Glucocorticoid usage in giant cell arteritis over six decades (1950-2009)

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ABSTRACT

Objective. *To evaluate the trends in glucocorticoid (GC) therapy in patients with giant cell arteritis (GCA).*

Methods. *Using a population-based inception cohort, GC therapy details were collected for all patients with GCA diagnosed between 1950-2009. GC usage for patients diagnosed with GCA between 1980-2009 was compared to those diagnosed between 1950-1979.*

Results. *The mean starting dose was similar in both time-periods but the mean cumulative dosages at different time points were significantly higher for patients diagnosed between 1980-2009 than in 1950-1979 (at 1-year: 6.3 vs. 4.1g; and at 5 years 10.7 vs. 7.6g, respectively, p<0.001). The median time to permanent discontinuation of GC was 2.6 years for 1980-2009 vs. 1.5 years for 1950-1979 (p=0.004). The risk for GC-associated adverse events was similar in both time periods (p=0.52).*

Conclusion. *GCA patients diagnosed in the last three decades were treated with higher cumulative GC doses and were less likely to achieve GC discontinuation. However, their risks for GC-related complications were not significantly higher than their earlier counterparts.*

Introduction

Giant cell arteritis (GCA) is the most common idiopathic vasculitis in individuals over the age of 50 years with an estimated incidence of 18.9 per 100,000/persons 50 years and older (1). Serious complications of the disease include visual loss, large-artery stenosis and aortic involvement with aneurysm formation (2, 3). Over the past six decades, glucocorticoids (GC) have become the mainstay of treatment for GCA especially after it was observed to prevent progression of vision loss in some cases (4, 5). Chronic GC therapy is associated with multiple adverse effects such as osteoporosis, avascular necrosis, diabetes mellitus, infections, gastrointestinal bleeding, posterior subcapsular cataract and hypertension (6). As a chronic disease, GCA requires long-term therapy and continued monitoring (7). There are conflicting data available in the literature about the duration and dosage of GC therapy and the adverse events due to long-term therapy. We sought to evaluate the trends in GC therapy and its complications in a population-based cohort of patients with GCA from 1950 to 2009.

Materials and methods

Incident GCA cases between 1950 and 2009 were identified using the Rochester Epidemiology Project (REP), which links the medical records of Olmsted County, MN residents (8). GCA was defined according to the 1990 American College of Rheumatology criteria (9). As previously described, all the medical records of GCA patients were retrospectively reviewed and longitudinally followed until death, migration or December 31, 2009 (7).

Data regarding dosing, duration of GC use and adverse effects were manually gathered by individual medical record and prescription information. Oral and parenteral exposures to GC were included; intraarticular or inhalational exposures were excluded. GC exposures were collected from inpatient, outpatient (including telephone calls), emergency department, and nursing home encounters as prednisone equivalents. Discontinuation was defined as physician instruction for discontinuation, and no record of any GC use thereafter in recent patients' record with at least 6 months of no GC use at last follow-up.

The adverse events selected for the study were the most commonly reported complications of GC therapy as previously

reported (7). These included diabetes mellitus (2 readings of fasting plasma glucose >140 mg/dl or glucose tolerance test levels >200 mg/dl, excluding readings obtained during emergency room or inpatient care); symptomatic vertebral fractures; Colles' fracture of the wrists; hip fracture; femoral neck fracture; avascular necrosis (the latter 5 clinical findings confirmed by radiography); cataracts (diagnosed or confirmed by an ophthalmologist); bacteremia or sepsis (confirmed by blood culture); pneumonitis (confirmed by radiography); other infections (diagnosed by a physician and/or confirmed by culture), excluding urinary tract infections and viral upper respiratory infections; upper gastrointestinal bleeding (endoscopic or clinical diagnosis supported by a drop in haemoglobin concentration of >1 gm); hypertension (2 consecutive blood pressure readings of at least 140/90 mm Hg, excluding readings obtained during emergency room or inpatient care); and myopathy (physician's diagnosis supported by documented proximal muscle weakness on physical examination). A new or incident diagnosis of any of the above conditions occurring after the diagnosis of GCA was defined as an adverse event.

