The Journal of Rheumatology

The Journal of Rheumatology Volume 38, no. 7

Development of Outcome Measures for Large-vessel Vasculitis for Use in Clinical Trials: Opportunities, Challenges, and Research Agenda

HANER DIRESKENELI, SIBEL Z. AYDIN, TANAZ A. KERMANI, ERIC L. MATTESON, MAARTEN BOERS, KAREN HERLYN, RAASHID A. LUQMANI, TUHINA NEOGI, PHILIP SEO, RAVI SUPPIAH, GUNNAR TOMASSON and PETER A. MERKEL

J Rheumatol 2011;38;1471-1479
http://www.jrheum.org/content/38/7/1471

1. Sign up for TOCs and other alerts
http://www.jrheum.org/alerts

2. Information on Subscriptions
http://jrheum.com/faq

3. Information on permissions/orders of reprints
http://jrheum.com/reprints_permissions

The Journal of Rheumatology is a monthly international serial edited by Earl D. Silverman featuring research articles on clinical subjects from scientists working in rheumatology and related fields.

Downloaded from www.jrheum.org on June 19, 2019 - Published by The Journal of Rheumatology

Development of Outcome Measures for Large-vessel Vasculitis for Use in Clinical Trials: Opportunities, Challenges, and Research Agenda

HANER DIRESKENELI, SIBEL Z. AYDIN, TANAZ A. KERMANI, ERIC L. MATTESON, MAARTEN BOERS, KAREN HERLYN, RAASHID A. LUQMANI, TUHINA NEOGI, PHILIP SEO, RAVI SUPPIAH, GUNNAR TOMASSON, and PETER A. MERKEL

ABSTRACT. Giant cell (GCA) and Takayasu's arteritis (TAK) are 2 forms of large-vessel vasculitis (LVV) that involve the aorta and its major branches. GCA has a predilection for the cranial branches, while TAK tends to affect the extracranial branches. Both disorders may also cause nonspecific constitutional symptoms. Although some clinical features are more common in one or the other disorder and the ages of initial presentation differ substantially, there is enough clinical and histopathologic overlap between these disorders that some investigators suggest GCA and TAK may be 2 processes within the spectrum of a single disease. There have been few randomized therapeutic trials completed in GCA, and none in TAK. The lack of therapeutic trials in LVV is only partially explained by the rarity of these diseases. It is likely that the lack of well validated outcome measures for LVV and uncertainties regarding trial design contribute to the paucity of trials for these diseases. An initiative to develop a core set of outcome measures for use in clinical trials of LVV was launched by the international OMERACT Vasculitis Working Group in 2009 and subsequently endorsed by the OMERACT community at the OMERACT 10 meeting. Aims of this initiative include: (1) to review the literature and existing data related to outcome assessments in LVV; (2) to obtain the opinion of experts and patients on disease content; and (3) to formulate a research agenda to facilitate a more data-based approach to outcomes development. (J Rheumatol 2011;38:1471–9; doi:10.3899/jrheum.110275)

Key Indexing Terms:
VASCULITIS OUTCOMES TAKAYASU'S ARTERITIS GIANT CELL ARTERITIS

Giant cell (GCA) and Takayasu's arteritis (TAK) are 2 forms of large-vessel vasculitis (LVV). Both diseases involve the aorta and its major branches; however, GCA has a predilection for the cranial branches, while TAK tends to affect the extracranial branches[1]. Although LVV may present with acute symptoms such as visual loss or cerebrovascular occlusions, both disorders may also cause nonspecific constitutional features such as fever, malaise, anorexia, and weight loss. LVV usually has a protracted clinical course and relapses are common. Features such as jaw claudication or polymyalgia rheumatica in GCA, or pulselessness and extremity claudication in TAK, are conventionally used to discriminate between

From Marmara University School of Medicine, Istanbul, Turkey; Leeds University, Leeds, United Kingdom; Department of Rheumatology, Divisions of Rheumatology and Epidemiology, Mayo Clinic College of Medicine, Rochester, MN, USA; Department of Clinical Epidemiology, VU University Medical Center, Amsterdam, The Netherlands; Department of Rheumatology, University Hospital of Schleswig-Holstein, Campus Luebeck, Luebeck, Germany; Section of Rheumatology and the Clinical Epidemiology Unit, Boston University Schools of Medicine and of Public Health, Boston, MA, USA; Nuffield Department of Orthopaedics, Rheumatology, and Musculoskeletal Sciences, University of Oxford, Oxford, UK; Division of Rheumatology, Johns Hopkins University, Baltimore, MD; and Section of Rheumatology and the Clinical Epidemiology Unit, Boston University School of Medicine, Boston, MA, USA.

The OMERACT Vasculitis Working Group is supported by the Vasculitis Clinical Research Consortium through The National Institutes of Health/National Institute of Arthritis and Musculoskeletal and Skin Diseases (U54AR057319, U01 AR51874, and P60 AR047785), the National Center for Research Resources (U54 RR01949703), and the Office of Rare Diseases Research. The Vasculitis Clinical Research Consortium is part of the NIH Rare Diseases Clinical Research Network (www.RareDiseasesNetwork.org/vcrc).

H. Direskeneli, MD, Professor of Rheumatology, Department of Rheumatology, Marmara University School of Medicine; S.Z. Aydin, MD, Research Fellow, Leeds University, and Department of Rheumatology, Marmara University School of Medicine; T.A. Kermani, MD, Vasculitis Fellow and Consultant, Division of Rheumatology, Mayo Clinic College of Medicine; E.L. Matteson, MD, MPH, Professor of Medicine, Division of Rheumatology, Consultant, Divisions of Rheumatology and Epidemiology, Mayo Clinic College of Medicine; M. Boers, MD, MSc, PhD, Professor of Clinical Epidemiology, Department of Clinical Epidemiology, VU University Medical Center; K. Herlyn, MD, MPH, Department of Rheumatology, University Hospital of Schleswig-Holstein; T. Neogi, MD, PhD, Associate Professor of Medicine and of Epidemiology, Section of Rheumatology and the Clinical Epidemiology Unit, Boston University Schools of Medicine and of Public Health; R. Suppiah, MBChB, FRACP, Honorary Vasculitis Research Fellow, Nuffield Department of Orthopaedics, Rheumatology and Musculoskeletal Sciences, University of Oxford; P. Seo, MD, MHS, Assistant Professor of Medicine, Division of Rheumatology, Johns Hopkins University; G. Tomasson, Research Associate, Section of Rheumatology and Clinical Epidemiology Unit, Boston University School of Medicine; R.A. Luqmani, DM, FRCP, FRCPE, Senior Lecturer, Nuffield Department of Orthopaedics, Rheumatology and Musculoskeletal Sciences, University of Oxford; P.A. Merkel, MD, MPH, Professor of Medicine, Section of Rheumatology and the Clinical Epidemiology Unit, Boston University School of Medicine.

Address correspondence to Dr. Merkel; E-mail: pmerkel@bu.edu

Personal non-commercial use only. The Journal of Rheumatology Copyright © 2011. All rights reserved.

Downloaded from www.jrheum.org on June 19, 2019 - Published by The Journal of Rheumatology

these 2 diseases. Further, GCA is defined as occurring only among people older than 50 years (usually much older), while TAK usually presents clinically before age 30 years.

