Takayasu Arteritis: It’s Time to Work Together

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Joshua A. Beckman, MD

Vanderbilt University, Nashville, TN

Address for Correspondence:
Joshua A. Beckman, MD
Vanderbilt University
1215 21st Avenue South
Medical Center East, 5th Floor
South Tower
Nashville, TN 37232-8802
Tel: 615-322-2318
Fax: 615-936-2437
E-mail: joshua.a.beckman@vanderbilt.edu

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In the United States, the Orphan Drug Act of 1983 defines a disease as rare if it affects fewer than 200,000 people. In the United States, there are more than 6,800 rare diseases that affect up to 30 million people. With an estimated incidence of 2 to 3 cases per million people in the United States, Takayasu arteritis (TA) easily meets this definition. As such it suffers from the challenges inherent to its limited patient base.

Takayasu arteritis is a large-vessel vasculitis originally described by a Japanese ophthalmologist, that meets the Orphan Drug act definition in the United States, but may be more prevalent in Japan; autopsy series show evidence of TA in 1 of every 3000 people. The disease is one of vascular inflammation with destruction of elastic fibers, vascular smooth muscle, and vessel wall matrix components. Arterial stenosis remains the most common vascular presentation, however, aortic aneurysmal disease has been reported in as many as one quarter of patients. The variation by nationality in incidence, clinical characteristics, and female/male ratio suggests a genetic component to the disease, but no reliable marker has been identified. The most common time of diagnosis is the second and third decade of life. In the United States, the age of the patient is important, for it is one method of distinguishing TA from giant cell arteritis, a disease whose diagnosis commonly occurs in the eighth decade of life but with many overlapping signs and symptoms. Patients who present with symptoms of inflammation or arterial occlusive disease in the fifth and early sixth decades of life present a diagnostic challenge in determining the diagnosis.

Despite the yeoman’s work of many in the field, the limited patient numbers and modest efforts to accrue larger numbers of patients across centers has slowed our understanding of the disease. As with many other rare diseases, the lack of animal models of disease, large patient numbers in any one center, and limited clinical development pathway render investigation both
more difficult and interpretation of small data sets challenging. It is with this background that the two publications in this issue of *Circulation* are so welcome.

Watanabe and colleagues have analyzed 1372 newly registered patients with Takayasu’s arteritis collected over 10 years in Japan. In Japan, registration is necessary for financial coverage, suggesting that the vast majority of new patients with the disease were identified. The variation in diagnostic criteria by nation are important here for interpretation of the data. In Japan, age is not a diagnostic criteria for TA and in this report a significant portion, approximately 20%, are more than 60 years old. Several important insights are identified including the interaction of time to diagnosis and hypertension, the frequency of head and neck complaints at presentation, and the confirmation of aortic aneurysmal disease in 25% of male patients but only 11% of women. To understand the value of this report, it must be made clear that this report of newly diagnosed patients may be 10 fold larger than any other similar publication of new patient presentations. These data will further refine our understanding of the presentation of TA, increase awareness of low frequency sequelae present in Japanese patients, and provide a pathway for others to follow in data collection.

The report by Mekinian and colleagues demonstrates the hard work necessary to advance disease therapeutics. In this retrospective study, the investigators determined the outcome of TA patients treated with tumor necrosis factor (TNF) alpha antagonists or tocilizumab, an interleukin(IL)-6 receptor antagonist. Of the 49 patients reported, 88% were inadequately controlled by standard therapy. The response to these agents significantly lowered markers of inflammation, reduced daily prednisone requirements, tended to reduce vascular complications, and improved relapse free survival to 90% at 3 years. These data affirm the use of the TNF-alpha and IL-6 receptor antagonists in TA. Unfortunately, because of the lack of prospective data
collection and disposition of treating physicians, this data carries the burdens of a retrospective trial and can not confirm the value of these agents. Still, the data are reassuring.

The care of patients with Takayasu arteritis and other large vessel vasculitides would benefit from two interventions. First, the development of an ongoing registry to aggregate cases in the United States. Two diseases provide strong models for this: aortic dissection and fibromuscular dysplasia. The International Registry of Acute Aortic Dissections (IRAD) was organized in 1996, now has participating centers in more than 11 nations, and has enrolled nearly 6000 patients with aortic dissection. In addition to significantly improving the understanding of disease presentation and outcome, IRAD has now embarked on clinical research to improve disease management with a committed group of investigators already used to working together. A registry for fibromuscular dysplasia was organized in 2007 with the first online database patient entry in 2009. Three years later, the group published findings on 447 patients and has provided insights into this disease previously undiscovered. Neither of these two registries were flush with resources or funds; what they had were clinician scientists interested in understanding disease and improving patient care. In addition, they had access to supportive expertise in distributed data collection (Michigan Clinical Outcomes Research and Reporting Program for both). TA needs a similar registry.

The second improvement in care would be the creation of clinical teams to care for these patients. As a vascular medicine specialist, I have been fortunate to work with a cadre of colleagues from rheumatology, interventional cardiology, cardiac surgery and vascular surgery to provide the highest level of care for these complicated patients. We each bring complementary perspectives to the bedside culminating in a thorough and granular approach to the patient. By
creating teams, the care of these patients can be organized within institutions fostering a systems approach that includes primary care providers and improves the longitudinal follow up.

It will be improvements in data collection and harnessing of complementary skill sets that improve the care of patients with TA in the future. Without these changes, the field is doomed to rely on heroic retrospective evaluation of presentation and treatment efficacy.

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**References:**


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