Development of a Core Set of Domains for Data Collection in Cohorts of Patients with Ankylosing Spondylitis Receiving Anti-Tumor Necrosis Factor-α Therapy

JANE ZOCHLING, JOACHIM SIEPER, DÉSIRÉE van der HEIJDE, and JÜRGEN BRAUN, on behalf of the Assessment in Ankylosing Spondylitis International Working Group

ABSTRACT. ***Objective.*** To create a core set of measurement concepts for use in the creation and maintenance of anti-tumor necrosis factor-α patient registries in ankylosing spondylitis (AS).

Methods. A Delphi-based approach was used to identify elements that best identify a patient's clinical state, disease progression, and potential drug-related toxicities. Decision-making was based on systematic literature reviews and clinical experience and expertise.

Results. A core set of measurement domains was defined including disease activity and physical function outcomes. Comparison with domains used in existing AS registries showed excellent agreement with current practice.

Conclusion. This core set is a basis for data collection across AS populations. (First Release May 1 2008; J Rheumatol 2008;35:1079–82)

Key Indexing Terms:
ANKYLOSING SPONDYLITIS TUMOR NECROSIS FACTOR-α INHIBITORS REGISTRIES

Since the introduction of anti-tumor necrosis factor (anti-TNF) agents for ankylosing spondylitis (AS), increasing numbers of patients are achieving significant symptomatic relief on biologic therapy[1]. Many research facilities have set up patient registries to follow the clinical efficacy and toxicities of these expensive therapies over time.

Standardization of the health concepts collected and the clinical measures used allows comparison of data across different registries with similar patient groups. The Assessment of SpondyloArthritis International Society (ASAS) has therefore proposed a core set of health concepts that should be included in all registries of patients with AS receiving biological therapy, in order to identify and record important patient data, to maximize the information yield within time and financial restraints, and to allow comparison of data across different registries. This study aims to define the most appropriate core set based on research evidence and clinical expertise.

From the Menzies Research Institute, Hobart, Australia; Charité Hospital, Berlin, Germany; Leiden University Medical Center, Leiden, The Netherlands; and Ruhr University and Rheumazentrum-Ruhrgebiet, Herne, Germany.

J. Zochling, MBBS, PhD, Research Fellow, Menzies Research Institute; J. Sieper, MD, Professor of Rheumatology, Charité Hospital Berlin; D. van der Heijde, MD, Professor of Rheumatology, Leiden University Medical Center; J. Braun, MD, Professor of Rheumatology, Ruhr University, Rheumazentrum-Ruhrgebiet.

Address reprint requests to Prof. J. Braun, Rheumazentrum-Ruhrgebiet, Landgrafenstrasse 15, 44652 Herne, Germany.
E-mail: j.braun@rheumazentrum-ruhrgebiet.de

Accepted for publication January 7, 2008.

MATERIALS AND METHODS

The complete ASAS membership was invited to participate in a modified e-mail-based 3-round Delphi exercise[2-4] to identify the measures that should be included in a registry of patients receiving biologic therapy for AS. Participants were instructed to consider what aspects of the disease must be assessed and recorded in such a database from an extensive list of items constructed from existing international databases. A range of measurement instruments (sourced from existing ASAS core sets for patient monitoring and clinical trials) and time intervals were suggested for each item, and supporting literature evidence was supplied. Inclusion cutoffs were 80% for the first 2 rounds (exclusion less than 20%) and 50% for the final round. Participants were able to add items they felt were missing from the initial set into the second round. In the final round, participants were also asked whether the selected domain is essential to the core set (expressed as an "inner circle" domain) or recommended but not essential (an "outer circle" domain).

The preliminary results of the Delphi exercise were presented to the ASAS group in Bath, UK, in January 2007 for discussion, and excluded items were reconfirmed. In a preliminary validation step, existing databases were reviewed to assess current compliance with the new core sets.

RESULTS

The survey was carried out between April and November 2006. Fifty-five (60%) of the invited ASAS members participated in the first 2 rounds and 52 in the final round. The final results of the Delphi rounds are given in Table 1, and recommended instruments and measurement time intervals are shown in Table 2. The core set is summarized in Figure 1.

Items reflecting other disease manifestations (osteoporosis, dactylitis/tendinitis, and psoriasis measures), social history and issues of economics, burden of illness, health utilities, and coping mechanisms were among the items excluded during the Delphi process. None of the new items sug-

Table 1. Results of a Delphi exercise to determine items for the ASAS biologic registry core set. Delphi round 1: first vote, > 80% indicates inclusion in the final core set; < 20%, excluded from the process (not shown); 20%–80%, represented in round 2. Delphi round 2: second vote, > 50% indicates inclusion in final core set. Delphi round 3: final agreement, % of participants.