Several findings suggest, however, that GCA and TAK may be 2 processes within the spectrum of a single disease[2]. Patients with TAK and GCA often present with similar symptoms, and arterial histopathology demonstrates granulomatous inflammation in both diseases. Additionally, it has been increasingly recognized that large-vessel involvement of the aorta and its branches may be more common in GCA than thought[2,3,4,5], and the arterial lesions of both diseases have a similar angiographic appearance.

There have been few randomized therapeutic trials in GCA, and none in TAK. This is in marked contrast to the situation for antineutrophil cytoplasmic autoantibody (ANCA)-associated vasculitis (AAV), for which an increasing number of large, multicenter, randomized controlled trials have been conducted in the past 20 years. The lack of therapeutic trials in LVV is only partially explained by the rarity of these diseases. It is likely that the lack of well validated outcome measures for LVV and uncertainties regarding trial design contribute to the paucity of trials for these diseases.

GOALS REGARDING OUTCOME MEASURE DEVELOPMENT IN LVV

With an understanding of the background outlined above, and with momentum generated by the Vasculitis Clinical Research Consortium-OMERACT Vasculitis Working Group's work on the core set for AAV, a new initiative for developing a core set of outcome measures for use in clinical trials of LVV was launched in 2009 and subsequently endorsed by the OMERACT community at the OMERACT 10 meeting. Because of the limited prior work to formally evaluate outcome measures in LVV, and the lack of sufficient numbers of therapeutic trials from which to gather data on the validity and feasibility of outcome tools, the projects' initial aims were (1) to review the literature to date and existing data related to outcome assessments in LVV; (2) to obtain the opinion of experts and patients on disease content; and (3) to formulate a research agenda to facilitate a more data-based approach to outcomes development. This article summarizes the work to date on each of these aims.

Clinical Trials in GCA and TAK

Although research into the clinical manifestations, epidemiology, and pathophysiology of GCA has been conducted steadily for over 50 years, only relatively few double-blind, controlled trials have been completed in GCA. Both investigator-initiated and industry-sponsored studies have evaluated the dosage and route of administration of glucocorticoids and "steroid-sparing" agents such as methotrexate and tumor necrosis factor antagonists[6,7,8,9,10,11,12].

For TAK, the situation is even more problematic since, to date, no controlled trials have been performed. Therapeutic studies in TAK have been small, open-label protocols or case series, usually focused on the potential glucocorticoid-sparing effect of immunosuppressive agents[11,12,13,14,15]. One randomized controlled therapeutic trial is currently in progress (http://www.clinicaltrials.gov/ct2/show/NCT00556439).

Although LVV is mainly treated with glucocorticoids[16], the limited efficacy and high toxicity of these agents continue to prompt a strong interest in incorporating new therapeutic options into clinical practice. The outcomes for many patients with LVV remain unacceptably poor[2,17,18].

Rationale and Need for LVV Outcome Measures

Despite the many cohort studies published in GCA and TAK and the few randomized clinical trials conducted in LVV, there are no fully validated outcome measures for use in clinical trials of LVV. More specifically, while there have been a variety of primary and secondary outcome measures included in trials of LVV, none can be said to fulfill the requirements of the OMERACT filter for outcome tool validation[19]. Nonetheless, for the following reasons, this is an excellent time for advancing outcome measure development in LVV:

1. There has been a marked increase in interest, capabilities, and success in conducting clinical trials in vasculitis over the past 15 years. Development of international multicenter collaborative groups in North America and Europe has resulted in successful performance of large, controlled studies, especially in AAV. These same collaborative groups hope to expand their work into LVV.
2. The successful development of validated outcome measures in AAV and the recent endorsement of the OMERACT core set of outcome measures for these diseases have generated interest in studying and advancing outcome measurement tools for LVV within OMERACT.
3. Fueled to some extent by the success in small-vessel vasculitis and other rare diseases, there is growing interest by biopharmaceutical companies in developing therapies for LVV.
4. Paralleling the interest of investigators and industry in trials for LVV, there is a need for development of valid outcomes that will be accepted by regulatory agencies for demonstrating the efficacy of new therapies for LVV.
5. Data from longitudinal cohorts of patients with LVV are available for use in analyses of outcome measures. Similarly, the ongoing availability of cohorts for study will substantially facilitate study of outcome measures in LVV.

Current Status of Outcome Measures for Use in LVV

Research directly focused on outcome measures in LVV has been limited. Most studies have focused on applying tools used in other diseases to LVV; no project has resulted in tools validated for use in LVV. However, some useful information and insight into outcome measures can be obtained from reviewing the methods used for disease assessment in published clinical trials and cohort studies of LVV.

Specific measures of disease activity in LVV. The Birmingham

Personal non-commercial use only. The Journal of Rheumatology Copyright © 2011. All rights reserved.

Downloaded from www.jrheum.org on June 19, 2019 - Published by The Journal of Rheumatology

Vasculitis Activity Score (BVAS) is a validated tool for small and medium-vessel vasculitis that records presence or absence of evidence of active vasculitis on a one-page form listing multiple manifestations of vasculitis, arranged by organ systems. Although used extensively in therapeutic trials of ANCA-associated vasculitis [granulomatosis with polyangiitis (Wegener's) and microscopic polyangiitis][20], BVAS has been used in only a few studies of GCA or TAK[21,22,23,24], but has not been fully validated for use in clinical trials of LVV.

Recently the Disease Extent Index for Takayasu's arteritis (DEI.Tak) was developed based on the BVAS. In the DEI.Tak, items directly related to large arterial disease (e.g., stenosis and claudication) are weighted more heavily for scoring than general items of disease (e.g., fever, fatigue). However, there is no strong evidence that DEI.Tak can serve as a measure of disease activity, as opposed to a catalog of disease-related damage. In a study of 145 Turkish patients with TAK, DEI.Tak was measured twice over a mean period of 28 months[25]. Most items commonly involved in small-vessel vasculitis and also present in BVAS (e.g., pulmonary nodules, skin lesions) changed in fewer than 5% of patients. Patients with active or persistent disease had higher DEI.Tak scores compared to patients in remission. Physician's global assessment (PGA) and DEI.Tak scores had modest agreement (68%). Sixty-nine percent of subjects with slow progression of disease demonstrated no change in the DEI.Tak. Further, 31% of patients deemed inactive by DEI.Tak had "active/persistent" disease according to the PGA. In contrast, 18% of the patients with a DEI.Tak ≥ 1 (active) were considered inactive by the PGA score. Thus, while DEI.Tak is simple to use and does not rely on imaging modalities and measures of acute-phase reactants, physician's treatment decisions are only partially reflected by the DEI.Tak. Similar results were also reported in a study of an Italian cohort of patients[26].

Disease-related damage and mortality. As with other vasculitides, disease-related damage is a major cause of morbidity for patients with both GCA and TAK. Prevention of damage is the primary goal of treatment in LVV. Some items of damage, such as permanent visual loss, a prominent feature of GCA, have important implications for patients' quality of life and ability to live independently. Large arterial disease in LVV often leads to vascular stenosis that is irreversible unless a surgical intervention is performed. In LVV it is critical to differentiate irreversible damage from disease activity, and thus avoid potential overtreatment with toxic agents.

Although the Vasculitis Damage Index is the standard tool for assessing damage in small-vessel vasculitis[27], data supporting its use in LVV are scant.

Few studies have evaluated mortality in LVV. Mortality may be increased in TAK[28], whereas in GCA, apart from the subgroup of patients who develop aortic dissection, no excess mortality has been observed[4]. Based on the available data and clinical experience, it appears unlikely that mortality would ever be a principal outcome measure for clinical trials in LVV.