Descriptive statistics (means, proportions, etc.) were used to summarise the data. Time trends were examined continuously and by dividing the study cohort into 2 30-year periods (patients diagnosed with GCA in 1950-1979 and in 1980-2009). Generalised additive models with smoothing splines were used to examine time trends continuously. Chi-square and Wilcoxon rank-sum tests were used to examine differences in baseline characteristics and cumulative GC doses between the 2 time periods. The cumulative incidences of GC discontinuation and of reaching lower GC dosages were estimated using Kaplan-Meier methods and differences between time periods were examined using logrank tests. Age and sex adjusted Cox models were used to assess differences in adverse events between the time periods.

Results

Among the 245 patients in our cohort, 205 (82%) patients had biopsy positive GCA; seven of the patients were included in this cohort based on radiologic criteria. The mean age at diagnosis was 76.2 years (±8.3), 79% were women, and the median follow-up in years was 9.5 years.

Table I. Clinical characteristics of patients with giant cell arteritis in 1950-1979 and 1980-2009.

Characteristic	1950-1979 (N=61)	1980-2009 (N=184)	*p* value
Age, years, mean (SD)	73.7 (8.2)	77.0 (8.1)	0.005
Sex, female	48 (79%)	146 (79%)	0.91
Erythrocyte sedimentation rate, mm/hr	**92.1 (19.6)**	**75.9 (62.6)**	**<0.001**
Fever >100^{O} F	11 (18%)	29 (16%)	0.70
Weight loss	14 (23%)	41 (22%)	0.94
Anorexia	**21 (34%)**	**30 (17%)**	**0.003**
Malaise	15 (256%)	34 (19%)	0.32
Fatigue	17 (289%)	61 (34%)	0.41
Weakness	11 (18%)	37 (21%)	0.67
Headache	45 (74%)	132 (72%)	0.85
Jaw claudication	31 (51%)	78 (43%)	0.28
Tongue claudication	4 (7%)	5 (3%)	0.17
Swallowing claudication	0 (0%)	8 (4%)	0.10
Arm claudication	0 (0%)	2 (1%)	0.41
Leg claudication	1 (2%)	2 (1%)	0.74
Other facial pain	8 (13%)	18 (10%)	0.46
Respiratory tract symptoms	11 (18%)	39 (21%)	0.57
Scalp tenderness	19 (35%)	84 (47%)	0.13
Tender temporal artery	**5 (13%)**	**60 (35%)**	**0.009**
Blurred vision	8 (13%)	25 (14%)	0.90
Transient vision loss	3 (5%)	7 (4%)	0.72
Vision, permanent partial loss	**8 (13%)**	**9 (5%)**	**0.03**
Vision, permanent complete loss	1 (2%)	4 (2%)	0.79
Other visual symptoms	6 (10%)	22 (12%)	0.63
Bruit	0 (0%)	9 (5%)	0.08
Absent pulse	5 (12%)	19 (11%)	0.84
PMR symptoms	14 (23%)	54 (30%)	0.31
Other musculoskeletal pain	10 (16%)	32 (18%)	0.84
Joint swelling	3 (5%)	12 (7%)	0.64
Other soft tissue swelling	0 (0%)	4 (2%)	0.24
Neurologic symptoms	**0 (0%)**	**14 (8%)**	**0.025**

Values in table are n (%) unless otherwise specified. Percentages are based on patients with available data. *p*-values of statistical significance are in bold.

Patient characteristics in the two time periods (1950-1979 and 1980-2009) were similar with a few exceptions (Table I). Erythrocyte sedimentation rate was lower in patients diagnosed in 1980-2008 than those diagnosed earlier ($p<0.001$). Anorexia and permanent partial vision loss were less common in patients diagnosed in 1980-2009 than those diagnosed earlier ($p=0.003$ and $p=0.03$, respectively). Tender temporal arteries and neurologic symptoms were more frequently documented in patients diagnosed in 1980-2009 than in those diagnosed earlier ($p=0.009$ and $p=0.025$, respectively).

