Outcome Measures Used in Clinical Trials for Behçet Syndrome: A Systematic Review

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ABSTRACT. Behçet syndrome (BS) is a multisystem vasculitis that is most active during young adulthood, causing serious disability and significant impairment in quality of life. Differences in the disease course, severity, and organ involvement between patients, depending on the age at presentation and sex, makes it impossible to determine a single management strategy. The diversity and variability in the outcome measures used in clinical trials in BS makes it difficult to compare the results or inform physicians about the best management strategy for individual patients. There is a large unmet need to determine or develop validated outcome measures for use in clinical trials in BS that are acceptable to researchers and regulatory agencies. We conducted a systematic review to describe the outcomes and outcome measures that have been used in clinical trials in BS. This review revealed the diversity and variability in the outcomes and outcome measures and the lack of standard definitions for most outcomes and rarity of validated outcome tools for disease assessment in BS. This systematic literature review will identify domains and candidate instruments for use in a Delphi exercise, the next step in the development of a core set of outcome measures that are properly validated and widely accepted by the collaboration of researchers from many different regions of the world and from different specialties, including rheumatology, ophthalmology, dermatology, gastroenterology, and neurology. (First Release Feb 1 2014; J Rheumatol 2014;41:599–612; doi:10.3899/jrheum.131249)

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Behçet syndrome (BS) is a multisystem vasculitis that affects both men and women during young adulthood with significant effects on quality of life (QOL); it can result in serious disability and premature death. Manifestations include mucocutaneous lesions such as oral ulcers, genital ulcers, papulopustular and nodular lesions, joint involvement (usually in the form of a self-limited monoarthritis or arthralgia), eye involvement typically manifesting as panuveitis that may lead to blindness if left untreated, vascular involvement causing arterial aneurysms that may be lethal, deep venous thrombi, neurologic involvement that can cause permanent disability, and gastrointestinal (GI) involvement that is often indistinguishable from inflammatory bowel disease. Given its pathophysiology and spectrum of manifestations, BS is best classified as a form of vasculitis. There are many reasons to call it a syndrome rather than a disease, in particular the considerable variation in disease presentation depending on demography and geography[1].

The disease course, severity, and types of organ involvement vary substantially among patients depending on their age and sex and the age of onset. Thus, it is impossible to determine a single management strategy[2]. Several clinical trials have been conducted in patients with BS, addressing different types of organ involvement such as mucocutaneous or ocular disease[3]. However, most of the

outcome measures used in these trials were neither validated nor widely accepted, leading investigators to add to the clutter by creating their own definitions of activity, severity, or response. The diversity and variability in the outcome measures used in trials of BS make it difficult to compare trial results, combine findings into metaanalyses, or guide physicians on management strategies.

The development of new biologic agents with immunomodulatory actions has increased the interest of both doctors and the pharmaceutical companies in conducting clinical trials in BS. However, the lack of uniform, widely accepted outcome measures is an obstacle to designing randomized controlled trials (RCT) that meet regulatory agencies' expectations. This in turn reduces the enthusiasm of industry support for such research. OMERACT has guided the development of data-driven outcome measures in several diseases. The OMERACT Vasculitis Working Group has developed a core set of outcome measures for use in clinical trials of antineutrophil cytoplasmic antibody–associated vasculitis and is continuing work on outcome measures for large-vessel vasculitis[4,5]. The Working Group is pursuing a similar approach, within the OMERACT framework, to develop validated outcome measures for clinical trials in BS.

As a first step in the development of a core set for BS, the aim of this systematic review is to describe the strengths and shortcomings of the outcomes and outcome measures that have been used in RCT, uncontrolled interventional studies, observational studies, longitudinal cohorts, case control studies, and biomarker and genetic association studies in BS.

METHODS

A systematic literature search was performed to identify all published articles that included defined outcome measures or outcomes in BS. PubMed was searched for articles published between January 1946 and November 2012. To avoid missing any relevant articles, no limits were used during the literature search, and titles and abstracts of all articles retrieved by the keywords "Behcet's syndrome OR Behcet's disease OR Adamantiades Behcet OR Behcet*" were evaluated for inclusion criteria.

