Review

Long-term outcome of giant cell arteritis

N. Pipitone, L. Boiardi, G. Bajocchi, C. Salvarani

Nicolò Pipitone, MD, PhD; Luigi Boiardi, MD, PhD; Gianluigi Bajocchi, MD; Carlo Salvarani, MD.

Rheumatology Unit, Arcispedale Santa Maria Nuova, Reggio Emilia, Italy.

Please address correspondence and reprint requests to: Dr. Carlo Salvarani, U.O. di Reumatologia, Arcispedale Santa Maria Nuova, Viale Risorgimento 80, 42100 Reggio Emilia, Italy.
E-mail: salvarani.carlo@asmn.re.it

Received on December 22, 2005; acccepted in revised form on January 30, 2006.

Clin Exp Rheumatol 2006; 24 (Suppl. 41): S65-S70.

Key words: temporal arteritis, mortality, morbidity, neoplasms, blindness, myocardial infarction, cerebrovascular accidents, aortic aneurysm, glucocorticoids.

ABSTRACT

Giant cell arteritis is usually a self-limiting disease with a variable duration of months to years. However, in a subset of patients the disease may follow a protracted course, requiring long-term treatment with glucocorticoids. To date, glucocorticoids are the only agents whose efficacy has been unquestionably proven. More specifically, they can both improve the clinical symptoms of giant cell arteritis and also prevent its complications, including visual loss. Glucocorticoids therapy is notoriously fraught with numerous side effects, therefore it is sensible to taper glucocorticoids as quickly as possible. Flares are not uncommon and tend often to occur upon tapering of glucocorticoids dosage or on withdrawal of glucocorticoids therapy. However, in most cases flares are mild and appear to respond favorably to an increase in glucocorticoids dosage or reintroduction of glucocorticoids therapy, respectively.

Mortality rates of giant cell arteritis patients are comparable to those of the general population, but there is evidence for an increased frequency of potentially life-threatening ischemic events, such as myocardial infarction and cerebro-vascular accidents, especially early on in the disease course. The risk conferred by the disease appears to decrease with time, presumably as a consequence of glucocorticoids treatment, whereas it can remain significantly elevated in patients whose disease activity is not sufficiently controlled by the treatment. By contrast, there is no evidence that giant cell arteritis is associated with an increased prevalence of malignancies or that it may represent a paraneoplastic syndrome.

Introduction

Giant cell arteritis (GCA) is a vasculitis affecting large- and medium-sized vessels with predominant involvement of the cranial arteries (1). Clinically, GCA presents with symptoms and signs that are mostly related to arterial involvement, but in some cases only constitutional manifestations may be present. Polymyalgia rheumatica (PMR) has been reported in up to 50% of patients with biopsy-proven GCA (2), although the pathogenic link between the two disorders remains to be fully elucidated (3). Histologically, GCA is characterized by intimal hyperplasia, and an inflammatory infiltrate consisting mainly of lymphomononuclear cells; in approximately 50% of cases, giant cells can be identified at the junction between the intima and media, but their presence is not a prerequisite for the diagnosis (4). These alterations are thought to lead to ischemic lesions such as amaurosis, myocardial infarction, and cerebro-vascular accidents (4). However, in a subset of GCA patients, inflammation appears to affect large vessels, with aneurysm formation, dissection, or stenosis (5).Observations from the pre-steroid era may suggest that GCA is a self-limiting disease with a duration varying from months to years (6). GC are effective in treating disease manifestations, whereas they may not shorten disease duration (7, 8). The principal aim of this paper was to review the evidence on mortality and morbidity in GCA and to discuss how GC can alter the natural course of the disease.

Disease-related mortality and morbidity in GCA

Survival studies in GCA have usually found comparable mortality rates in patients and in the background population (9-16), while only a few surveys have shown increased (17, 18) or decreased (6) mortality in GCA.

In a large study from the Mayo Clinic, Olmsted County, US, survivorship was characterized in 205 patients (95.8%)

of the original cohort of 214 patients enrolled in different Hospitals in the 1990 American College of Rheumatology vasculitis classification study (10). All patients were treated according to usual practice. Standardized mortality ratios (SMR) were calculated comparing mortality data from GCA patients versus the general population. There were 49 deaths (33 women and 16 men) among the 205 patients available for follow-up. Survivorship was virtually identical to that of the general population (SMR 1.034), and was similar for women and men. This study was not designed to address differences in disease severity or co-morbid conditions, but a high (8.2%) frequency of aortic aneurysms as cause of death was recorded, consistent with a previous report from Olmsted County (19).