Health-related quality of life in LVV. In cases of vasculitis, physicians and patients may rate disease status and importance of disease manifestations differently[29]. Disease manifestations in LVV vary greatly from nonspecific constitutional symptoms (e.g., fever, fatigue, weight loss) to symptoms due to vascular occlusion (e.g., visual loss or claudication). Based on clinical experience and a study that evaluated qualitative data in GCA, the spectrum of disease- and treatment-related problems in LVV appears to substantially affect patients' quality of life (HRQOL)[30]. Incorporation of HRQOL measurements with a generic instrument such as the Medical Outcomes Study Short-Form 36 (SF-36) will likely add to the content validity of outcome measures for LVV.

Measurement of HRQOL through the use of the SF-36 has been evaluated in 2 studies of TAK. These studies demonstrated that patients with TAK had reduced SF-36 scores, similar to other chronic inflammatory disorders such as rheumatoid arthritis and ankylosing spondylitis[31,32].

Outcomes and Data Elements Used in Clinical Trials and Case Series of LVV

Given the lack of international standards for assessing disease activity in GCA and TAK, it is not surprising that multiple definitions of active disease and response to treatment have been used in clinical studies of LVV. A review of clinical trials and large-cohort studies in GCA and TAK has revealed several groups of outcomes common to multiple studies. These outcomes were chosen by a series of experts in the field and are a reasonable starting point for ongoing discussions and formation of a research agenda.

Information on clinical assessments and outcome measures was gathered from published studies of GCA including reports of therapeutic clinical trials, treatment case series, biomarker studies, and a systematic review[6,7,8,9,10,11,12,33,34,35,36,37,38,39,40,41,42,43,44,45,46,47,48,49,50,51]. These outcomes fall into a few main groups: GCA-related outcomes, laboratory tests, and glucocorticoid-related outcomes. A more detailed list of the outcomes used in aforementioned studies of GCA is summarized in Table 1. These outcomes range from those with highly specific definitions to vague concepts such as "definite" or "possible" relapse. The usual primary outcomes for the trials were rate of relapse, time to relapse, or glucocorticoid-sparing effect of additional treatments.

No controlled trials have been performed in TAK, but open-label protocols or case series usually cite the definition of active disease from the US National Institutes of Health (NIH) study[52]: presence of constitutional symptoms, new bruits, acute-phase response, or new angiographic features[18,53,54]. A literature search performed for TAK with keywords "outcome, activity, relapse, remission, and assessment" yielded 73 articles describing clinical studies, including cohort descriptions, imaging studies, and studies of biomarkers[13,14,18,21,24,25,31,52-116]. A more detailed list of the outcomes used in these studies of TAK is summarized in Table 2. The 4

Personal non-commercial use only. The Journal of Rheumatology Copyright © 2011. All rights reserved.

Downloaded from www.jrheum.org on June 19, 2019 - Published by The Journal of Rheumatology

Table 1. Summary of outcome measures used in trials of giant cell arteritis (GCA) by study type[†(6-12,33-51)]. Values are expressed as number (%) of studies reporting the listed outcome variable.

Outcome	Clinical Trials, n = 9 (%)	Treatment Series or Metaanalysis, n = 11 (%)	Biomarker Studies, n = 6 (%)	Overall, n = 26 (%)
GCA-related outcomes				
GCA disease activity scale	1 (11)	0 (0)	2 (33)	3 (11)
GCA complications	5 (56)	8 (73)	2 (33)	15 (58)
Flare	2 (22)	2 (18)	3 (50)	7 (27)
Remission	3 (33)	4 (36)	0 (0)	7 (27)
Relapse	5 (56)	6 (55)	3 (50)	14 (54)
Symptoms and/or physical examination	9 (100)	8 (77)	6 (100)	23 (89)
Other GCA-related outcomes*	2 (22)	2 (18)	0 (0)	4 (15)
Laboratory testing outcomes				
Erythrocyte sedimentation rate	9 (100)	5 (46)	5 (83)	19 (73)
C-reactive protein	6 (67)	2 (18)	5 (83)	13 (50)
Complete blood count	7 (78)	3 (27)	2 (33)	12 (46)
Glucocorticoid-related outcomes				
Duration of GC treatment	2 (22)	3 (27)	0 (0)	5 (19)
Cumulative GC dose	7 (78)	5 (45)	0 (0)	12 (46)
Percentage on GC at end of study	2 (22)	0 (0)	1 (17)	3 (12)
GC dose at end of study	3 (33)	0 (0)	0 (0)	3 (12)
GC-related adverse events	6 (67)	5 (46)	0 (0)	11 (42)
Other GC-related outcomes**	5 (56)	3 (27)	1 (17)	9 (35)
Other outcomes				
Mortality	1 (11)	1 (9)	0 (0)	2 (8)
Study drug-related adverse event (non-GC)	5 (56)	2 (18)	NA	5 (25)
Imaging	0 (0)	0 (0)	0 (0)	0 (0)
Patient-reported assessments	1 (11)	0 (0)	1 (17)	2 (8)

† Data from studies that included ≥ 20 patients. * Recurrence, exacerbation, cure, time to first relapse; ** Time to specific GC dose, GC resistance, GC failure, maintenance GC dose. GC: glucocorticoid; NA: not applicable.

Table 2. Summary of outcome measures used in trials of Takayasu's arteritis (TAK) by study type[13,14,18,21,24,25,31,52-116]. Values are number (%) of studies reporting the listed outcome variable.

Outcome	Treatment and Outcome Series, n = 34 (%)	Imaging*, n = 15 (%)	Biomarker Studies, n = 24 (%)	Overall, n = 73 (%)
TAK-related outcomes				
Remission	7 (21)	0 (0)	7 (29)	14 (19)
Relapse	3 (9)	0 (0)	1 (4)	4 (6)
Stable	4 (12)	0 (0)	1 (4)	5 (7)
Activity according to definition by Kerr[52]	14 (41)	8 (53)	11 (46)	36 (49)
TAK disease activity scale (DEI.TAK/ITAS)	2 (6)	0 (0)	0 (0)	2 (3)
Interventions (PTCA + surgery)	23 (68)	1 (7)	1 (4)	25 (34)
Laboratory testing outcomes				
ESR, CRP, or CBC	23 (68)	12 (80)	21 (88)	56 (77)
Glucocorticoid-related outcomes				
Dose or duration	25 (96)	7 (54)	17 (74)	49 (79)
Other outcomes				
Mortality	13 (46)	0 (0)	0 (0)	13 (20)
Patient-reported assessments	3 (11)	0 (0)	0 (0)	3 (5)
Angiography	21 (62)	8 (53)	11 (46)	40 (55)

* Studies on imaging modalities other than conventional angiography. DEI.TAK/ITAS: Disease Extent Index for Takayasu's arteritis/Indian Takayasu's Arteritis Score; PTCA: percutaneous transluminal coronary angioplasty; ESR: erythrocyte sedimentation rate; CRP: C-reactive protein; CBC: complete blood count.

Personal non-commercial use only. The Journal of Rheumatology Copyright © 2011. All rights reserved.

Downloaded from www.jrheum.org on June 19, 2019 - Published by The Journal of Rheumatology

items in the NIH series were preferred by most studies to define active disease. Activity defined by imaging only (magnetic resonance, positron emission tomography, or computerized tomography) is used mainly in a small group of imaging studies. Remission (19%) or relapse (6%) is also defined in a limited subset of studies. A composite disease assessment tool such as BVAS or SF-36 is also used in a small number of studies.