Publications reviewed included all RCT, uncontrolled observational or retrospective interventional studies, longitudinal or retrospective cohort studies, case-control studies, biomarker studies, or genetic association studies reporting on at least 20 patients with BS and including at least 1 outcome or outcome measure. Original articles involving humans, published in English, German, French, or Turkish were included. A hand search of references of selected articles for identifying relevant studies was also performed. Unpublished reports, congress proceedings, or abstracts were excluded.

From the selected articles, data were extracted regarding the outcome measures and outcomes used in interventional studies and cohorts, as well as definitions of activity and severity used in biomarker and genetic association studies and case control studies. The outcomes and outcome measures were analyzed in 3 groups based on study type: (1) randomized controlled studies; (2) biomarker and genetic association studies; and (3) all other studies.

We also evaluated the outcomes and outcome measures in terms of their appropriateness to the OMERACT 2.0 Filter. We identified outcomes that addressed at least 1 of the 4 core areas incorporated into Filter 2.0: "death", "life impact", "pathophysiological manifestations", and "resource use/economical impact area."[6]

Quality assessment of the articles was not done because the aim of the exercise was to determine all outcomes and outcome measures used in trials of BS regardless of the methodological quality.

RESULTS

Figure 1 shows the flowchart of the systematic review results. In the first phase of the review, 8286 articles were identified. The following types of articles were excluded: informative reviews; case reports and other studies reporting on fewer than 20 patients; trials in languages other than English, French, German, or Turkish; clinical trials not reporting any outcomes such as epidemiological studies on the prevalence and types of involvement of BS in a country; trials not related to BS or where the primary area of interest was not BS such as general uveitis trials; and animal studies. Basic science studies including genetic association studies were excluded after reading the title and abstract. The full text of the remaining 259 articles were retrieved. Among these, 249 articles were ultimately determined to meet the full set of inclusion criteria. Tables 1–3 show the outcome measures used in these trials[7-256].

Outcome measures for overall disease assessment. The outcomes and outcome measures that are used for the overall evaluation of BS without organ-specific endpoints are given in Table 1. The most commonly used measure for evaluating disease activity was the Behçet's Disease Current Activity Form, which was used in 24/248 (9.6%) of the published studies[7-30]. There are 4 other activity measures that were used in a few trials each[18,20,31-37]. Several researchers used their own definition of activity[38-87]. The definitions of activity varied from requiring a minimum of 1 to 3 manifestations, including oral ulcers, genital ulcers, skin lesions, uveitis, vascular lesions, or neurologic lesions. Some studies did not provide an explanation of how active patients were defined[88,89,90,91]. Mortality is rarely used as a primary or even secondary endpoint of interest in studies of BS[92-103].

For evaluating disease severity, the most commonly used index was the Krause Total Severity Score. This was used in 15/248 (6.0%) of published studies[38,46,51,57,104-114]. Several researchers used their own definition of disease severity[12,32,60,65,82,115,116,117]. Similarly, many studies incorporated outcomes unique to that study for definitions of relapse, response (complete/partial), and remission (complete/partial)[30,71,72,90,118,119,120,121,122,123].

There was 1 validated health-related QOL measure specific for BS: the Behçet Disease Quality of Life. This measure has been used in only a few clinical trials[19,124,125].

Organ-specific outcomes and outcome measures. Organ-specific outcomes and outcome measures used in trials are summarized in Table 2. The only organ-specific outcome measure that was developed for mucocutaneous BS and