Decreased survivorship among female, but not male GCA patients has been reported by Graham *et al.* (18). Overall, 90 biopsy-proven GCA patients from St Thomas' Hospital (London, UK) treated with initial high-dose GC with a tapering scheme were followed up from 6 months to 12 years. The causes of death of those that died within six weeks were brainstem infarction (four cases), ruptured aortic aneurysm (one), myocardial infarction (one), perforated diverticula (one), and pulmonary aneurysm (one). Necropsy was carried out in three of the four patients that died from brainstem infarction: in two patients widespread arteritic changes were noted, while one patient had thrombosis of the left carotid artery and of both vertebral arteries.

By contrast, a study by Bengtsson and Malmvall showed that mortality rates were actually lower in GCA patients than in the background population. 90 patients (67 female, 23 male) diagnosed as having GCA during 1968-75 were followed up 3-10 years after the diagnosis (6). Temporal artery biopsy (TAB) was positive in 65 patients. 89 patients received GC treatment. 38 patients experienced at some point disease flares, most of them during the first year of treatment and when a low dose of GC was given. The observed mortality rate adjusted for age and gender (thirteen) was slightly lower than expected (twenty-five). Three patients died of myocardial infarction; one of the two patients that underwent autopsy had evidence of widespread vasculitic lesions affecting the coronary arteries.

Jonasson *et al.* compared survivorship in 136 patients with histologically proven GCA and in the general population of about 750,000 from the Lothian Region of Scotland in the 14-year period 1964-77 (11). 124 patients (30 male and 94 female) could be followed up and were included in the final analysis. All patients received aggressive treatment with GC at a starting dose of 60 mg daily in 80% of cases. Survival rates of males and females, both individually and combined, did not differ significantly from expected deaths in the general population, nor was there an increase in mortality related to cardiovascular or cerebro-vascular disease. One death was judged to be related to treatment (disseminated pulmonary TB after onset of GC therapy) and one to the disease itself (diffuse arteritic changes in cranial and carotid arteries in a patient with multiple cerebral infarctions), respectively.

Gonzalez-Gay *et al.* analyzed survival rates in consecutive biopsy-proven patients with GCA referred to the Hospital Xeral-Calde (the only referral center for central Galicia) in Lugo, Spain, in the period from January 1982 to March 1996 (13). Patients were followed from time of diagnosis until either their death or the beginning of October 1996. By that time, full information on 109 patients (59 men and 50 women) was available. All patients were treated with GC, usually starting with 40 to 60 mg daily. After a median follow-up of 54 months, 22 patients (20.2%) had died. Three died within the first month after diagnosis due to either vascular complications related to GCA or therapy complications. The majority of deaths were due to cardiovascular and cerebro-vascular disease. No significant differences were observed when causes of death in the patients' group were compared with causes of death by age and gender in the general population.

A study from the Department of Rheumatology of Umeå, the reference center for the county of Västerbotten, Northern Sweden, was designed to ascertain mortality in 136 patients with GCA and 35 with PMR diagnosed between 1973 and 1979 and followed up until December 1995 (17). At follow-up, 114 patients with GCA and 25 with PMR were deceased. The overall mortality was significantly increased in the female patients. 61% of patients developed cardiovascular events after diagnosis, including 40 cases of cerebro-vascular accidents, 38 cases of myocardial infarction, and 4 cases of aortic aneurysms. Death due to cardiovascular disease was significantly increased in both women and men, mainly owing to ischemic heart disease. An excess mortality was found in women with the highest ESR, higher prescribed dose of GC at diagnosis, or a daily prednisolone-equivalent dose of 10 mg or more one year after diagnosis. In multiple Cox regression analysis, male sex and hypertension significantly increased the risk of cardiovascular events. Increased mortality was felt to be related to GC therapy or insufficient control of inflammation.