	Vote (% participants)			
	Round 1 (n = 55), %	Round 2 (n = 55) %	Round 3 (n = 52), %	Current Registry Use (n = 10), %
Demographic data	96	—	96	100
Date of birth	98	—		100
Gender	100	—		100
Date of first symptoms	95	—		80
Date of diagnosis	95	—		80
Diagnostic criteria fulfilled	71	63		20
Classification criteria fulfilled	84	—		40
HLA-B27 status	93	—		70
Family history of spondyloarthritis	89	—		50
Medications related to AS (current and past)	95	—		70
Comorbidities	84	—		60
Presence and/or history of extra-axial disease	72	61		70
(peripheral arthritis, anterior uveitis, inflammatory bowel disease, psoriasis, infection)	95	71*		
Biologic-specific data	96	—	96	100
Current biologic therapy, change/cessation of	91	—		100
biologic therapy and reasons for change/cessation	98			
Changes in concurrent medications	73	75		100
Adverse events (AE), including AE due to	80	—		100
biologic therapy, malignancy, pregnancy outcomes and death	91			
Job status/situation	78	75		70
Time off work/sick leave	65	60		50
Any AE	69	60		80
Major comorbid events, hospitalizations	89	—		90
Clinical parameters	92	—	92	100
Morning stiffness–spine	71	60		70
Morning stiffness–duration	87	—		70
Pain–spine	89	—		80
Pain–peripheral joints	65	54		90
Nocturnal pain	82	—		80
Patient global assessment of health	87	—		100
Fatigue	76	68		80
Swollen joint count	89	—		80
Spinal mobility	89	—		80
Enthesitis measure	71	58		60
CRP	93	—		100
ESR	73	60		100
Physical function	96	—	98	100
Disease activity	98	—	98	100
Imaging	73	60	87	70
Quality of life	76	68	92	80

* Second vote only for those components of the item that did not receive > 80% of the vote in round 1, including history of infection and enthesitis.

gested by participants in the first round received more than 50% of the vote in round 2. Diagnostic criteria performed poorly, and after discussion at the ASAS meeting, they were voted out as there are no validated diagnostic criteria for AS, only classification criteria.

A majority vote was predefined as the cutoff for including items in the inner circle. Imaging and quality of life were voted into the outer circle by only a small majority, imaging receiving 52% of the vote as a nonessential, recommended core item, and quality of life receiving 54%.

Information from 10 international cohorts of patients with AS representing data from over 2000 patients was available for analysis. Six of these were purely registries of patients receiving biologic therapy; the remaining 4 were

Table 2. Recommended measurement instruments and intervals for the ASAS biologic registry core set.

Item	Instrument	Measurement Interval
Demographic data	NA	Baseline
Biologic-specific data	NA	At each visit
Clinical parameters	BASDAI questions on pain, morning stiffness, and fatigue. VAS nocturnal spinal pain. Modified Schober's, chest expansion, occiput-to-wall, cervical rotation, and lateral spinal flexion or BASMI. 44 swollen-joint count. VAS patient global assessment. ESR, CRP. A measure of enthesitis.*	At each visit
Physical function	BASFI	Annually, and at change of therapy
Disease activity	BASDAI	Every 6 mo, and at change of therapy
Imaging	Plain radiograph AP pelvis, lateral lumbar spine	Every 2 yrs
Quality of life	ASQOL and a generic measure	Annually, and at change of therapy

* All these measures are included in the ASAS core set for clinical record-keeping[8]. NA: not applicable; BASDAI: Bath AS Disease Activity Index; BASMI: Bath AS Metrology Index; BASFI: Bath AS Functional Index; ASQOL: AS Quality of Life index.

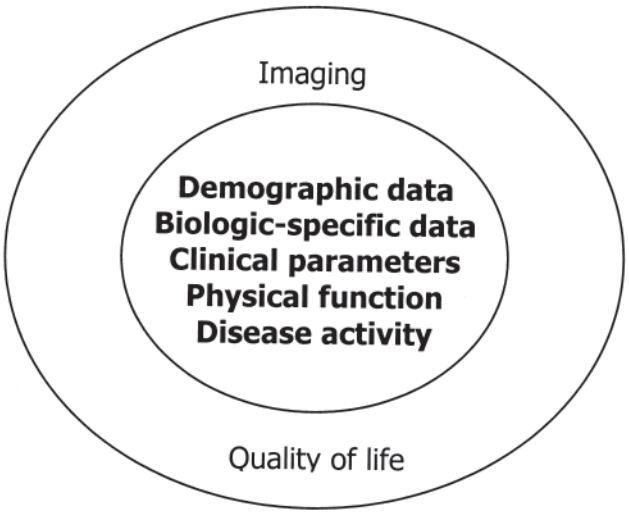

Figure 1. The ASAS biologic registry core set. Inner circle: essential elements for databases of AS patients receiving biologic therapy. Outer circle: recommended elements.

general AS cohorts. The majority of registries and cohorts measured each domain as frequently as proposed in the core set, or more often (90%) (Table 2). There was no consensus as to which instrument to use to measure enthesitis or quality of life (QOL), only 40% measuring both ASQOL and a generic measure.