GC dosage information was available for 242 patients. With slight variation over the period of the study, the median initial dosage of GC was 60 mg/day and was similar in the two time periods (1950-1979 and 1980-2009; $p=0.59$; Fig. 1). The mean 1-year cumulative GC dosage was 4.1 g (SD 2.3 g) in the 1950-1979 time period compared with 6.2 g (SD 2.7) in the 1980-2009 time period ($p<0.001$). This trend in increasing cumulative GC dosage over time was observed throughout follow-up. At two years, the mean cumulative dosage was 5.6g (SD 3.6 g) for 1950-1979 and 8.4 g (SD 4.0 g) for 1980-2009 ($p<0.001$). At five years, the mean cumulative dosage was 7.6 g (SD 6.2 g) for 1950-1979, and 10.7 g (SD 6.3 g) for 1980-2009 ($p=0.002$). Ten patients received initial intravenous high dose GC (*e.g.* 1 gm per day for 3 days) during the 1980-2009 time period. When these intravenous doses were excluded, the trend of higher cumulative doses in more recent years remained unchanged.

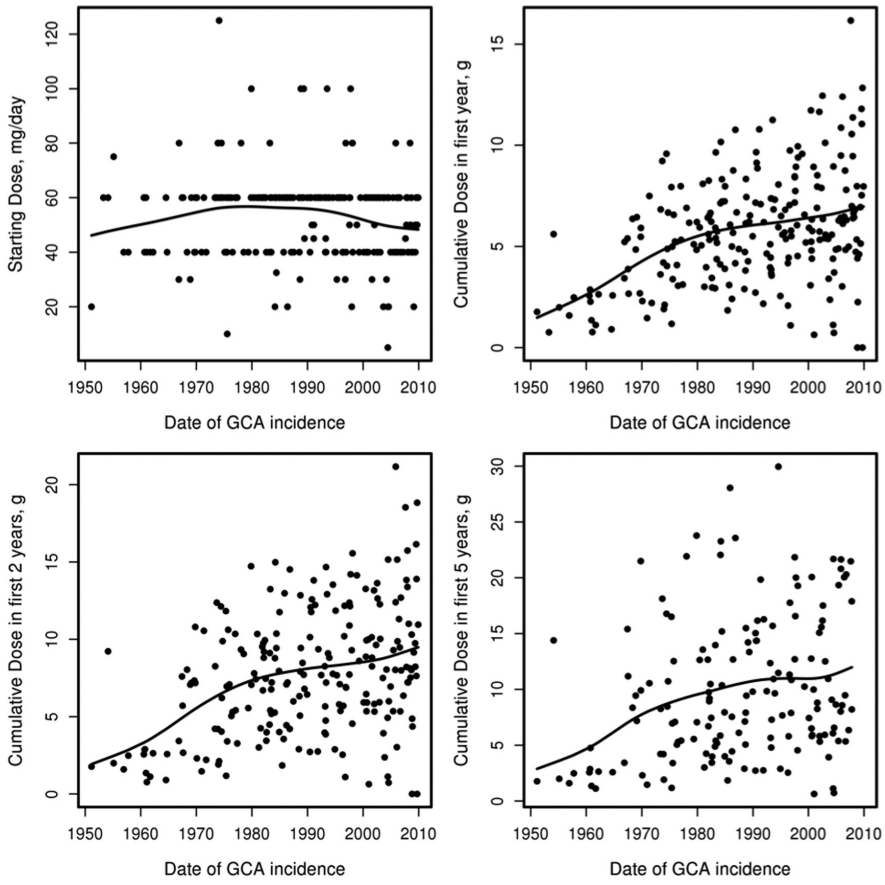

Fig. 1. Median initial dose, and cumulative dose of glucocorticoid (prednisone equivalent) at the end of 1, 2 and 5 years of treatment in patient with giant cell arteritis over 6 decades.