Nordborg and Bengtsson investigated mortality in GCA by reviewing the temporal artery biopsies performed in Göteborg, Sweden, from January 1977 through December 1986 (9). Two hundred and eighty-four patients with histologically verified GCA were identified. Death rates in the patients and in the general population were calculated in December 1987. Survival analysis showed no significant difference between observed (eighty-two) and expected (sixty-eight) number of deaths. However, one year after diagnosis, there was a significant increase in the observed number of deaths from vascular disease (21 versus 7 expected) in the patients' group. 17 of these 21 patients died within the first four months, eight of cerebro-vascular disease, three of myocardial infarction, three from cardiac failure, two from rupture of a dissecting aortic aneurysm, and one from pulmonary embolism. All these 17 patients had been treated with GC, but in 13 of them treatment had been considered insufficient to control

disease activity as assessed by clinical (symptoms) and laboratory (ESR normalization) criteria. Necropsy, performed in 7 of the 17 deceased patients, showed widespread arteritic changes, affecting the coronary arteries in four patients, the aorta in five, and the cerebral arteries in six.

Nuenninghoff *et al.* did not investigate specifically mortality, but aimed to determine the incidence of potentially life-threatening large-artery complications, including aortic aneurysm, aortic dissection, and/or large-artery stenosis in patients with GCA (5). The cohort of all residents of Olmsted County, Minnesota, in whom GCA was diagnosed between January 1, 1950, and December 31, 1999, was followed up. Forty-six incident cases of large-artery complication (27% of the 168 patients in the cohort) were identified. These included 30 incident cases (18%) of aortic aneurysm and/or aortic dissection. Of these cases, 18 (11%) involved the thoracic aorta, with aortic dissection developing in 9 (5%). There were 21 incident cases (13%) of large-artery stenosis. Fifteen patients (9%) had incident cervical artery stenosis, and 6 (4%) had incident subclavian/axillary/brachial artery stenosis. One patient had incident iliac/femoral artery stenosis attributable to GCA. Cranial symptoms and a high ESR were negatively associated with large-artery stenosis. These results thus provide evidence both that large-artery complications are not uncommon and that they may contribute to mortality in GCA.

On the upshot, the evidence available suggests that mortality is not increased in GCA patients, but that there may be an increased frequency of ischemic events, some of which potentially lethal, particularly in first months after GCA onset and/or when disease activity is insufficiently controlled by GC therapy. Large-vessel involvement including aneurysm formation and dissection, although less extensively studied, may also give rise to life-threatening complications in GCA. However, a population-based study demonstrated no difference in survival between patients with aortic aneurysms, dissection, or both, compared with patients without such complications (5).

Visual loss in GCA

Vascular occlusion leading to ischemia, particularly of the optic nerve, is a usually precocious and one of the most serious complications of GCA (4). Studies comparing the prevalence of amaurosis in GCA before and after the introduction of GC therapy have unequivocally demonstrated a significant drop in the number of patients that developed blindness, suggesting that GC are able to prevent visual loss. For instance, in a case series, 15 out of 25 patients not receiving GC incurred visual impairment, compared with none of the 10 patients treated with GC (reported in (20)). Similarly, in Olmsted County, blindness was found in 19% of patients with GCA between 1950-1960, compared with 6% between 1980 and 1985 (21).

However, while GC are effective in preventing visual loss and other ischemic manifestations, they are mostly unable to reverse them (22-24). Therefore, it is vital to try to identify those patients that have a high risk of incurring ischemic events. Evidence from well-designed prospective studies has shown that a strong inflammatory response characterized by raised acute-phase reactants and by overt constitutional symptoms are protective factors against the development of ischemic complications (22, 25, 26). Conversely, thrombocytosis, and previous ischemic events have been linked to a poor prognosis (25, 27). The role of genetic factors in the determinism of GCA-related ischemic complications is largely unknown, but a in a Spanish study the HLA-DRB1*04 allele was significantly over-represented in patients that developed permanent visual loss (19.2%) compared with those that did not (8.3%) (28). The risk of incurring ischemic events appears to be further increased by the presence of traditional risk factors for atherosclerosis with an OR of 1.79 (CI 1.03-3.11) (29).

Brain and heart ischemic events in GCA have been studied less systematically, but there seems to be an increased risk for such complications too, as discussed elsewhere in this paper.

Prevalence of malignancies in GCA

Malignancies and GCA affect both preferentially the elderly population. Furthermore, tumors associated with vasculitis have been described (30). These observations have raised the issue of whether GCA might in some cases be a paraneoplastic syndrome. Numerous studies over the past decades have addressed this question, none of which has found an increased frequency of malignancies in GCA patients compared to age-matched controls (6, 31-33). Recently, however, the debate has been rekindled by a prospective controlled study from Norway on 185 patients with PMR and GCA diagnosed during 1978-83 and 925 matched controls (34). Patients were classified as having PMR, GCA, or both, on the basis of the clinical manifestations and of the result of the TAB. PMR patients with a positive TAB were considered as having both PMR and GCA. TAB was performed in 117 patients; 75.9% of all GCA cases had a positive TAB. Malignancy was registered in 14.6% patients (24.6% of those with biopsy-proven GCA) and 14.2% controls between 1953 and the end of 1987. The hazard rate for developing malignancy after diagnosis for the patients' population was not significantly different from the controls. However, the hazard rate for developing malignancy in patients with positive biopsy was 2.35 times higher than in the controls.