Challenges and Opportunities for Outcome Measure Development in LVV

Investigators face significant challenges to the development of outcome measures for LVV. Some of these challenges are common to multisystem rare diseases while others are fairly specific to LVV. Because these are rare diseases, recruitment of sufficient sample sizes for cohorts and clinical trials is problematic. Further, while some clinical manifestations are vague and subjective (e.g., fatigue, arthralgias), other more serious disease manifestations may be asymptomatic until later stages when they are often irreversible (e.g., proximal aortitis leading to myocardial infarction or sudden monocular visual loss). The chronic relapsing and remitting course of LVV and the broad clinical spectrum of manifestations also make assessing outcomes difficult and require long timelines for trials. Beyond glucocorticoids, there are few therapies deemed effective for treatment of these diseases; hence, there are only limited comparative data for evaluation of usefulness and validity of outcome tools.

Reasons for optimism exist about current opportunities to develop outcome measures in LVV. Several senior investigators with relevant clinical experience in LVV and expertise in outcomes development are involved in the OMERACT initiative and a wider group of researchers within the international vasculitis research community are interested in participating in the process. There is willingness to start anew in the process of outcomes development for LVV and thus allow for incorporation of new ideas and a data-based rationale for creating a core set of measures. Further, there are several ongoing research projects on LVV regarding utility of new imaging modalities and exploration of new biomarkers for use in clinical research.

Should One Set of Outcomes Be Used for Both Giant Cell Arteritis and Takayasu's Arteritis?

Among the major issues to resolve in the field of outcome measures for LVV is whether GCA and TAK are similar enough to justify use of the same set of outcome measures. GCA and TAK are both LVV that share a number of clinical features. Both diseases predominantly affect women, but each one has different age and genetic associations. GCA, as currently defined, is almost exclusively seen in people over age 50 years and predominantly affects people of Northern European ancestry; TAK typically first affects women under the age of 40 years and is more common among people of Asian ancestry (but by no means exclusive to that group). Both vasculitides feature systemic symptoms including fever and weight loss, and are associated with large-vessel inflammation, which can lead to arterial stenosis, claudication, aortitis, and aneurysm formation. Histologic features include the presence of granulomatous inflammation in both diseases. These similarities have raised the question of whether GCA and TAK are really part of one disease spectrum.

Although clinical presentations often differ for GCA versus TAK, these differences may have been overstated in the past. More recent studies report that many features typically associated more exclusively with GCA (e.g., headache) or TAK (e.g., aortic branch disease and claudication) are actually not uncommon in the other disease[2,17]. Detection bias may partially explain previously described differences between GCA and TAK. Imaging of the aorta and its branches is performed in almost all patients with TAK but in a lesser proportion of GCA patients[2,17]. A comparison of important clinical features of both diseases is displayed in Table 3.

At this time, it appears reasonable to study patients with GCA and TAK using the same set of outcomes and data elements. Ongoing work will continue to assess the relative utility of considering them separate diseases versus considering them as entities in a single spectrum of illness.

ACTIVITIES OF THE OMERACT VASCULITIS WORKING GROUP: SOURCES OF DATA, AND RESEARCH AGENDA

The goals of the OMERACT Vasculitis Working Group include development of disease assessment tools in the vasculitides. This group has successfully developed a validated and accepted core set of outcome measures for AAV and initiated a project to develop disease-specific patient-reported outcomes in vasculitis[117]. The success of the OMERACT initiatives for AAV, including not only endorsement of the core set, but also establishment and maintenance of an international group of investigators willing to work cooperatively on common goals, provides substantial optimism as the group moves forward with plans for LVV.

In anticipation of the OMERACT 10 meeting, a preliminary discussion of outcomes for TAK was the subject of a separate meeting of TAK experts in Istanbul, Turkey. This meeting was helpful in starting the discussions regarding domains of illness, use of available instruments, "gold standards" of disease assessment, and exploring the range of data elements investigators felt important to consider when studying TAK. As the gold standard for disease activity assessment, new vessel involvement was favored by 84%, as determined by either clinical examination or imaging, whereas physician's global assessment was found suitable by only 13%. A scalable index was supported over a dichotomous outcome by 89% of participants and weighting of items was strongly endorsed (87%). However, 80% accepted that it is not clearly possible to differentiate "low" versus "high" disease activity or damage versus activity (83%) in TAK. Discussions from this meeting

Personal non-commercial use only. The Journal of Rheumatology Copyright © 2011. All rights reserved.

Downloaded from www.jrheum.org on June 19, 2019 - Published by The Journal of Rheumatology

Table 3. Comparison of the clinical features in patients with giant cell arteritis (GCA) and Takayasu's arteritis (TAK). Data derived and table modified from Michel, *et al*. J Rheumatol 1996[17] and Maksimowicz-McKinnon, *et al*. Medicine (Baltimore) 2009[2].

Clinical Feature	Predominant in TAK*	Predominant in GCA*	Commonly Present in Both*
Female predominance			X
Caucasian predominance		X	
Younger age at presentation	X		
Older age at presentation		X	
Fever			X
Weight loss			X
Elevated markers of inflammation			X
Anemia			X
New headache		X	
Jaw claudication		X	
Scalp tenderness		X	
Vision loss		X	
Arthralgia			X
Vascular bruits			X
Diminished or absent upper extremity pulse			X
Upper extremity blood pressure discrepancy			X
Upper extremity claudication			X
Lower extremity claudication	X		
Temporal artery abnormalities		X	
Granulomatous inflammation on arterial histopathology			X
Aortic aneurysm			X
Aortic narrowing or occlusion	X		
Subclavian arterial disease			X
Renal artery involvement			X
Mesenteric arterial involvement†	X		

* While most of these clinical features can be present in patients with both giant cell arteritis and Takayasu's arteritis, assignment of predominance was made based on percentages of patients with giant cell arteritis and Takayasu's arteritis with these clinical features in these 2 reports. † Assessed only in Maksimowicz-McKinnon[2].

informed the subsequent breakout session at OMERACT 10 devoted to LVV. The OMERACT session confirmed the need for investigators to analyze existing cohort data on validity of existing assessment tools and organize a new initiative to gather new data focused on outcome assessment in LVV.

Several issues regarding studying outcomes in LVV remain unresolved: (1) combining GCA and TAK (see section above); (2) how to incorporate patient preferences/perspectives into LVV assessment; (3) whether to pursue composite outcomes or individual elements; (4) the roles and usefulness of both traditional biomarkers (sedimentation rate and C-reactive protein) and newer markers; (5) the role of imaging in the set of outcomes for LVV; and (6) definition of disease states.

RESEARCH AGENDA REGARDING OUTCOME MEASURE DEVELOPMENT IN LVV

OMERACT 10 led to the drafting of a preliminary research agenda for outcome development in LVV that includes:

- Conducting a Delphi exercise with a large group of international experts on GCA and TAK. The goal of this exercise will be to generate a broad list of candidate domains, endpoints, and outcome elements of interest and the list will be subsequently refined to a smaller key set for further study. As LVV have an ethnically uneven distribution, this effort should bring the experts from Europe, the Americas, and Asia.
- Analysis of patient-reported outcome data from ongoing cohort studies of GCA and TAK and completed clinical trials.
- Evaluation of imaging data from cohorts to gain insight into the likely key role that vascular imaging will play in disease assessment in LVV. Use of imaging to assess arterial narrowing, occlusion, or aneurysm is well established. However, the utility of imaging data to determine disease status using vessel wall thickness, edema, and enhancement is controversial.
- Prospective collection of data incorporating new elements and outcome tools as suggested by the Delphi exercise.

