history, disease remission, disease flare, quality of life, mental health effect) and 41 open-ended questions. Twenty patients with BD with different types of organ involvement were included (Table 1). Interviews were transcribed and entered into an NVivo 10 database to support qualitative analyses. A preliminary qualitative analysis was performed using a constant comparative method of careful line-by-line review of interview narratives[5,6]. Seven broad themes were identified, 3 of which (lack of knowledge, genetic factors, healthcare needs) were considered not related to disease assessment and were not included in further analysis. The remaining themes were symptoms, effect on functions and activities, psychological effect, and social effect. Each theme included several domains and subdomains (Table 2). We compared the domains/subdomains that were retrieved through these interviews with items of the currently available BD-specific quality-of-life scale. Several domains/concepts, including work disability, difficulty in eating and drinking, difficulty in concentrating, suicidal ideation, anxiety, feeling judged or pitied by others, and sleep problems, were missing from currently used PRO.

Delphi

Our next step for identifying domains, subdomains, and outcomes to be assessed in trials of BD was a 3-round Delphi exercise among experts in and patients with BD (approved by Ethics Committee of Cerrahpasa Medical Faculty: 83045809/604.01). The Delphi questionnaire included a list of possible domains, subdomains, and outcomes that were derived from the results of the systematic literature review on outcomes assessed in previous Behçet studies[1], patient priorities identified through our qualitative interviews, and expert opinion. Item selection was also influenced by the framework of the OMERACT Filter 2.0[7]. It included 7 sections asking "what needs to be measured in…" (1) all trials, and then trials of (2) mucocutaneous disease, (3) ocular disease, (4) vascular disease, (5) central nervous system disease, (6) gastrointestinal disease, and (7) arthritis.

The patient survey was the same as the expert survey with medical terms explained. An invitation was e-mailed to 123 physicians and 130 patients. Items that were agreed on by ≥ 70% of either experts or patients were accepted.

A total of 74 physicians and 59 patients participated in Round 1. The physicians were experts in BD from 21 countries and from a wide range of specialties, including rheumatology (50%), dermatology (16%), ophthalmology (12%), internal medicine (12%), gastroenterology (3%), and neurology (1%). Table 3 shows the domains and subdomains to be measured in trials of BD that received ≥ 70% endorsement by expert physicians and/or the patients. Domains that were endorsed for assessment in all trials of BD and the additional subdomains endorsed for trials on each type of involvement are listed separately. In addition to all of the domains identified by physicians, ≥ 70% of patients endorsed the assessment of other domains such as fatigue, sleep, sexual functioning, psychological functioning, and acute-phase reactants in all trials of BD (Table 3).

When we attempted to map the outcomes and outcome measures that were endorsed during the Delphi on the areas defined by the OMERACT Filter 2.0[7], we observed that all the core areas were covered. Several domains were endorsed, such as activity, damage, and quality of life covering "life effect," work productivity covering "resource use/economic effect," function and imaging covering "pathophysiological manifestations," and finally, "death."

Discussion at the OMERACT 2016 SIG Meeting

One of the main discussions was whether the aim should be to develop a core set of outcomes for all trials of BD or different core sets for each type of involvement. Although skin and mucosal lesions are seen in almost all patients, it is not common to have more than 1 active major organ system involved at a time. Moreover, differences in response to certain drugs have been observed between types of organ involvement. Thus, most trials conducted to date in BD have each focused on 1 type of involvement such as eye, mucocutaneous, or joint involvement, using outcomes and outcome measures specific to that organ or organ system. Instruments for overall disease assessment have been developed, but these have not been widely used. There is also a lot of hetero-geneity in the outcomes and outcome measures used for specific types of involvement. Assessment of all organ systems in detail

even if they are not involved during drug trials would be time consuming and inefficient. However, there was consensus that a basic evaluation of all organ systems is necessary to not miss any new manifestations during a trial. This approach would enable detection of potential effects of the study drug for protecting from new organ involvement. The conclusion of this part of the discussion was that we should strive for a main core set for all trials in addition to organ-specific outcomes and outcome measures for trials that focus on a specific type of involvement.

Patient interviews revealed several important themes and clues to the life effect of BD. Although patients with a variety of organ involvement were included, all of them were from Turkey. The possibility of conducting interviews among patients with BD from other countries was discussed. This would reveal any cultural differences regarding outcomes important to patients. The need for a reliable and validated PRO was emphasized.