While the cumulative GC dosage has been on a steadily increasing trend from the start of the study period, the percentage of patients who have completely discontinued GC has been decreasing (p=0.004). Only 12% of patients were able to permanently discontinue GC in one year from their incidence date in the 1980-2009 cohort compared with 40% of patients in the 1950-1979 cohort (Fig. 2). At two years, 64% of patients in the 1950-1979 cohort discontinued GC compared to 38% in the 1980-2009 cohort.At five years of follow-up, 76% of patients in the 1950-1979 cohort had discontinued GC, compared to 69% in the 1980-2009 cohort. The median time for permanent discontinuation of GC in the 1980-2004 cohort was 2.61 years, which was nearly twice as long as the median time of 1.46 years (95% CI – 0.89 to 2.02) in the 1950-1979 cohort.

Among patients diagnosed between 1950-1979, 36% and 65% were able to reach the dose of <5mg/day for at least 6 months within 1 and 2 years after GCA diagnosis respectively compared to only 7% and 50% in the cohort diagnosed between 1980-2004 cohort. However, 93% of patients in both the cohorts achieved this dosage by 5 years after diagnosis.

The median time to reach <5 mg/day dosage for 6 months following diagnosis was 1.46 years in 1950-1979 cohort and 2.0 years in the 1980-2009 cohort. The median time to be tapered to a dosage of <10 mg/day was 0.27 years in the former cohort and 0.65 years in the latter. This dose was reached in one year in 73% in the former cohort and 93% in the latter. There has been no difference in mortality among both cohorts (median time to death – 10.7 in former *vs*. 10.6 years in the latter).

A few patients (n=17; 6.9%) of the patients in this cohort received disease-modifying anti-rheumatic drugs (DMARDs) as steroid sparing agents (drug, number of patients: methotrexate 8; cyclophosphamide 2; azathioprine 5; methotrexate then azathioprine 2); no patients in this cohort received biologic agents. The use of DMARDs did not affect the time to discontinuation of steroids (p=0.33). There was also no difference in the one and two year cumulative doses of steroids between DMARD users and non-users (p=0.78 and p=0.17, respectively). However, the 5 year cumulative steroid dose was higher among the DMARD users than the non-users (p=0.0048), but there were only 10 DMARD users who were alive and completed 5 years of follow-up, so this comparison is based on small numbers. Because of the small number of patients receiving DMARSDs, and because DMARDs were only used in patients on longer term GC who were thought either refractory to GC therapy, or had unacceptable side effects from GCs, it is unsurprising that no effect of DMARD use could be established.

Specific adverse events related to GC that occurred after the diagnosis of GCA were recorded in 95% patients (excluding hypertension, hyperlipidaemia and cataracts). The risk of adverse events was similar in both time periods (by 10 years after GCA diagnosis: 50% for 1950-1979 and 57% for 1980-2009; p=0.52). The risks for Colles' fracture of the wrist (n=9; hazard ratio [HR]: 2.59; 95% confidence interval [CI]: 0.32, 20.81 comparing 1980-2009 to 1950-1979), gastro intestinal bleeding (n=19; HR: 3.20; 95% CI: 0.73, 14.10) and infections (n=93; HR: 1.58; 95% CI: 0.93, 2.67) were marginally higher in the 1980-2009 cohort than in the 1950-1979 cohort, but these associations did not reach statistical significance. There were no apparent changes in the risk of other possible adverse events of GC usage (data not shown).

Discussion

Over the last six decades since first being used for management for GCA, GC use has varied in dosage, type of preparation, duration, frequency and mode of administration (4). Initial doses and tapering regimens vary, with a view towards disease remission and discontinuation of treatment when possible, and avoidance of GC related side effects.

