Editorial

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 risk[1]. The outcomes of GCA patients with marked tissue tropism in certain vascular regions might be strongly influenced by CV events[2]. 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 exposure[5]. 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 GCA[5]. 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 condition[5].

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 disease[2]. The inflamed vessel is characterized by intimal hyperplasia and vascular remodeling that might lead to luminal occlusion and thus to ischemic complications[8]. 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 algorithm[9]. 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 days[12]. 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 GCA[7].

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 syndromes[15].

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 elucidated[16], 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 unclear[17].

Glucocorticosteroid treatment may lead to side effects

See GCA and cardiovascular hospitalization, *page 2162*

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 relapses[18]. 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 GCA[19]. Pugnet, *et al* confirm this, showing that no patient taking ASA had any event[5].

The reported amount of overall risk reduction with statins[5] 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 effect[5]. 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

REFERENCES

1. Weyand CM, Goronzy JJ. Medium- and large-vessel vasculitis. N Engl J Med 2003;349:160–9.
2. Mohan SV, Liao YJ, Kim JW, Goronzy JJ, Weyand CM. Giant cell arteritis: immune and vascular aging as disease risk factors. Arthritis Res Ther 2011;13:231.
3. Tomasson G, Peloquin C, Mohammad A, Love TJ, Zhang Y, Choi HK, et al. Risk for cardiovascular disease early and late after a diagnosis of giant-cell arteritis: a cohort study. Ann Intern Med 2014;160:73–80.
4. Larivière D, Sacre K, Klein I, Hyafil F, Choudat L, Chauveheid MP, et al. Extra- and intracranial cerebral vasculitis in giant cell arteritis: an observational study. Medicine 2014;93:e265.
5. Pugnet G, Sailler L, Fournier JP, Bourrel R, Montastruc JL, Lapeyre-Mestre M. Predictors of cardiovascular hospitalization in giant cell arteritis: effect of statin exposure. A French population-based study. J Rheumatol 2016;43:2162–70.
6. Gonzalez-Gay MA, Piñeiro A, Gomez-Gigirey A, Garcia-Porrua C, Pego-Reigosa R, Dierssen-Sotos T, et al. Influence of traditional risk factors of atherosclerosis in the development of severe ischemic complications in giant cell arteritis. Medicine 2004;83:342–7.
7. Gonzalez-Gay MA, Vazquez-Rodriguez TR, Lopez-Diaz MJ, Miranda-Filloy JA, Gonzalez-Juanatey C, Martin J, et al. Epidemiology of giant cell arteritis and polymyalgia rheumatica. Arthritis Rheum 2009;61:1454–61.
8. Ly KH, Régent A, Tamby MC, Mouthon L. Pathogenesis of giant cell arteritis: more than just an inflammatory condition? Autoimmun Rev 2010;9:635–45.
9. Diamantopoulos AP, Haugeberg G, Lindland A, Myklebust G. The fast-track ultrasound clinic for early diagnosis of giant cell arteritis significantly reduces permanent visual impairment: towards a more effective strategy to improve clinical outcome in giant cell arteritis? Rheumatology 2016;55:66–70.
10. Bley TA, Markl M, Schelp M, Uhl M, Frydrychowicz A, Vaith P, et al. Mural inflammatory hyperenhancement in MRI of giant cell (temporal) arteritis resolves under corticosteroid treatment. Rheumatology 2008;47:65–7.
11. Narváez J, Bernad B, Roig-Vilaseca D, García-Gómez C, Gómez-Vaquero C, Juanola X, et al. Influence of previous corticosteroid therapy on temporal artery biopsy yield in giant cell arteritis. Semin Arthritis Rheum 2007;37:13–9.
12. Saleh M, Turesson C, Englund M, Merkel PA, Mohammad AJ. Visual complications in patients with biopsy-proven giant cell arteritis: a population-based study. J Rheumatol 2016;43:1559–65.
13. Moiseev S, Novikov P, Meshkov A, Smitienko I. Biological agents for giant cell arteritis: treat to target. Ann Rheum Dis 2016;75:e58.
14. Baslund B, Helleberg M, Faurschou M, Obel N. Mortality in patients with giant cell arteritis. Rheumatol 2015;54:139–43.
15. Udayakumar PD, Chandran AK, Crowson CS, Warrington KJ, Matteson EL. Cardiovascular risk and acute coronary syndrome in giant cell arteritis: a population-based retrospective cohort study. Arthritis Care Res 2015;67:396–402.
16. Sherer Y, Shoenfeld Y. Mechanisms of disease: atherosclerosis in autoimmune diseases. Nat Clin Pract Rheumatol 2006;2:99–106.
17. Kermani TA, Warrington KJ, Crowson CS, Ytterberg SR, Hunder GG, Gabriel SE, et al. Large-vessel involvement in giant cell arteritis: a population-based cohort study of the incidence-trends and prognosis. Ann Rheum Dis 2013;72:1989–94.
18. Labarca C, Koster MJ, Crowson CS, Makol A, Ytterberg SR, Matteson EL, et al. Predictors of relapse and treatment outcomes in biopsy-proven giant cell arteritis: a retrospective cohort study. Rheumatology 2016;55:347–56.
19. 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.

J Rheumatol 2016;43:2092–3; doi:10.3899/jrheum.161237