

Causes of Cardiovascular Ischemic Events in Giant Cell Arteritis

Giant cell arteritis (GCA) is a granulomatous vasculitis with rising incidence in the sixth to eighth decade of age, when cardiovascular (CV) events put survival, health, and function *per se* at risk¹. The outcomes of GCA patients with marked tissue tropism in certain vascular regions might be strongly influenced by CV events². CV disease seems to be pronounced in patients with GCA in the first month after diagnosis compared to the age-matched general population, but the risk may also be increased in the followup period (median 3.9 yrs)³.

CV events including strokes in patients with GCA, especially in the longterm followup, are not well explored. It remains difficult to distinguish whether the events are related to the inflammatory disease or to nonspecific atherosclerotic lesions, other arterial wall changes due to vascular aging, or other accompanying CV risk factors^{3,4}.

In the current issue of *The Journal*, Pugnet, *et al* describe predictors for CV hospitalization of patients with GCA in France based on an administrative database, focusing on the effect of statin exposure⁵. The authors conclude that patients with GCA have a higher risk for a “new” CV disease leading to an inpatient stay in a cardiology unit, stroke unit, a cardiothoracic surgery department, a neurosurgery unit, or an intensive care unit, counting events at least 1 month after the index date of GCA⁵. Their approach of defining “new” atherosclerotic CV diseases in GCA after 1 month raises the question of at what point in the course of GCA a CV outcome can be attributed to vasculitis rather than to a premorbid or even unrelated comorbid condition⁵.

CV risk factors such as arterial hypertension (HTN) or smoking history before the onset of GCA are reported as preexisting risk factors for ischemic complications in GCA^{6,7}. Age-induced vessel wall structure changes may be accelerated by vascular damage due to the inflammatory disease². The inflamed vessel is characterized by intimal hyperplasia and vascular remodeling that might lead to luminal occlusion and thus to ischemic complications⁸. Inflammation results in thrombocytosis and hyperfibrinogenemia, which promote thromboembolic complications. Vessel occlusion and thromboembolism are always feared in

GCA. Reported ischemic complications vary and could be reduced by a fast diagnostic algorithm⁹. Vessel wall inflammation in GCA responds rapidly to glucocorticosteroid therapy: Wall thickening, contrast media uptake in magnetic resonance imaging, or giant cells as histological signs of acute inflammation are hard to detect after 2 weeks of therapy^{10,11}. Even complete vessel occlusions might resolve under therapy. Thus the onset of visual manifestations from date of diagnosis of GCA is usually short — the median onset was reported recently as 3 days¹². Strokes are usually attributed to GCA when they occur in the first month after initiation of glucocorticosteroids and are not regarded as late complications of GCA⁷.

The longterm mortality rate in GCA is still regarded as comparable or slightly increased in comparison to the general population^{7,13,14}. Even lower rates of revascularization procedures were described by Udayakumar, *et al*, who followed patients with GCA over decades and did not find an increased risk of acute coronary syndromes¹⁵.

To date, the term *inflammation* has not been defined precisely and it remains unanswered how long vessel wall and/or systemic inflammation are necessary to cause detectable atherosclerosis. Experiences from other inflammatory rheumatic diseases suggest that longer periods of uncontrolled inflammation are necessary to cause atherosclerosis, and a controlled disease results in risk normalization. Even the complex involvement of the immune system in the pathogenesis of atherosclerosis in patients without inflammatory systemic disease has not been fully elucidated¹⁶, and traditional risk factors play an important role. Thus, it remains unknown whether a CV outcome starting, for example, 35 days after GCA diagnosis is attributable to GCA or its therapy, or whether it is the manifestation of a premorbid condition.

Other associations between GCA and vascular complications such as thoracic and abdominal aneurysms or dissections are also undetermined. They mainly occur more than 5 years after diagnosis, and the true relative risk and the time course of that risk remain unclear¹⁷.

Glucocorticosteroid treatment may lead to side effects

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such as HTN and diabetes. In those cases it is hard to distinguish whether the HTN that might cause CV-associated hospitalization is attributable to the disease or to side effects of the medication. It seems hard to fix time frames because they might depend on dosage and duration of glucocorticosteroid treatment. In addition, GCA patients with HTN and diabetes at baseline are reported to be at higher risk for relapses¹⁸. The risk of thromboembolic complications is increased by glucocorticosteroids, but again, dosages needed and time frames of relevance are unknown. Disease relapses might again lead to increases of glucocorticosteroid dosage and longer treatment intervals, leading to a vicious circle situation.

Thrombocyte aggregation inhibition with low-dose acetylsalicylic acid (ASA) reduces the risk of vascular complications in GCA¹⁹. Pugnet, *et al* confirm this, showing that no patient taking ASA had any event⁵.

The reported amount of overall risk reduction with statins⁵ is comparable to that of ASA but might be related to lowering low-density lipoprotein cholesterol or other effects modulating immunity and preventing intimal hyperplasia. Hence there are no data available demonstrating lower rates of inflammatory vessel occlusion or wall size in those GCA patients treated with statins, and Pugnet, *et al* found no steroid-sparing effect of statins, suggesting a minor effect⁵. Myalgias are common side effects of statins, as most patients and physicians are aware. Thus, myalgic pain in GCA might be recognized earlier and statin therapy might result not in pharmacological but logistical benefit, with an earlier diagnosis of GCA with fewer complications.

It is hard to know whether CV events are related to the inflammatory disease or nonspecific atherosclerotic lesions, other wall changes due to vascular aging, or other accompanying CV risk factors. Longterm population-based studies and animal models are warranted. Recommended are fast, effective control and regular monitoring of GCA disease activity as well as of preexisting CV comorbidities, control of fats, and at least low-dose ASA.

JUTTA G. RICHTER, MD,

Policlinic for Rheumatology and Hiller Research Centre for Rheumatology, Medical Faculty, Heinrich Heine University Düsseldorf;

OLIVER SANDER, MD,

Policlinic for Rheumatology and Hiller Research Centre for Rheumatology, Medical Faculty, Heinrich Heine University Düsseldorf;

MATTHIAS SCHNEIDER, MD, Prof.,

Policlinic for Rheumatology and Hiller Research Centre for Rheumatology, Medical Faculty, Heinrich Heine University Düsseldorf, Düsseldorf, Germany.

Address correspondence to Dr. J.G. Richter, Policlinic for Rheumatology and Hiller Research Centre for Rheumatology, Medical Faculty, Heinrich Heine University Düsseldorf, Moorenstr. 5, 40225 Düsseldorf, Germany. E-mail: richter@rheumanet.org

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