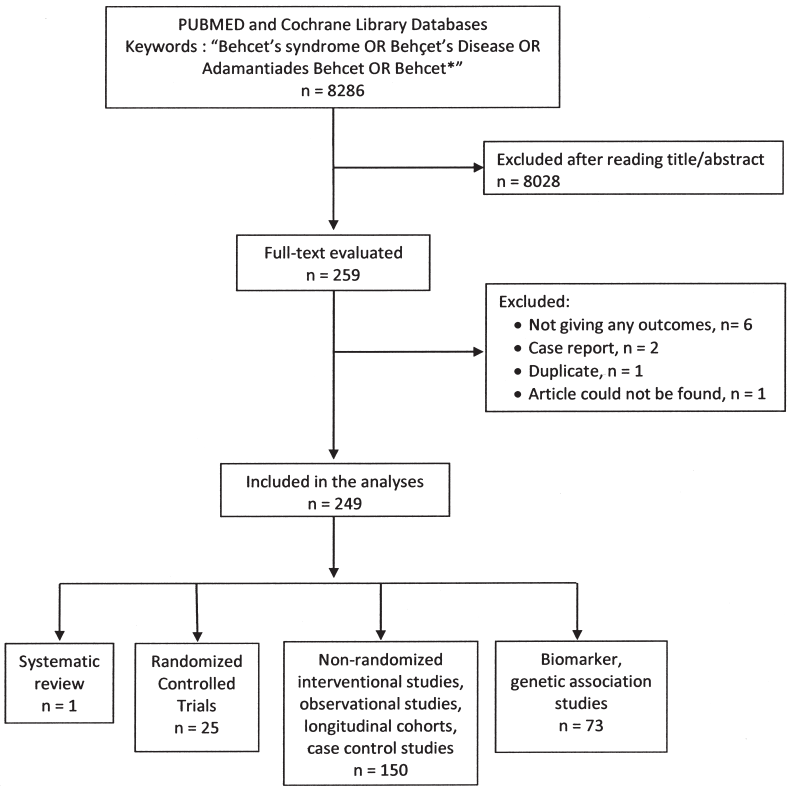

Figure 1. Outcomes and outcome measures used in studies of Behçet syndrome: systematic literature search strategy and results.

Table 1. Overall disease assessment outcomes and outcome measures used in studies of Behçet syndrome. Numerals in parentheses indicate references.

	RCT*, n = 25	Other**, n = 150	Biomarker, n = 73	Overall, n = 248
Behçet's Disease Current Activity Form (BDCAF) (7–30)	—	17	7	24
Clinical Disease Activity Index (32)	—	1	—	1
Clinical Manifestations Index (33,34,35)	1	2	—	3
Iranian BD Dynamic Activity Measure (18,20,31,37)	1	3	—	4
1994 Criteria for Disease Activity of BD (36)	—	1	—	1
Activity, self-defined (38–87)	—	4	46	50
Activity, not defined (88–91)	—		4	4
Krause's total severity score (38,46,51,57,104–114)	—	11	4	15
Severity (self-defined) (12,32,60,65,82,115–117)	1	2	6	9
Relapse (30,119–121)	—	2	1	3
Response (complete/partial) (30,122,123)	—	3		3
Remission (complete/partial) (71,72,90,119–121)	1	1	4	6
Physicians Global Assessment (18,211)	—	2	—	2
BD Quality of Life (19,124,125)	—	3	—	3
Proportion of patients remaining on treatment (30)	—	1	—	1
Development of major organ involvement (98,122,174)	1	2	—	3
Death (92–103)	—	11	—	11

* Only 4 of the 25 RCT used an outcome measure for overall disease assessment. ** The outcome measures used in uncontrolled interventional studies, cohorts, and case control studies are given together under the "other studies" column. A total of 66 outcome measures for overall disease assessment were used in these 150 studies. Similarly, biomarker studies and generic association studies are given together under the "Biomarker" column. RCT: randomized controlled trial; BD: Behçet disease.

Table 2. Organ specific outcomes and outcome measures used in studies of Behçet syndrome for mucocutaneous, musculoskeletal, eye, vascular, neurologic, and gastrointestinal involvement. Numerals in parentheses indicate references.