We also discussed the results of the Delphi, where too many items were endorsed by the physicians and/or the patients to be feasibly addressed in any one study or a reasonable set of instruments. We decided to rate and rank the endorsed items during the second round of Delphi, and some items could be gathered under a single domain such as activity or function. This approach would advance development of the main core set of domains under the OMERACT Filter 2.0 guidelines.

Future Steps

Qualitative patient interviews will be further analyzed, more interviews will be conducted in other countries, and these data will be used for developing a PRO for BD or accumulating a set of currently available PRO for use in trials.

The second round of the Delphi will be conducted among experts and patients with ranking of the endorsed domains/subdomains. The third round will be a combined patient and physician Delphi to determine the main core set of domains to be measured in all trials and additional ones specific to each type of organ involvement.

DISCUSSION

The qualitative patient interviews revealed several themes including difficulty in work and home participation, impaired quality of life, and impaired personal independence. The first round of the Delphi showed that the majority of domains and subdomains were endorsed by experts including activity, function, damage, and remission, and additional domains were endorsed by patients. At the end of the 3-round Delphi process, we aim to determine the domains that need to be assessed in all trials of BD and then develop a core set of data-driven outcome measures to assess these domains in clinical trials for BD.

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Table 1.

Demographic and disease characteristics of the patients with Behçet syndrome who underwent qualitative interviews. Values are n unless otherwise specified.

Characteristic	Values
No. patients	20
Age, yrs, median (range)	36 (29–46)
Sex	5 female, 15 male
Disease duration, yrs, median (range)	11 (9–18)
Education	
Middle or high school	16
Some college or higher	4
Marital status	
Single	7
Married	13
Employment status	
Employed	10
Unemployed due to disease	5
Homemaker	5
Type of organ involvement	
Eye	10
Vascular	8
Joint	6
Neurologic	5
Gastrointestinal	3
Isolated mucocutaneous	2

Table 2.

Themes and domains/subdomains retrieved from the qualitative interviews.

Symptoms	Effect on Function and Activities	Psychological Effect	Social Effect
Difficulty sleeping	Difficulty in concentrating	Anger	Feeling inadequate
Fatigue	Difficulty in eating and drinking	Anxiety	Feeling judged or pitied by others
Genital ulcers	Difficulty in taking care of children	Depression	Feeling restricted
Headache	Difficulty in talking	Fear	Feeling that others underestimate the severity of their symptoms
Lethargy	Difficulty in walking	Lack of self-confidence	Need for support
Oral ulcers	Difficulty with household tasks	Stress	Problems in relationship with partner
Pain	Effect on family	Reduced strength	Reduced social activities and participation
Swelling	Effect on personal independence	Suicidal ideation	
Visual impairment	Impaired vision, inability to work, reduced quality of life		

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Table 3.

Domains and subdomains of Behçet syndrome endorsed by ≥ 70% of physician experts and/or patients as necessary to measure in clinical trials.

Focus of Trial	Domains and Subdomains Endorsed*
All trials	Endorsed by both patients and physicians: activity, damage, death, function, patient's global assessment, physician's global assessment, quality of life, remission, work productivity
	Endorsed by patients only: no. papulopustular lesions, pain of nodular lesions
Mucocutaneous disease	Endorsed by both patients and physicians: duration of oral ulcers, duration of genital ulcers, duration of nodular lesions, new organ involvement, no. oral ulcers, no. genital ulcers, pain of genital ulcers, pain of oral ulcers
	Endorsed by patients only: no. papulopustular lesions, pain of nodular lesions
Ocular disease	Endorsed by both patients and physicians: blurry vision, cystoid macula edema, ocular attack, retinal vasculitis, visual acuity
	Endorsed by patients only: duration of ocular attack, glucocorticoid tapering
Vascular disease	Endorsed by both patients and physicians: disease-related damage, extended venous thrombus, hemoptysis, new aneurysm, new arterial thrombus, new venous thrombus, post-thrombotic syndrome
	Endorsed by patients only: shortness of breath
Neurologic disease	Endorsed by both patients and physicians: cognitive functioning, headache, progression on magnetic resonance imaging
	Endorsed by patients only: disease-related damage, dizziness, neuropathic pain, neuropathy
Gastrointestinal disease	Endorsed by both patients and physicians: abdominal pain, clinical remission, diarrhea, endoscopic remission
	Endorsed by patients only: nausea, disease-related damage, weight loss
Joint disease	Endorsed by both patients and physicians: duration of arthritis episodes, no. arthritis episodes, physical function, swollen joint count, tender joint count

*Results based on responses by 56 patients and 74 physicians.