In this examination of trends in the usage of GC for GCA, we found that pa-

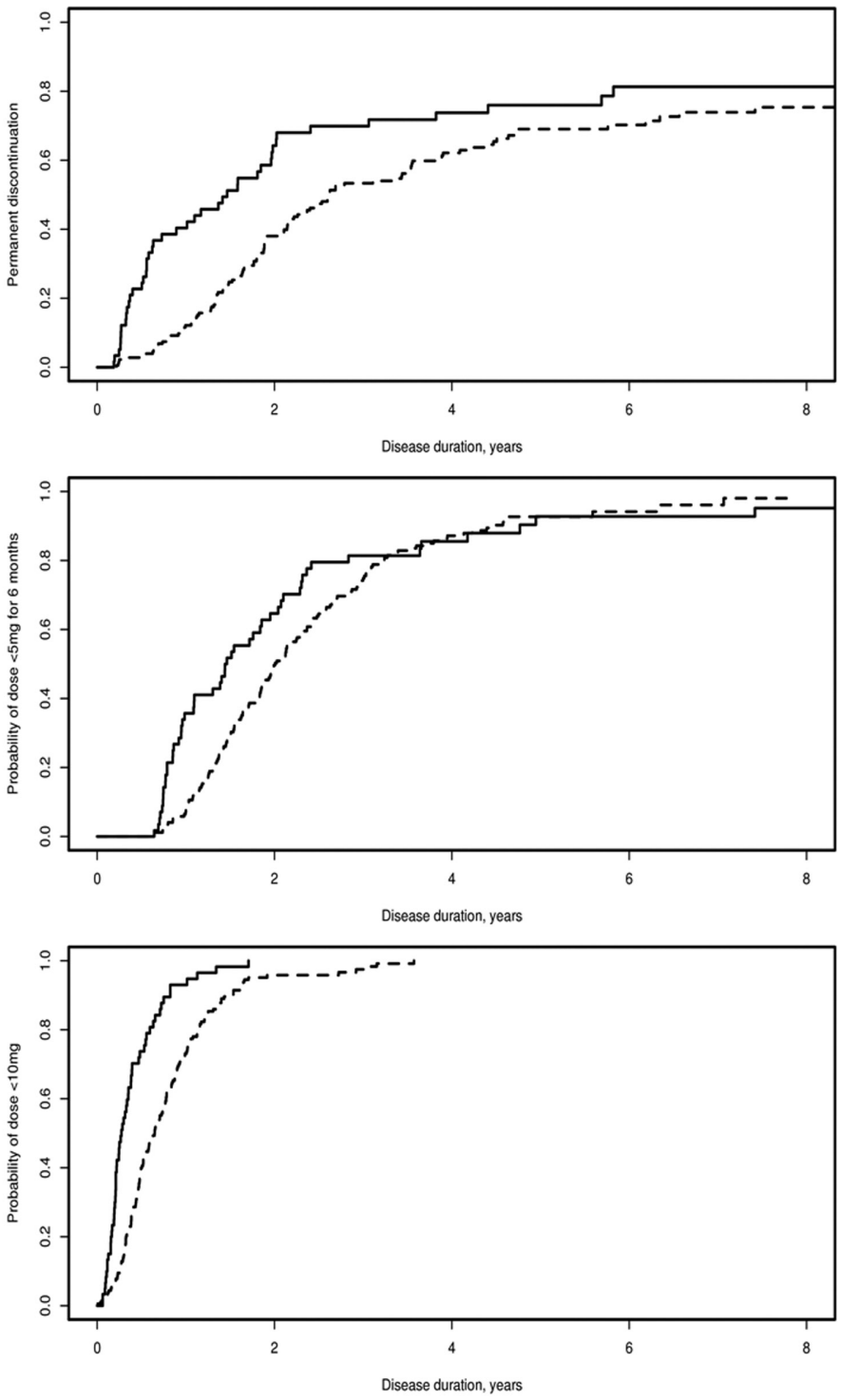

Fig. 2. Rates of glucocorticoid dosage discontinuation for 242 patients with giant cell arteritis throughout disease duration.

tients diagnosed in recent decades are receiving more GC overall as reflected by the higher cumulative dosage of GC used in the recent years. At the same time, discontinuation rates for GC in recent years are lower than in the past indicating longer exposure to GC as part of management.