	RCT	Other*	Biomarker	Overall
Mucocutaneous disease (n)	18	14	0	32
Frequency of oral ulcers/genital ulcers/nodular lesions/papulopustular lesions (57,120,131,135,138,139,243,245)	6	2	—	8
Number of oral ulcers/genital ulcers/nodular lesions/papulopustular lesions (127,128,130,132–135,137,139,140,185,244,246–248)	10	5	—	15
Duration of oral ulcers/genital ulcers/nodular lesions/papulopustular lesions (118,120,135,138)	3	1	—	4
Size of oral ulcers/genital ulcers (129,130,135,244,249)	3	2	—	5
Pain of oral ulcers/genital ulcers (120,129–131,134,243)	4	2	—	6
Severity of oral ulcers/genital ulcers (118,246)	1	1	—	2
Healing time of oral ulcers/genital ulcers (57,128–131,243,249)	2	5	—	7
Depth of oral ulcers/genital ulcers (244)		1	—	1
Pathergy positivity (35,133,244)	1	2	—	3
Oral Ulcer Activity Index (126)		1	—	1
Response (complete/partial) (30,118,136,137,250)	3	2	—	5
Remission (complete/partial) (251)	—	1	—	1
Musculoskeletal disease (n)	6	1	_	7
No. arthritis episodes (132,133,137,139,142)	5		—	5
Frequency of arthritis episodes (139,141)	1	1	—	2
Severity of arthritis episodes (142)	1	—	—	1
Duration of arthritis episodes (139,142,143)	3	—	—	3
Tender joint score (143)	1	—	—	1
Degree of joint swelling (143)	1	—	—	1
Arthritis pain visual analog scale (143)	1	—	—	1
Vascular (n)	—	14	—	14
Venous thrombosis relapse (92,95,197)	—	3	—	3
New/recurrent aneurysm (96,100,198,199,201,203)	—	6	—	6
Disappearance of intracardiac thrombus (202)	—	1	—	1
Remission (93,94)	—	2	—	2
Death (92–96,100,102,199)	—	8	—	8
Amputation (96)	—	1	—	1
Operation need (95)	—	1	—	1
Postoperative complications (96,100,199,200,203)	—	5	—	5
Graft occlusion/patency (96,100,199,200,201,203)	—	6	—	6
Neurologic (n)	—	7	—	8
Functional outcome (independent/dependent/death) (206,210)	—	2	—	2
Improvement (97,204)	—	2	—	2
Poor outcome (97)	—	1	—	1
Death (97)	—	1	—	1
Relapse (204,205)	—	2	—	2
Progressive course (205)	—	1	—	1
Expanded Disability Status Scale (205,208,209)	—	3	—	3
Neuropathic pain (207)	—	1	—	1
Multiple sclerosis functional compound scale (208)	—	1	—	1
Eye involvement (n)	7	53	3	63
Ocular inflammatory attack (9,15,120,144,147,155–158, 161,162,164–166,169–171,173,176,181,183,184,186,188–196)	6	25	1	32
Visual acuity (9,15,16,120,144–190)	7	43	1	51
Loss of useful vision/blindness (99,160,163,167,174–177)	—	8	—	8
Improvement of uveoretinitis (145)	—	1	—	1
Retinal vasculitis (149,166,181,185)	2	1	1	4
Hypopyon (149,166,181,185)	2	1	1	4
Ben Ezra Disease Activity Index (15,25,152,153)	1	3	—	4
Total Inflammatory Activity Index (152,153)	—	2	—	2
Total Adjusted Disease Act Index (152,153)	—	2	—	2
Worsening of intraocular inflammation (190)	1		—	1
Regression of inflammatory signs (252)	—	1	—	1
Improvement in fundus fluorescein angiography findings (168)	1	—	—	1
Macular thickness (146,181)	1	1	—	2

Table 2. Continued.