A subsequent population based study 1987-97 was designed to clarify whether or not GCA and PMR patients had an increased prevalence of malignancies (35). Three hundred and ninety-eight patients with PMR or GCA and 1592 controls were recruited. All patients and controls were cross-checked with data files at the Cancer Registry of Norway, for malignancies registered up to the end of 1998. Prior to inclusion, cancer was diagnosed in 32 patients with PMR or GCA (8.0%) and 153 controls (9.6%) with an OR of 0.82 (95% CI 0.55-1.22). After inclusion, malignant neoplasms were dis-

covered in 34 patients with PMR or GCA (9.3%) compared to 143 controls (10.8%) with a relative risk of 0.86 (95% CI 0.59-1.26). None of these differences between patients with PMR or GCA and their controls regarding prevalence or incidence of cancer was statistically significant. The interval between inclusion and the time of diagnosis of malignant neoplasm did not differ between patients and controls.
Therefore, on the basis of the best evidence available, GCA does not appear to be associated with an increased risk of cancer, nor can it be considered a paraneoplastic condition.

Flares in GCA

Longitudinal studies have demonstrated that one of the commonest causes of disease flares (50-90% of treated patients) in GCA is tapering of GC dose or withdrawal of GC therapy. In several cases, flares have been reported as occurring when the dosage of GC was decreased too quickly and/or when it reached the low-dose range of 5 to 10 mg of prednisone-equivalent per day (reviewed in (36)). However, most cases of reported flares were not accompanied by severe manifestations and tended to respond favorably to an increase in GC dosage or reintroduction of GC therapy (6, 18, 37). Disease exacerbation unrelated to GC regimens has also been described (4). In addition, a sizeable minority of patients appears to require long-term treatment with GC, often at low doses. In a Scandinavian study on ninety patients with GCA (sixty-five) or PMR (twenty-five), 25% of surviving patients followed up for 9 years were still on prednisone at an average daily dose of 5 mg per day (38). Attempts to wean the patients off GC resulted in an approximately 50% relapse rate regardless of the time elapsed from the diagnosis to GC withdrawal. Likewise, in a group of ninety patients with biopsy-verified GCA one third developed a chronic relapsing disease requiring low-dose GC treatment indefinitely (18).
Inflammatory markers, notably the ESR and CRP, are often used in clinical practice both to support the diagnosis and to assess disease activity of GCA. However, in a minority of cases ESR and, less frequently, CRP may be normal at diagnosis (39, 40). Relapses and recurrences of GCA are often, but by no means invariably, associated with elevated inflammatory indices (41, 42). It is yet unclear whether the CRP is superior to the ESR in assessing disease activity and thus in guiding therapeutic decisions (41, 43). There is some evidence that interleukin-6 (IL-6), may be a more sensitive marker than ESR and CRP for predicting disease flares, but measurement of IL-6 is not feasible in most centers (44). A decreased peripheral CD8 count (45) and raised soluble IL-2 receptor (45, 46), anticardiolipin antibody titer (47-49) and von Willebrand factor (50) have been described in GCA patients, but their respective roles in predicting disease flares have not been adequately validated in prospective clinical studies.

