Hospitalized Infections in Giant Cell Arteritis — A Population-based Retrospective Cohort Study

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ABSTRACT. ***Objective.*** To assess the occurrence of infections requiring or acquired during hospitalization in patients with giant cell arteritis (GCA).

Methods. We retrospectively reviewed a population-based incidence cohort of patients with GCA diagnosed between 1950 and 2009 and compared this cohort with a non-GCA one matched for age, sex, and calendar year from the same population.

Results. We identified 245 patients in the GCA cohort and 245 patients in the non-GCA cohort. Seventy-four GCA subjects (134 episodes) and 79 non-GCA (153 episodes) had infections requiring or acquired during hospitalization [rate ratio (RR) 0.94; 95% CI 0.74, 1.18]. Sixty-seven subjects (107 episodes) in the GCA cohort and 63 subjects (110 episodes) in non-GCA cohort required hospitalization secondary to an infection (RR 1.04; CI 0.80, 1.36). Pneumonia, urinary tract infections (UTI), skin and soft tissue infections accounted for the majority of infections requiring hospitalization and had similar occurrence in both cohorts. UTI accounted for the majority of infections requiring hospitalization in the first 6 months after GCA incidence (RR 3.93; CI 0.85, 56.52). No difference between the 2 cohorts was noted in overall infections acquired during hospitalization (RR 0.68; CI 0.41, 1.08).

Conclusion. There is no overall increased risk of infections requiring or acquired during hospitalization in patients with GCA who are taking glucocorticoid therapy. There may be an increased risk of infections requiring hospitalization, especially of the urinary tract, in the first 6 months after GCA incidence, although this did not achieve statistical significance in our study. (J Rheumatol First Release Oct 15 2014; doi:10.3899/jrheum.140124)

Key Indexing Terms:
GIANT CELL ARTERITIS INFECTION HOSPITALIZATION COHORT STUDIES

Giant cell arteritis (GCA) is the most common primary systemic vasculitis, and it typically affects large and medium-size arteries[1,2]. Glucocorticoids (GC) have been the mainstay of treatment for GCA since the 1950s. While some patients are treated with GC for 1–2 years, others experience recurrent disease relapses and require longterm treatment. Indeed, chronic GC therapy has been reported to be used up to a mean duration of 45 or more months in some cohorts[3,4]. In view of the immunosuppressive properties of GC, patients with GCA may have a higher risk for infections. However, detailed data from population-based studies on different types of infections in GCA are lacking. We aimed to assess the occurrence of infections requiring or acquired during hospitalization in patients with GCA.

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MATERIALS AND METHODS

This is a retrospective population-based study performed using resources of the Rochester Epidemiology Project (REP) medical record linkage system[5]. The REP allows virtually complete access to medical records from all community medical providers including the Mayo Clinic, Olmsted Medical Center and its affiliated hospitals, local nursing homes, and the few private practitioners in Olmsted County, Minnesota, USA. The patient identifiers from all medical providers are linked for each resident of Olmsted County. Persons enter the REP when they first become residents of Olmsted County, and the REP has demonstrated virtually complete ascertainment of all county residents (http://rochesterproject.org/for-researchers/population-overview). The uniqueness of the REP and its advantages in performing population-based studies in rheumatic diseases have been described[5].

We retrospectively reviewed the incidence cohort of patients with GCA diagnosed between 1950 and 2009 in Olmsted County based on American College of Rheumatology 1990 GCA classification criteria[6]. We also included patients diagnosed with GCA ≥ 50 years of age with elevation of erythrocyte sedimentation rate or C-reactive protein and computed tomography, magnetic resonance imaging, or positron emission tomography evidence of large vessel vasculitis involving the ascending aorta and its branches. The medical charts of all the patients included in the GCA cohort were manually reviewed by 1 or more of the study investigators. We did not include asymptomatic patients with incidental finding of aortitis on histopathological examination of specimens obtained at aortic aneurysm

repair or aortic valve replacement. We compared this GCA cohort with a randomly selected cohort matched for age, sex, and calendar year of GCA incidence/index date from Olmsted County residents without GCA. Each comparator subject in the non-GCA cohort was assigned an index date corresponding to the GCA incidence date of the matched patient in the GCA cohort.

All subjects were longitudinally followed through all available community medical records until death, migration from Olmsted County, or April 30, 2013. Data were collected on all documented episodes of infection requiring or acquired during hospitalization after the GCA incidence/index date.

Various infections were defined through physician diagnosis and confirmed by features as documented in the medical records. They were septic arthritis: positive microbiologic culture from joint aspirate fluid; bacteremia/septicemia: isolation of a pathogenic microorganism from 1 or more blood cultures, with fever (> 38.0°C); urinary tract infection (UTI): isolation of > 100,000 colony-forming units/ml of urine; pyelonephritis: UTI plus documentation of radiological evidence of renal or perinephric abscess; lower respiratory tract infection: presence of new infiltrates, consolidation, or effusion seen in chest radiography; and osteomyelitis: definite radiologic findings or positive bone culture. Skin and soft tissue infections included a physician diagnosis of cellulitis, abscesses, wound infections, herpes zoster, or diabetic foot infections. Gastrointestinal (GI) infections included a physician diagnosis of acute gastroenteritis, colitis, acute cholecystitis, ascending cholangitis, appendicitis, diverticulitis, or peritonitis. Other infections such as episodes of meningitis, acute viral illness, herpes zoster, and influenza B were based on physician diagnosis.