	RCT	Other*	Biomarker	Overall
Remission (16,155,157,163,165,169,186,193)	—	7	1	8
Response (complete/partial) (155,161)	—	2	—	2
Time to remission (191)	—	1	—	1
Time to relapse/recurrence (15,191,194)	—	3	—	3
National Eye Institute Visual Functioning Questionnaire (151)	—	1	—	1
Number of relapse-free patients (147)	—	1	—	1
Inflammation score — self-defined (159)	—	1	—	1
Duration of ocular attacks (171,188)	—	2	—	2
Vascular sheathing (181)	—	1	—	1
Venous occlusion (181)	—	1	—	1
Vitreous condensation (181)	—	1	—	1
SUN visual loss (16)	—	1	—	1
SUN lowering glucocorticoid dose to < 10 mg/day (253)	—	1	—	1
SUN control of uveitis with quiescence during maintenance (150)	—	1	—	1
SUN ocular relapse per patient year (150)	—	1	—	1
SUN intraocular inflammation (146,154,176)	—	3	—	3
SUN level of steroid dependence (154)	—	1	—	1
SUN complete/partial/no response (154)	—	1	—	1
SUN improvement/worsening (15,176)	—	2	—	2
Hogan's ocular inflammatory attack criteria for anterior uveitis (180,188,254)	—	3	—	3
Kimura's ocular inflammatory attack criteria for posterior uveitis (180,188)	—	2	—	2
Development of new eye disease (174,185)	1	1	—	2
Gastrointestinal (n)	—	14	3	17
Disease Activity Index for Intestinal BD (211,216,218,220,221)	—	4	1	5
Inflammatory Bowel Disease Questionnaire (224)	—	1	—	1
Crohn's Disease Activity Index (211,224,227)	—	3	—	3
Harvey Bradshaw Index for Activity (224,227)	—	2	—	2
St. Mark's Activity Index (224)	—	1	—	1
Relapse/recurrence (212–215,217,219,222,223,225,226)	—	9	1	10
Remission (212–214,223)	—	3	1	4
Operation need (211,212,214,217,221,223)	—	5	1	6
Reoperation need (213,217,219,222,225,226)	—	6		6
Physician's global assessment (211)	—	1		1
Immunosuppressive need (217,221)	—	2		2
Glucocorticoid requirement (217,221)	—	2		2

* The outcome measures used in uncontrolled interventional studies, cohorts, and case control studies are given together under the "Other Studies" column. Similarly, biomarker studies and genetic association studies are given together under the "Biomarker" column. RCT: randomized controlled trial; BD: Behçet disease; SUN: Standardization of Uveitis Nomenclature.

validated was the oral ulcer composite index[126]. The frequency, duration, size, pain, severity, and healing time of each of the mucocutaneous lesions were used as outcomes in different combinations in several studies[57,118,120,127-135,138-140,185,243-251]. Similarly, the number, frequency, severity, duration, and pain of arthritis episodes were reported in several studies[132,133,137,139,141,142,143].

Organ-specific outcome measures used in trials for eye involvement are given in Table 2. Visual acuity[9,15,16,120,144-196,252-254] and inflammatory attacks[9,15,120,144,147,155-158,161,162,164,165,166,169,170,171,173,176,181,183,184,186,188-196] are the most widely used outcome measures. However, the definition of an inflammatory flare varied widely among studies, and visual acuity was reported in several different ways, including change on Snellen chart or Japanese standard Landolt visual acuity chart, calculating the LogMar (logarithm of the minimum angle of resolution), or the percentage of patients who had a certain level of improvement. Loss of useful vision is another similar outcome used[99,160,163,167,174,175,176,177]. Different components of the Standardization of Uveitis Nomenclature Working Group Criteria, a generic uveitis measure, were used in some of the trials for BS[14-16,146,150,154,176]. The Ben Ezra Disease Activity Index, specifically developed for evaluating uveitis in BS, was also used in a few studies[15,25,152,153].

Outcomes and outcome measures used in trials for vascular [92,93,94,95,96,100,102,197-203], neurologic[97,204-210], and GI involvement[211-227] are given in Table 2. There were no RCT or prospective interventional trials for vascular involvement of BS. Studies that report on longterm followup of patients with BS with vascular involvement or retrospective reviews of surgical outcomes usually reported relapses/recurrences, remission, operation and reoperation

Table 3. Nondisease–specific outcome measures used in studies of Behçet syndrome. Numerals in parentheses indicate references.