SUMMARY

There is a clear need to develop a validated set of outcome measures for use in clinical trials of LVV. The OMERACT Vasculitis Working Group has taken on this task, reviewed current evidence, created a research agenda, and plans to develop a core set of outcomes for LVV.

REFERENCES

1. Borg FA, Dasgupta B. Treatment and outcomes of large vessel arteritis. Best Pract Res Clin Rheumatol 2009;23:325-37.
2. Maksimowicz-McKinnon K, Clark TM, Hoffman GS. Takayasu arteritis and giant cell arteritis: a spectrum within the same disease? Medicine (Baltimore) 2009;88:221-6.
3. Evans JM, O'Fallon WM, Hunder GG. Increased incidence of aortic aneurysm and dissection in giant cell (temporal) arteritis. A population-based study. Ann Intern Med 1995;122:502-7.
4. Nuenninghoff DM, Hunder GG, Christianson TJ, McClelland RL, Matteson EL. Mortality of large-artery complication (aortic aneurysm, aortic dissection, and/or large-artery stenosis) in patients with giant cell arteritis: a population-based study over 50 years. Arthritis Rheum 2003;48:3532-7.
5. Garcia-Martinez A, Hernandez-Rodriguez J, Arguis P, Paredes P, Segarra M, Lozano E, et al. Development of aortic aneurysm/dilatation during the followup of patients with giant cell arteritis: a cross-sectional screening of fifty-four prospectively followed patients. Arthritis Rheum 2008;59:422-30.
6. Chevalet P, Barrier JH, Pottier P, Magadur-Joly G, Pottier MA, Hamidou M, et al. A randomized, multicenter, controlled trial using intravenous pulses of methylprednisolone in the initial treatment of simple forms of giant cell arteritis: a one year followup study of 164 patients. J Rheumatol 2000;27:1484-91.
7. Jover JA, Hernandez-Garcia C, Morado IC, Vargas E, Banares A, Fernandez-Gutierrez B. Combined treatment of giant-cell arteritis with methotrexate and prednisone. A randomized, double-blind, placebo-controlled trial. Ann Intern Med 2001;134:106-14.
8. Spiera RF, Mitnick HJ, Kupersmith M, Richmond M, Spiera H, Peterson MG, et al. A prospective, double-blind, randomized, placebo controlled trial of methotrexate in the treatment of giant cell arteritis (GCA). Clin Exp Rheumatol 2001;19:495-501.
9. Hoffman GS, Cid MC, Hellmann DB, Guillevin L, Stone JH, Schousboe J, et al. A multicenter, randomized, double-blind,

Personal non-commercial use only. The Journal of Rheumatology Copyright © 2011. All rights reserved.

Downloaded from www.jrheum.org on June 19, 2019 - Published by The Journal of Rheumatology