The trend towards what appears to be a pattern of long-term use of near physiologic doses of GC (about 5 mg prednisone daily) in GCA may be because of increasing recognition or concern that the disease persists longer at a lower intensity requiring continuation of small GC doses. We could not specifically address this question in this retrospective study. As well, symptoms of hypoadrenalism with taper of GC to low dose may have been difficult to distinguish from mild active disease, which may have caused some physicians to continue small doses for longer times, however this is highly speculative. With the increased awareness about GCA and its complications, relapse may be over-diagnosed and hence GC continued for longer period at higher doses. A further possibly contributing factor which we were unable to specifically address is that with increased use of imaging studies, we are appreciating that subclinical vascular inflammation persists for several years requiring more protracted and possibly higher doses of GC than have been used in the more distant past.

Initial high dose GC has been used in various regimens starting from 80 mg/day to 100 mg intramuscular cortisone injections (5, 10-13). There have been mixed results ranging from sustained remission to early and increasing frequency of relapse with GC tapering (5, 9). Most relapses occur within the first few months after diagnosis and about half of the relapses occurred in relation to attempted GC reduction, usually at a daily dose of around 10mg (1, 7, 14). In general, intravenous high dose GC therapy has not been more effective than oral therapy in preventing disease related complications, although the strategy has been used for threatened visual loss (9, 10). In many cases, low dose therapy can be successfully used to control disease flare and ischemic complications in patients with GCA (14-16).

In this study, the time taken to taper patients to near physiologic dosages of GC (generally, 3–5 mg/day prednisone equivalent has been consistently increasing in the recent years. This is in contrast to the prior period of the study where a higher percentage of patients achieved permanent discontinuation at an earlier time and with lower cumulative dosages. In recent years, the median time to reach the first steroid dose of less than 10mg has increased almost two fold (0.25 in 1950-1979 *vs*. 0.65 in 1980-2004), underscoring the signifi-

cance that GCA patients are now being treated for longer duration with higher dosages. While it was not possible to interrogate the reasons for this in this retrospective study, it is speculative that with wider availability and use of imaging particularly of large vessels, and heightened concern about persistent large vessel disease, GC are being used for longer periods than in the past.

Adverse events related to GC use that occurred after the diagnosis of GCA were common and were recorded in over half of patients. Some studies have shown that high dose GC therapy is associated with major adverse outcomes, mainly infections and fractures (7, 16-18). A study of intravenous initial high dose "pulse" GC therapy resulted in somewhat decreased cumulative dosage over two years and a marginal decrease in short term side effects (11). We found no difference in the risk of developing adverse outcomes for patients diagnosed in recent years compared to patients in the earlier period of the study who were on lower steroid dosages. This might stem from the fact that most adverse outcomes might already have occurred within the range of GC dosages used in these patient cohorts. While there were too few patients in this study receiving DMARDs to examine the effects of adjuvant therapy on GC doses, the well documented detrimental effects of high GC dosages should provide justifiable evidence to substitute steroid sparing agents for initial, and perhaps long therm therapy of GCA.

To our knowledge, this is the first population-based study comparing GC usage over a long time interval. As a retrospective study, a limitation is that is not possible to interrogate the reasons for individual clinician decisions regarding GC management in the clinic. Patients with GCA are on higher cumulative GC dosages and longer duration of therapy in more recent years, although adverse events related to GC use do not seem to have increased in the dosing ranges of GC used in these patients over the long period of the study. In light of growing concern about the morbidity and mortality due to GC therapy, the potential for GC sparing agents for GCA management must be further explored.

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