DISCUSSION

The ASAS biologic registry core set is a simple set of 7 disease concepts that are recommended to be addressed for databases of AS patients receiving biologic therapies. It is small enough to be practical, but inclusive enough not to miss important information. The core set is in no way exclusive; the items presented are thought to represent the minimum information to be collected, and individual registry groups will have their own specific goals and issues to be addressed over and above the concepts outlined here. The core set forms a baseline of information that can allow the comparison of data between registries and therefore between countries and populations, can facilitate collaboration between research groups and potential combination of data into larger observational studies, and can allow a systematic collection of adverse events and toxicities associated with biologic therapy.

Consensus was good among the ASAS participants, with only a few items progressing to a second vote. Most measurement instruments were recommended in agreement with the ASAS core sets for endpoints in AS[5-8], with the addition of the ASQOL and a generic measure for quality of life. Definition of recommended measurement intervals was more controversial, largely due to the absence of definitive research evidence and differing individual clinical practice. Nevertheless, when existing patient registry practices were examined, the predefined intervals put forward in the core set were well supported.

Our results are comparable to the Core Set for Longitudinal Observational Studies in Rheumatology (LOSR) published in 1999[9], with the exception of the omission of psychosocial function and costs from the ASAS core set. It can be argued that for a biologics registry, psychosocial issues are adequately covered by assessing quality of life. Costs, however, are intuitively of relevance, and the ASAS group spent some time discussing this issue before it

was finally excluded in a majority vote. The LOSR core set group also allowed that costs were not recognized as a requirement for all longitudinal observational studies, and this should be decided on an individual study or registry basis.

The ASAS core set for biologic registries represents a combination of research evidence and expert opinion to best define those concepts we need to measure and follow in observational cohorts of AS patients receiving biologic therapy.

ACKNOWLEDGMENT

Many thanks to the members of the ASAS International Working Group whose input was invaluable, and to the coordinators of the 10 participating AS biologic registries and patient cohorts, Dr. Ulrich Weber (Switzerland), Dr. Martin Rudwaleit (Germany), Prof. Marjatta Leirisalo-Repo (Finland), Prof. Eduardo Collantes-Estévez (Spain), Dr. Irene van der Horst-Bruinsma (The Netherlands), Prof. Pal Géher (Hungary), Prof. Tore Kvien (Norway), Dr. Kurt de Vlam (Belgium), Prof. Mikkel Ostergaard (Denmark), and Prof. Walter Maksymowych (Canada).

REFERENCES

1. Henderson C, Davis JC. Drug insight: anti-tumor-necrosis therapy for ankylosing spondylitis. Nat Clin Pract Rheumatol 2006;2:211-8.
2. Delbecq AL, van de Ven AH, Gustofon DH. Group techniques for program planning. A guide to nominal group and Delphi processes. Glenview, IL: Scott, Foresman and Company; 1975.
3. Linstone HA, Turoff M. The Delphi method. London: Addison-Wesley; 1975.
4. Murphy MK, Black NA, Lamping DL, et al. Consensus development methods, and their use in clinical guideline development. Health Technol Assess 1998;2:i-88.
5. van der Heijde D, Bellamy N, Calin A, et al. Preliminary core sets for endpoints in ankylosing spondylitis. Assessments in Ankylosing Spondylitis Working Group. J Rheumatol 1997;24:2225-9.
6. van der Heijde D, Calin A, Dougados M, Khan MA, van der Linden S, Bellamy N. Selection of instruments in the core set for DC-ART, SMARD, physical therapy, and clinical record keeping in ankylosing spondylitis. J Rheumatol 1999;26:951-4.
7. van der Heijde D, van der Linden S, Dougados M, et al. Ankylosing spondylitis: plenary discussion and results of voting on selection of domains and some specific instruments. J Rheumatol 1999;26:1003-5.
8. Zochling J, Braun J, van der Heijde D. Assessments in ankylosing spondylitis. Best Pract Res Clin Rheumatol 2006;20:521-37.
9. Wolfe F, Lassere M, van der Heijde D, et al. Preliminary core set of domains and reporting requirements for longitudinal observational studies in rheumatology. J Rheumatol 1999;26:484-89.