placebo-controlled trial of adjuvant methotrexate treatment for giant cell arteritis. Arthritis Rheum 2002;46:1309-18.
10. Mazlumzadeh M, Hunder GG, Easley KA, Calamia KT, Matteson EL, Griffing WL, et al. Treatment of giant cell arteritis using induction therapy with high-dose glucocorticoids: a double-blind, placebo-controlled, randomized prospective clinical trial. Arthritis Rheum 2006;54:3310-8.
11. Hoffman GS, Cid MC, Rendt-Zagar KE, Merkel PA, Weyand CM, Stone JH, et al. Infliximab for maintenance of glucocorticosteroid-induced remission of giant cell arteritis: a randomized trial. Ann Intern Med 2007;146:621-30.
12. Martinez-Taboada VM, Rodriguez-Valverde V, Carreno L, Lopez-Longo J, Figueroa M, Belzunegui J, et al. A double-blind placebo controlled trial of etanercept in patients with giant cell arteritis and corticosteroid side effects. Ann Rheum Dis 2008;67:625-30.
13. Valsakumar AK, Valappil UC, Jorapur V, Garg N, Nityanand S, Sinha N. Role of immunosuppressive therapy on clinical, immunological, and angiographic outcome in active Takayasu's arteritis. J Rheumatol 2003;30:1793-8.
14. Molloy ES, Langford CA, Clark TM, Gota CE, Hoffman GS. Anti-tumour necrosis factor therapy in patients with refractory Takayasu arteritis: long-term follow-up. Ann Rheum Dis 2008;67:1567-9.
15. Goel R, Danda D, Mathew J, Edwin N. Mycophenolate mofetil in Takayasu's arteritis. Clin Rheumatol 2010;29:329-32.
16. Mukhtyar C, Guillevin L, Cid MC, Dasgupta B, de Groot K, Gross W, et al. EULAR recommendations for the management of large vessel vasculitis. Ann Rheum Dis 2009;68:318-23.
17. Michel BA, Arend WP, Hunder GG. Clinical differentiation between giant cell (temporal) arteritis and Takayasu's arteritis. J Rheumatol 1996;23:106-11.
18. Maksimowicz-McKinnon K, Clark TM, Hoffman GS. Limitations of therapy and a guarded prognosis in an American cohort of Takayasu arteritis patients. Arthritis Rheum 2007;56:1000-9.
19. Boers M, Brooks P, Strand CV, Tugwell P. The OMERACT filter for Outcome Measures in Rheumatology. J Rheumatol 1998;25:198-9.
20. Merkel PA, Aydin SZ, Boers M, Direskeneli H, Herlyn K, Seo P, et al. The OMERACT core set of outcome measures for use in clinical trials of ANCA-associated vasculitis. J Rheumatol 2011;38:1480-6.
21. Ureten K, Ozturk MA, Onat AM, Ozturk MH, Ozbalkan Z, Guvener M, et al. Takayasu's arteritis: results of a university hospital of 45 patients in Turkey. Int J Cardiol 2004;96:259-64.
22. Becker H, Maaser C, Mickholz E, Dyong A, Domschke W, Gaubitz M. Relationship between serum levels of macrophage migration inhibitory factor and the activity of antineutrophil cytoplasmic antibody-associated vasculitides. Clin Rheumatol 2006;25:368-72.
23. Both M, Ahmadi-Simab K, Reuter M, Dourvos O, Fritzer E, Ullrich S, et al. MRI and FDG-PET in the assessment of inflammatory aortic arch syndrome in complicated courses of giant cell arteritis. Ann Rheum Dis 2008;67:1030-3.
24. Henes JC, Muller M, Krieger J, Balletshofer B, Pfannenberg AC, Kanz L, et al. [18F] FDG-PET/CT as a new and sensitive imaging method for the diagnosis of large vessel vasculitis. Clin Exp Rheumatol 2008;26 Suppl 49:S47-52.
25. Aydin SZ, Yilmaz N, Akar S, Aksu K, Kamali S, Yucel E, et al. Assessment of disease activity and progression in Takayasu's arteritis with Disease Extent Index-Takayasu. Rheumatology 2010;49:1889-93.
26. Magnani L, Versari A, Salvo D, Casali M, Germano G, Meliconi R, et al. Disease activity assessment in large vessel vasculitis [abstract]. Arthritis Rheum 2010;62 Suppl:S537.
27. Seo P, Luqmani RA, Flossmann O, Hellmich B, Herlyn K, Hoffman GS, et al. The future of damage assessment in vasculitis. J Rheumatol 2007;34:1357-71.
28. Phillip R, Luqmani R. Mortality in systemic vasculitis: a systematic review. Clin Exp Rheumatol 2008;26 Suppl 51:S94-104.
29. Herlyn K, Hellmich B, Seo P, Merkel PA. Patient-reported outcome assessment in vasculitis provides important data and a unique perspective. Arthritis Care Res 2010;62:1639-45.
30. Hellmann DB, Uhlfelder ML, Stone JH, Jenckes MW, Cid MC, Guillevin L, et al. Domains of health-related quality of life important to patients with giant cell arteritis. Arthritis Rheum 2003;49:819-25.
31. Abularrage CJ, Slidell MB, Sidawy AN, Kreishman P, Amdur RL, Arora S. Quality of life of patients with Takayasu's arteritis. J Vasc Surg 2008;47:131-6; discussion:6-7.
32. Akar S, Can G, Binicier O, Aksu K, Akinci B, Solmaz D, et al. Quality of life in patients with Takayasu's arteritis is impaired and comparable with rheumatoid arthritis and ankylosing spondylitis patients. Clin Rheumatol 2008;27:859-65.
33. Hunder GG, Sheps SG, Allen GL, Joyce JW. Daily and alternate-day corticosteroid regimens in treatment of giant cell arteritis: comparison in a prospective study. Ann Intern Med 1975;82:613-8.
34. Bengtsson BA, Malmvall BE. Prognosis of giant cell arteritis including temporal arteritis and polymyalgia rheumatica. A follow-up study on ninety patients treated with corticosteroids. Acta Med Scand 1981;209:337-45.
35. Park JR, Jones JG, Hazleman BL. Relationship of the erythrocyte sedimentation rate to acute phase proteins in polymyalgia rheumatica and giant cell arteritis. Ann Rheum Dis 1981;40:493-5.
36. Delecoeuillerie G, Joly P, Cohen de Lara A, Paolaggi JB. Polymyalgia rheumatica and temporal arteritis: a retrospective analysis of prognostic features and different corticosteroid regimens (11 year survey of 210 patients). Ann Rheum Dis 1988;47:733-9.
37. Kyle V, Cawston TE, Hazleman BL. Erythrocyte sedimentation rate and C reactive protein in the assessment of polymyalgia rheumatica/giant cell arteritis on presentation and during follow up. Ann Rheum Dis 1989;48:667-71.
38. Lundberg I, Hedfors E. Restricted dose and duration of corticosteroid treatment in patients with polymyalgia rheumatica and temporal arteritis. J Rheumatol 1990;17:1340-5.
39. Nesher G, Rubinow A, Sonnenblick M. Efficacy and adverse effects of different corticosteroid dose regimens in temporal arteritis: a retrospective study. Clin Exp Rheumatol 1997;15:303-6.
40. Schaufelberger C, Andersson R, Nordborg E. No additive effect of cyclosporin A compared with glucocorticoid treatment alone in giant cell arteritis: results of an open, controlled, randomized study. Br J Rheumatol 1998;37:464-5.
41. Liozon E, Roblot P, Paire D, Loustaud V, Liozon F, Vidal E, et al. Anticardiolipin antibody levels predict flares and relapses in patients with giant-cell (temporal) arteritis. A longitudinal study of 58 biopsy-proven cases. Rheumatology 200;39:1089-94.
42. Weyand CM, Fulbright JW, Hunder GG, Evans JM, Goronzy JJ. Treatment of giant cell arteritis: interleukin-6 as a biologic marker of disease activity. Arthritis Rheum 2000;43:1041-8.
43. Myklebust G, Gran JT. Prednisolone maintenance dose in relation to starting dose in the treatment of polymyalgia rheumatica and temporal arteritis. A prospective two-year study in 273 patients. Scand J Rheumatol 2001;30:260-7.
44. Hernandez-Rodriguez J, Segarra M, Vilardell C, Sanchez M, Garcia-Martinez A, Esteban MJ, et al. Elevated production of interleukin-6 is associated with a lower incidence of disease-related ischemic events in patients with giant-cell arteritis: angiogenic activity of interleukin-6 as a potential protective mechanism. Circulation 2003;107:2428-34.
45. Garcia-Martinez A, Hernandez-Rodriguez J, Grau JM, Cid MC.

Personal non-commercial use only. The Journal of Rheumatology Copyright © 2011. All rights reserved.

Downloaded from www.jrheum.org on June 19, 2019 - Published by The Journal of Rheumatology