	RCT, n = 0	Other, n = 36	Biomarker, n = 0	Overall, n = 36
SF-36 (46,57,151,239)	—	4	—	4
Health-related QOL (224,239)	—	2	—	2
WHO QOL 100 (46)	—	1	—	1
WHO QOL BREF (240)	—	1	—	1
EQ-5D (229)	—	1	—	1
Dermatology Life Quality Index (12,255)	—	2	—	2
Oral Health Related Quality of Life (57)	—	1	—	1
Oral Health Impact Profile (57,128,131,234)	—	4	—	4
Nottingham Health Profile (23,141)	—	2	—	2
Life Satisfaction Index (23)	—	1	—	1
Lawton Instrumental Activities of Daily Living (125)	—	1	—	1
Kate Index of Activities of Daily Living (125)	—	1	—	1
Health Assessment Questionnaire (HAQ) (124,141)	—	2	—	2
Multidimensional HAQ (MDHAQ) (237,256)	—	2	—	2
Brief Symptom Inventory (230)	—	1	—	1
Beck Depression Scale (17,60,141,208,230,232,235,236,238,239,240)	—	11	—	11
Beck Anxiety Scale (230,238,239,241)	—	4	—	4
Beck Hopelessness Scale (238)	—	1	—	1
Hamilton Depression Rating Scale (12,228,241)	—	3	—	3
Hamilton Anxiety Rating Scale (12,228)	—	2	—	2
Center for Epidemiologic Studies Depression Scale (19)	—	1	—	1
Psychological General Wellbeing Scale (124,207)	—	2	—	2
Automatic Thoughts Questionnaire (238)	—	1	—	1
Hospital Depression Scale (231)	—	1	—	1
Hospital Anxiety Scale (231)	—	1	—	1
State Trait Anxiety Inventory (60,141)	—	2	—	2
Toronto Alexithymia Scale (241)	—	1	—	1
Epworth Sleepiness Scale (12)	—	1	—	1
Respiratory Disturbance Index (12)	—	1	—	1
Apneahypopnea Index (12)	—	1	—	1
Pittsburgh Sleep Quality Index (12,207)	—	2	—	2
Female Sexual Function Index (236)	—	1	—	1
International Index of Erectile Function (235)	—	1	—	1
Arizona Sexual Experience Scale (228)	—	1	—	1
Golombok Rust Sexual Satisfaction Scale (228)	—	1	—	1
Voice Handicap Test (233)	—	1	—	1
Fibromyalgia Impact Questionnaire (10,60)	—	2	—	2
Fatigue Severity Scale (12)	—	1	—	1

SF-36: Medical Outcomes Study Short Form-36; WHO: World Health Organization; QOL: quality of life.

rates and postoperative complications[92,93,94,95,96,100,102,197-203]. Relapses/recurrences were defined as a new lesion or a progression of an already present lesion. Remission was defined as the absence of a new or progressing lesion.

There were also no RCT for neurologic or GI involvement of BS. There is 1 GI index that was developed and validated specifically for BS (Disease Activity Index for Intestinal Behçet Disease)[211,216,218,220,221]. This index showed a higher correlation with physician global assessment and higher responsiveness than the Crohn Disease Activity Index. Many studies used indexes and outcomes developed for inflammatory bowel diseases[211,224,227].

Laboratory outcome measures. Erythrocyte sedimentation rate[9,16,22,24,34,40,43,47,49,59,60,61,63,66,67,68,69,76,77,85,89,94,139,143,177,220,228] and C-reactive protein[9,16,24,40,43,47,49,59,60,66,67,76,77,85,89,94,143,177,216,220,228] levels were used as indicators of disease activity. No laboratory measure has been validated as a biomarker of disease activity in BS.