Complications related to glucocorticoid therapy in GCA

GC are currently the only agents in GCA with proven efficacy (36). Since both GCA itself and GC can give rise to complications, ideally GC regimens should be adequate to control disease activity, but the dosage of GC should also be tapered as quickly as possible to minimize treatment-related adverse reactions. Two large studies have indeed documented that GC therapy carries a significant burden in terms of morbidity and, to a lesser extent, of mortality, in patients with GCA.
In a population-based study of 120 patients with GCA diagnosed between 1950 and 1991 in the Olmsted County in the US, 86% patients developed adverse events judged to be related to GC therapy (51). Adverse events included bone fractures in 46 patients, avascular necrosis of the hip in 3, diabetes mellitus in 11, infections in 37, generalized infection in 2, pneumonia in 18, gastro-intestinal hemorrhage in 5, hypertension in 26, and posterior subcapsular cataract in 49. Age and a higher cumulative GC dose were both predictors of adverse events.
Similarly, a 15-year (1978-1992) survey from Israel revealed that 58% of patients with GCA developed serious GC-related complications (52). More specifically, fractures occurred in 15 patients, infections in 9, diabetes mellitus, congestive heart failure and hypertension in 8, psychiatric symptoms in 3, hemorrhage secondary to peptic ulcer in 2, and avascular necrosis of the hip in 2. The earliest side effects were hypertension, diabetes mellitus, fluid retention and psychotic reactions, while fractures and avascular necrosis tended to occur at later times (after a mean of 12 and 19 months, respectively). GC-related side effects were dose related, occurring more commonly in patients starting with doses of prednisone-equivalent higher than 40 mg daily and in those taking high maintenance dosage. Mortality judged to be probably related to GC therapy was recorded in 7 (21%) patients. In 6 cases, death was caused by infection, while one patient succumbed to a fatal bleeding ulcer. The mortality rate found in this survey is very similar to that reported in another large study on 292 GCA patients (53).
Data from a population-based prescription database and from a case-control study have documented that GC use is accompanied by an increased risk of developing malignant lymphomas (54, 55). However, since many of the conditions for which GC are prescribed carry a higher lymphoma risk *per se*, it is difficult to ascertain whether such increased risk is attributable to GC therapy or to the disease itself. On this background, a recent case-control study (56) has examined the association between GCA/PMR and malignant lymphomas in a Swedish population. However, no association was found between hospital admission for PMR/GCA and subsequent lymphoma development (OR for a pre-lymphoma hospital admission due to GCA 0.67 [CI 0.48 to 0.98]).
Some reports have described a deterioration of GCA, characterized particularly by ischemic complications, shortly after the introduction of GC therapy (57-60). These observations have thus raised the issue of whether GC might possibly induce worsening of GCA in the short term (61). In many of the cases reported, the manifestations of GCA

had been present for a considerable amount of time prior to the initiation of GC therapy. However, on the basis of the limited data available, it is impossible to establish whether GC may indeed temporarily worsen GCA in selected cases by yet to define mechanisms, or whether the association described is purely coincidental.

In conclusion, GC therapy in GCA appears to have a substantial impact in terms of morbidity and, to a lesser extent, of mortality. On the other hand, there is at present no reliable alternative to GC treatment of GCA. Quite aptly, GC have been termed a "double-edged sword" (62). Therefore, care should be taken both to taper GC as quickly as possible (63), and to implement an adequate scheme of prevention of common, treatable iatrogenic effects such as hypertension, hyperglycemia, and osteoporosis.

Discussion

GCA is usually a self-limiting disease with a duration varying from months to years (6). However, a subgroup of patients appears to follow a chronic course, requiring virtually indefinite treatment with GC, mostly at low doses (18, 38). GC are effective in controlling the clinical manifestations of GCA and in preventing its complications, including visual loss (36). There is an inevitable trade-off between the clinical benefit imparted by GC and their side effects. Therefore, it is sensible to taper GC therapy as quickly as feasible, and efforts should be made to maintain GC dosage as low as possible for the shortest periods of time.

Mortality rates of GCA patients are comparable to those of the general population, but there is evidence for an increased frequency of serious and even potentially life-threatening ischemic events (9). The risk conferred by the disease appears to decrease with the passage of time, presumably as a consequence of GC treatment, but it can remain significantly elevated in patients whose disease activity is not sufficiently controlled by the treatment. The contribution of ischemic complications to mortality may in fact be underestimated since autopsy, which is the only reliable way of causatively linking these events to the disease process, is rarely performed (15). By the same token, large-vessel involvement, another potentially life-threatening complication especially in late GCA, is also most probably underreported because it is often clinically silent for long periods of time, and because it can only be captured by studies with sufficiently long follow-up duration that include specific investigations. By contrast, there is no evidence that GCA is associated with an increased prevalence of malignancies or that it may represent a paraneoplastic syndrome.

In conclusion, GCA is mostly a manageable condition, although numerous disease- and treatment-related complications can occur. On balance, GC therapy has definitely contributed to ameliorate the prognosis of GCA patients despite its numerous side effects. At the same, there is a need to explore new therapeutic avenues to achieve even better results with less adverse reactions.

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