Treatment with statins does not exhibit a clinically relevant corticosteroid-sparing effect in patients with giant cell arteritis. Arthritis Rheum 2004;51:674-8.
46. Nesher G, Berkun Y, Mates M, Baras M, Rubinow A, Sonnenblick M. Low-dose aspirin and prevention of cranial ischemic complications in giant cell arteritis. Arthritis Rheum 2004:50:1332-7.
47. Lee MS, Smith SD, Galor A, Hoffman GS. Antiplatelet and anticoagulant therapy in patients with giant cell arteritis. Arthritis Rheum 2006;54:3306-9.
48. Schaufelberger C, Mollby H, Uddhammar A, Bratt J, Nordborg E. No additional steroid-sparing effect of cyclosporine A in giant cell arteritis. Scand J Rheumatol 2006;35:327-9.
49. Mahr AD, Jover JA, Spiera RF, Hernandez-Garcia C, Fernandez-Gutierrez B, Lavalley MP, et al. Adjunctive methotrexate for treatment of giant cell arteritis: an individual patient data meta-analysis. Arthritis Rheum 2007;56:2789-97.
50. Narvaez J, Bernad B, Nolla JM, Valverde J. Statin therapy does not seem to benefit giant cell arteritis. Semin Arthritis Rheum 2007;36:322-7.
51. Narvaez J, Bernad B, Gomez-Vaquero C, Garcia-Gomez C, Roig-Vilaseca D, Juanola X, et al. Impact of antiplatelet therapy in the development of severe ischemic complications and in the outcome of patients with giant cell arteritis. Clin Exp Rheumatol 2008;26 Suppl 49:S57-62.
52. Kerr GS, Hallahan CW, Giordano J, Leavitt RY, Fauci AS, Rottem M, et al. Takayasu arteritis. Ann Intern Med 1994;120:919-29.
53. Vanoli M, Daina E, Salvarani C, Sabbadini MG, Rossi C, Bacchiani G, et al. Takayasu's arteritis: A study of 104 Italian patients. Arthritis Rheum 2005;53:100-7.
54. Bicakcigil M, Aksu K, Kamali S, Ozbalkan Z, Ates A, Karadag O, et al. Takayasu's arteritis in Turkey — clinical and angiographic features of 248 patients. Clin Exp Rheumatol 2009;27 Suppl 52:S59-64.
55. Andrews J, Al-Nahhas A, Pennell DJ, Hossain MS, Davies KA, Haskard DO, et al. Non-invasive imaging in the diagnosis and management of Takayasu's arteritis. Ann Rheum Dis 2004;63:995-1000.
56. Arnaud L, Cambau E, Brocheriou I, Koskas F, Kieffer E, Piette JC, et al. Absence of Mycobacterium tuberculosis in arterial lesions from patients with Takayasu's arteritis. J Rheumatol 2009;36:1682-5.
57. Arnaud L, Haroche J, Limal N, Toledano D, Gambotti L, Costedoat Chalumeau N, et al. Takayasu arteritis in France: a single-center retrospective study of 82 cases comparing white, North African, and black patients. Medicine (Baltimore) 2010;89:1-17.
58. Arnaud L, Haroche J, Malek Z, Archambaud F, Gambotti L, Grimon G, et al. Is (18)F-fluorodeoxyglucose positron emission tomography scanning a reliable way to assess disease activity in Takayasu arteritis? Arthritis Rheum 2009;60:1193-200.
59. Bezerra MC, Calomeni GD, Caparbo VF, Gebrim ES, Rocha MS, Pereira RM. Low bone density and low serum levels of soluble RANK ligand are associated with severe arterial calcification in patients with Takayasu arteritis. Rheumatology 2005;44:1503-6.
60. Cakar N, Yalcinkaya F, Duzova A, Caliskan S, Sirin A, Oner A, et al. Takayasu arteritis in children. J Rheumatol 2008;35:913-9.
61. Canas CA, Jimenez CA, Ramirez LA, Uribe O, Tobon I, Torrenegra A, et al. Takayasu arteritis in Colombia. Int J Cardiol 1998;66 Suppl 1:S73-9.
62. Chauhan SK, Tripathy NK, Sinha N, Nityanand S. T-cell receptor repertoire of circulating gamma delta T-cells in Takayasu's arteritis. Clin Immunol 2006;118:243-9.
63. Choe YH, Han BK, Koh EM, Kim DK, Do YS, Lee WR. Takayasu's arteritis: assessment of disease activity with contrast-enhanced MR imaging. AJR Am J Roentgenol 2000;175:505-11.
64. Chun YS, Park SJ, Park IK, Chung H, Lee J. The clinical and ocular manifestations of Takayasu arteritis. Retina 2001;21:132-40.
65. de Carvalho JF, Bonfa E, Bezerra MC, Pereira RM. High frequency of lipoprotein risk levels for cardiovascular disease in Takayasu arteritis. Clin Rheumatol 2009;28:801-5.
66. de Souza AW, Ataide Mariz H, Torres Reis Neto E, Diniz Arraes AE, da Silva NP, Sato EI. Risk factors for cardiovascular disease and endothelin-1 levels in Takayasu arteritis patients. Clin Rheumatol 2009;28:379-83.
67. de Souza AW, Machado NP, Pereira VM, Arraes AE, Reis Neto ET, Mariz HA, et al. Antiplatelet therapy for the prevention of arterial ischemic events in Takayasu arteritis. Circ J 2010;74:1236-41.
68. Dhawan V, Mahajan N, Jain S. Role of C-C chemokines in Takayasu's arteritis disease. Int J Cardiol 2006;112:105-11.
69. Espinola-Zavaleta N, Soto-Lopez ME, Carreon-Torres E, Gamboa R, Mejia AM, Marquez-Velasco R, et al. Altered flow-mediated vasodilatation, low paraoxonase-1 activity, and abnormal high-density lipoprotein subclass distribution in Takayasu's arteritis. Circ J 2009;73:760-6.
70. Fields CE, Bower TC, Cooper LT, Hoskin T, Noel AA, Panneton JM, et al. Takayasu's arteritis: operative results and influence of disease activity. J Vasc Surg 2006;43:64-71.
71. Filocamo G, Buoncompagni A, Viola S, Loy A, Malattia C, Ravelli A, et al. Treatment of Takayasu's arteritis with tumor necrosis factor antagonists. J Pediatr 2008;153:432-4.
72. Hoffman GS, Leavitt RY, Kerr GS, Rottem M, Sneller MC, Fauci AS. Treatment of glucocorticoid-resistant or relapsing Takayasu arteritis with methotrexate. Arthritis Rheum 1994;37:578-82.
73. Hoffman GS, Merkel PA, Brasington RD, Lenschow DJ, Liang P. Anti-tumor necrosis factor therapy in patients with difficult to treat Takayasu arteritis. Arthritis Rheum 2004;50:2296-304.
74. Jain S, Kumari S, Ganguly NK, Sharma BK. Current status of Takayasu arteritis in India. Int J Cardiol 1996;54 Suppl:S111-6.
75. Karadag O, Aksu K, Sahin A, Zihni FY, Sener B, Inanc N, et al. Assessment of latent tuberculosis infection in Takayasu arteritis with tuberculin skin test and Quantiferon-TB Gold test. Rheumatol Int 2010;30:1483-7.
76. Karageorgaki ZT, Bertsias GK, Mavragani CP, Kritikos HD, Spyropoulou-Vlachou M, Drosos AA, et al. Takayasu arteritis: epidemiological, clinical, and immunogenetic features in Greece. Clin Exp Rheumatol 2009;27 Suppl 52:S33-9.
77. Kasuya N, Kishi Y, Isobe M, Yoshida M, Numano F. P-selectin expression, but not GPIIb/IIIa activation, is enhanced in the inflammatory stage of Takayasu's arteritis. Circ J 2006;70:600-4.
78. Keenan NG, Mason JC, Maceira A, Assomull R, O'Hanlon R, Chan C, et al. Integrated cardiac and vascular assessment in Takayasu arteritis by cardiovascular magnetic resonance. Arthritis Rheum 2009;60:3501-9.
79. Khandelwal N, Kalra N, Garg MK, Kang M, Lal A, Jain S, et al. Multidetector CT angiography in Takayasu arteritis. Eur J Radiol 2011;77:369-74.
80. Kim SY, Park JH, Chung JW, Kim HC, Lee W, So YH, et al. Follow-up CT evaluation of the mural changes in active Takayasu arteritis. Korean J Radiol 2007;8:286-94.
81. Kobayashi Y, Ishii K, Oda K, Nariai T, Tanaka Y, Ishiwata K, et al. Aortic wall inflammation due to Takayasu arteritis imaged with 18F-FDG PET coregistered with enhanced CT. J Nucl Med 2005;46:917-22.
82. Lee SG, Ryu JS, Kim HO, Oh JS, Kim YG, Lee CK, et al. Evaluation of disease activity using F-18 FDG PET-CT in patients with Takayasu arteritis. Clin Nucl Med 2009;34:749-52.
83. Liang P, Tan-Ong M, Hoffman GS. Takayasu's arteritis: vascular interventions and outcomes. J Rheumatol 2004;31:102-6.
84. Ma J, Luo X, Wu Q, Chen Z, Kou L, Wang H. Circulation levels of

Personal non-commercial use only. The Journal of Rheumatology Copyright © 2011. All rights reserved.