Generic measures. Several generic measures were used to evaluate the QOL and psychological, cognitive, or sexual effect of BS (Table 3)[10,17,19,23,46,57,60,124,125,128,141,151,207,208,228-241,255,256]. Among these, only the oral health-related QOL was specifically validated for BS[128]. The most frequently used psychological indexes were the Beck Depression Index[17,60,141,208,230,232,235,236,238,239,240] and Beck Anxiety Scale[230,238,239,241].

Evaluation of the outcomes that were reviewed according to

the OMERACT 2.0 Filter. Death, which is one of the core areas in the Filter 2.0, was included as an outcome in 12 trials[92-103]. None of the RCT reported death. Life impact was addressed by 1 BS specific measure, Behçet Disease Quality of Life[19,124,125], and several generic measures given in Table 3 [10,17,19,23,46,57,60,124,125,128,141,151,207,208,228-241,255,256]. There was 1 cost analysis study in BS that retrospectively analyzed direct costs such as medication, diagnostic tests, hospital visits, hospitalization fees, and lodging and transportation expenses and indirect costs such as lost workdays and wages by questioning the patients[242]. However, none of the interventional trials included an instrument to address the "resource use/economical impact area." The rest of the outcomes given in Table 1 and 2 are related to the "pathophysiological manifestations" area.

DISCUSSION

This systematic review revealed the diversity and variability in the outcomes and outcome measures used in clinical research in BS. It shows that there are no standard definitions for most outcomes and few validated outcome tools for any aspect of disease assessment in BS. The number of different outcomes assessed and the inconsistency in assessment methods is problematic. For example, visual acuity was used in 51 of the 63 trials studying eye disease in BS, but 5 different assessment methods were used among the 51 trials, making comparison of trial results extremely difficult.

There are 5 activity scales, 1 severity scale, a composite index for oral ulcers, and a QOL scale that were developed for BS. However, these measures have not been widely adopted for use by clinical researchers. Many investigators have preferred to use their own definitions of activity[38-87] or severity[12,32,60,65,82,115,116,117], or have included "generic" measures such as the Medical Outcomes Study Short Form-36 in their trials[46,57,151,239]. Similarly, some authors studying specific physiologic manifestations of BS have used outcome tools developed for other diseases, for example, uveitis scales or measures of inflammatory bowel disease; however, these tools have not been validated for BS. It may be appropriate to adapt existing tools for use in BS, but such use should be supported by properly conducted data analyses. Regarding the disease specific scores, they are composite scores of each item such as oral ulcers, genital ulcers, skin lesions, and eye lesions, and were not developed with the purpose of evaluating the individual items separately; however, it would be interesting to study the performance of each item outside composite scores and compare them to the organ-specific outcome measures.

During the OMERACT 11 meeting, the new Filter 2.0 was introduced. The Filter 2.0 approach suggests that all core sets of outcome measures should include at least 1 instrument from the 3 core areas of "death", "life impact", and "pathophysiological manifestations", and preferably 1 outcome measure addressing "resource use/economical impact area." Thus, we evaluated the outcomes and outcome measures used in BS trials in terms of their relevance to these core areas. None of the RCT reported death. It can be assumed that there were no deaths since it was not mentioned among the adverse events; however, death was not formally reported in any of the trials. Similarly "resource use/economical impact area" was not covered in any of the interventional trials. The outcomes and outcome measures used were mostly related to the "life impact" and "pathophysiological manifestations" areas. Work on the development of a core set of outcomes for BS should strive to address each of the core areas of Filter 2.0.

Part of the evolving research agenda for the OMERACT Vasculitis Working Group is to work toward developing a core set of outcomes in BS. Among the next steps in this process is to conduct a Delphi exercise among international investigators and clinical experts in BS to reach consensus on outcomes of interest in BS. Apart from determining the current status of outcomes research in BS, the data derived from this systematic literature review will be used as a starting point to identify the domains and candidate instruments for use in the Delphi exercise. The collaboration of investigators from many different regions of the world and from different medical specialties, including rheumatology, ophthalmology, dermatology, gastroenterology, and neurology will be needed to develop a core set of outcome measures that are properly tested, well validated, and broadly acceptable for use in randomized trials in BS.

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