Downloaded from www.jrheum.org on June 19, 2019 - Published by The Journal of Rheumatology

acute phase proteins in patients with Takayasu arteritis. J Vasc Surg 2010;51:700-6.
85. Mahajan N, Dhawan V, Malik S, Jain S. Implication of oxidative stress and its correlation with activity of matrix metalloproteinases in patients with Takayasu's arteritis disease. Int J Cardiol 2010;145:286-8.
86. Matsuyama A, Sakai N, Ishigami M, Hiraoka H, Kashine S, Hirata A, et al. Matrix metalloproteinases as novel disease markers in Takayasu arteritis. Circulation 2003;108:1469-73.
87. Min PK, Park S, Jung JH, Ko YG, Choi D, Jang Y, et al. Endovascular therapy combined with immunosuppressive treatment for occlusive arterial disease in patients with Takayasu's arteritis. J Endovasc Ther 2005;12:28-34.
88. Mustafa KN, Hadidy A, Sweiss NJ. Clinical and radiological features of Takayasu's arteritis patients in Jordan. Rheumatol Int 2010;30:1449-53.
89. Mwipatayi BP, Jeffery PC, Beningfield SJ, Matley PJ, Naidoo NG, Kalla AA, et al. Takayasu arteritis: clinical features and management: report of 272 cases. ANZ J Surg 2005;75:110-7.
90. Nityanand S, Mishra K, Shrivastava S, Holm G, Lefvert AK. Autoantibodies against cardiolipin and endothelial cells in Takayasu's arteritis: prevalence and isotype distribution. Br J Rheumatol 1997;36:923-4.
91. Noris M, Daina E, Gamba S, Bonazzola S, Remuzzi G. Interleukin-6 and RANTES in Takayasu arteritis: a guide for therapeutic decisions? Circulation 1999;100:55-60.
92. Ogawa Y, Hayashi K, Sakamoto I, Matsunaga N. Pulmonary arterial lesions in Takayasu arteritis: relationship of inflammatory activity to scintigraphic findings and sequential changes. Ann Nucl Med 1996;10:219-23.
93. Ozen S, Duzova A, Bakkaloglu A, Bilginer Y, Cil BE, Demircin M, et al. Takayasu arteritis in children: preliminary experience with cyclophosphamide induction and corticosteroids followed by methotrexate. J Pediatr 2007;150:72-6.
94. Park MC, Lee SW, Park YB, Chung NS, Lee SK. Clinical characteristics and outcomes of Takayasu's arteritis: analysis of 108 patients using standardized criteria for diagnosis, activity assessment, and angiographic classification. Scand J Rheumatol 2005;34:284-92.
95. Park MC, Lee SW, Park YB, Lee SK. Serum cytokine profiles and their correlations with disease activity in Takayasu's arteritis. Rheumatology 2006;45:545-8.
96. Park MC, Lee SW, Park YB, Lee SK, Choi D, Shim WH. Post-interventional immunosuppressive treatment and vascular restenosis in Takayasu's arteritis. Rheumatology 2006;45:600-5.
97. Park MC, Park YB, Jung SY, Lee KH, Lee SK. Anti-endothelial cell antibodies and antiphospholipid antibodies in Takayasu's arteritis: correlations of their titers and isotype distributions with disease activity. Clin Exp Rheumatol 2006;24 Suppl 41:S10-6.
98. Petrovic-Rackov L, Pejnovic N, Jevtic M, Damjanov N. Longitudinal study of 16 patients with Takayasu's arteritis: clinical features and therapeutic management. Clin Rheumatol 2009;28:179-85.
99. Pugliese F, Gaemperli O, Kinderlerer AR, Lamare F, Shalhoub J, Davies AH, et al. Imaging of vascular inflammation with [11C]-PK11195 and positron emission tomography/computed tomography angiography. J Am Coll Cardiol 2010;56:653-61.
100. Ringleb PA, Strittmatter EI, Loewer M, Hartmann M, Fiebach JB, Lichy C, et al. Cerebrovascular manifestations of Takayasu arteritis in Europe. Rheumatology 2005;44:1012-5.
101. Robles M, Reyes PA. Takayasu's arteritis in Mexico: a clinical review of 44 consecutive cases. Clin Exp Rheumatol 1994;12:381-8.
102. Sato EI, Lima DN, Espirito Santo B, Hata F. Takayasu arteritis. Treatment and prognosis in a university center in Brazil. Int J Cardiol 2000;75 Suppl 1:S163-6.
103. Seth S, Goyal NK, Jagia P, Gulati G, Karthikeyan G, Sharma S, et al. Carotid intima-medial thickness as a marker of disease activity in Takayasu's arteritis. Int J Cardiol 2006;108:385-90.
104. Shinjo SK, Pereira RM, Tizziani VA, Radu AS, Levy-Neto M. Mycophenolate mofetil reduces disease activity and steroid dosage in Takayasu arteritis. Clin Rheumatol 2007;26:1871-5.
105. Soto ME, Espinola N, Flores-Suarez LF, Reyes PA. Takayasu arteritis: clinical features in 110 Mexican Mestizo patients and cardiovascular impact on survival and prognosis. Clin Exp Rheumatol 2008;26 Suppl 49:S9-15.
106. Tripathy NK, Chandran V, Garg NK, Sinha N, Nityanand S. Soluble endothelial cell adhesion molecules and their relationship to disease activity in Takayasu's arteritis. J Rheumatol 2008;35:1842-5.
107. Tripathy NK, Chauhan SK, Nityanand S. Cytokine mRNA repertoire of peripheral blood mononuclear cells in Takayasu's arteritis. Clin Exp Immunol 2004;138:369-74.
108. Tripathy NK, Sinha N, Nityanand S. Anti-annexin V antibodies in Takayasu's arteritis: prevalence and relationship with disease activity. Clin Exp Immunol 2003;134:360-4.
109. Tripathy NK, Sinha N, Nityanand S. Antimonocyte antibodies in Takayasu's arteritis: prevalence of and relation to disease activity. J Rheumatol 2003;30:2023-6.
110. Tripathy NK, Sinha N, Nityanand S. Interleukin-8 in Takayasu's arteritis: plasma levels and relationship with disease activity. Clin Exp Rheumatol 2004;22 Suppl 36:S27-30.
111. Tripathy NK, Upadhyaya S, Sinha N, Nityanand S. Complement and cell mediated cytotoxicity by antiendothelial cell antibodies in Takayasu's arteritis. J Rheumatol 2001;28:805-8.
112. Tso E, Flamm SD, White RD, Schvartzman PR, Mascha E, Hoffman GS. Takayasu arteritis: utility and limitations of magnetic resonance imaging in diagnosis and treatment. Arthritis Rheum 2002;46:1634-42.
113. Vargas-Alarcon G, Soto ME, Perez-Hernandez N, Cicero-Sabido R, Ramirez E, Alvarez-Leon E, et al. Comparative study of the residues 63 and 67 on the HLA-B molecule in patients with Takayasu's arteritis and tuberculosis. Cell Biochem Funct 2008;26:820-3.
114. Verma DK, Tripathy NK, Verma NS, Tiwari S. Interleukin 12 in Takayasu's arteritis: plasma concentrations and relationship with disease activity. J Rheumatol 2005;32:2361-3.
115. Watanabe T, Kishi Y, Numano F, Isobe M. Enhanced platelet sensitivity to prostacyclin in patients in an active stage of Takayasu arteritis. Thromb Res 2001;104:77-83.
116. Webb M, Chambers A, Al-Nahhas A, Mason JC, Maudlin L, Rahman L, et al. The role of 18F-FDG PET in characterising disease activity in Takayasu arteritis. Eur J Nucl Med Mol Imaging 2004;31:627-34.
117. Merkel PA, Herlyn K, Mahr AD, Neogi T, Seo P, Walsh M, et al. Progress towards a core set of outcome measures in small-vessel vasculitis. Report from OMERACT 9. J Rheumatol 2009;36:2362-8.

Personal non-commercial use only. The Journal of Rheumatology Copyright © 2011. All rights reserved.

Downloaded from www.jrheum.org on June 19, 2019 - Published by The Journal of Rheumatology