Statistical methods. Descriptive statistics (means, percentages, etc.) were used to summarize the characteristics of the 2 cohorts. Comparisons of baseline characteristics in the 2 cohorts were performed using chi-square and rank-sum tests. Infection rates were calculated using person-year methods. Rate ratios (RR) were used to compare infection event rates in GCA and non-GCA cohorts. CI for RR were calculated using an F approximation. Conditional frailty models were used to examine differences in infection rates for GCA compared to non-GCA after adjusting for age, sex, and calendar year. Interactions between GCA/non-GCA status and these adjusting factors were also examined. Conditional frailty models are a modification of Cox models, which can incorporate multiple events (e.g., infections) per patient that are not independent using a random effect per patient. Statistical analyses were performed using SAS (SAS Institute) and R (R Foundation for Statistical Computing).

RESULTS

We identified 245 patients in the GCA cohort and 245 patients in the non-GCA cohort matched for age, sex, and calendar year. Baseline characteristics including mean age, sex, and length of followup were similar except for diabetes mellitus between the 2 groups, as noted in Table 1. Of the 245 GCA subjects, 17 (7%) had diabetes mellitus at GCA incidence/index date as opposed to 40 of 245 (16%) non-GCA subjects. A total of 74 GCA subjects (134 episodes) and 79 non-GCA (153 episodes) had infections requiring or acquired during hospitalization (RR 0.94; 95% CI 0.74, 1.18; Table 2). A total of 67 subjects (107 episodes) in the GCA cohort and 63 subjects (110 episodes) in the non-GCA cohort required hospitalization secondary to an infection (RR 1.04; 95% CI 0.80, 1.36; Table 3). Lower respiratory tract infection/pneumonia (RR 0.76; 95% CI 0.48, 1.17), pyelonephritis/UTI (RR 0.81; 95% CI 0.43, 1.47), and skin/soft tissue infections (RR 0.83; 95% CI 0.36, 1.87) accounted for the majority of infections requiring hospitalization and had similar occurrence in both cohorts. GI infections requiring hospitalization occurred more often in the GCA cohort than in the non-GCA cohort (RR 2.84; 95% CI 1.50, 6.00); of the 30 such infections, 2 were due to *Clostridium difficile* colitis (and 1 additional case of *C. difficile* colitis was hospital-acquired). One episode of osteomyelitis, 1 episode of meningitis, and no episodes of active tuberculosis, diabetic foot infection, or acute hepatitis required hospitalization in the GCA cohort.

Table 1. Baseline characteristics of giant cell arteritis (GCA) and non-GCA cohorts at index dates.

	GCA, n = 245	Non-GCA, n = 245	p
Age, yrs (SD)	76.2 (8.3)	75.9 (8.5)	0.74
Females	194 (79%)	194 (79%)	1.0
Length of followup, yrs (SD)	9.7 (6.7)	10.4 (7.8)	—
Chronic kidney disease (physician diagnosis, %; n = 242 in GCA cohort and 242 in non-GCA cohort)	12 (5.0)	7 (2.9)	0.24
BMI, kg/m^2 (SD)	25.2 (5.1)	26.0 (5.3)	0.12
BMI ≥ 30 kg/m^2	38 (16%)	41 (17%)	0.71
Smoking status, ever (n = 228 in GCA cohort and 230 in non-GCA cohort)	97 (42%)	103 (45%)	0.63
Diabetes mellitus	17 (7%)	40 (16%)	0.001*

* Statistically significant. BMI: body mass index.

In the first 6 months after GCA diagnosis, 12 episodes of infections requiring or acquired during hospitalization occurred in the GCA cohort compared to 7 in the first 6 months after index date in the non-GCA cohort (RR 1.79; 95% CI 0.74, 4.81). UTI was the most common type of infection requiring or acquired during hospitalization seen in the first 6 months in the GCA cohort; 7 episodes of UTI requiring or acquired during hospitalization occurred in the GCA cohort, while only 1 episode occurred in the non-GCA cohort (RR 5.36; 95% CI 1.29, 76.43).

In the subset of infections requiring hospitalization (excluding those acquired during hospitalization), 9 episodes occurred in the first 6 months in the GCA cohort, while there were 5 in the non-GCA cohort (RR 1.85; 95% CI 0.67, 6.01). Again, UTI accounted for the majority of infections requiring hospitalization in the first 6 months after GCA incidence (RR 3.93; 95% CI 0.85, 56.52). The rate of infections requiring hospitalization appears to be highest among patients with GCA in the first 6 months of disease compared to later in their disease course and compared to subjects without GCA (Table 4). However, the CI for the rates and the RR are large. Because of limited statistical power, we were unable to detect a difference in the rates over time among the patients with GCA (p = 0.6) or among the RR comparing GCA to non-GCA (p = 0.5).

Table 2. Infections requiring or acquired during hospitalization in patients with giant cell arteritis (GCA) compared to subjects without GCA (non-GCA).

Infection Type	GCA Subjects with Infection	Non-GCA Subjects with Infection	GCA Infections	Non-GCA Infections	GCA Rate* (95% CI)	Non-GCA Rate* (95% CI)	Rate Ratio (95% CI)
Overall	74	79	134	153	5.64 (4.73–6.69)	6.01 (5.10–7.04)	0.94 (0.74, 1.18)
Septic arthritis	2	0	2	0	0.08 (0.00–0.30)	0.00 (0.00–0.14)	5.36 (0.54, 4943)
Bacteremia/ septicemia	10	9	11	10	0.46 (0.23–0.83)	0.39 (0.19–0.72)	1.17 (0.50, 2.80)
Skin/soft tissue infection	12	12	12	17	0.51 (0.26–0.88)	0.67 (0.39–1.07)	0.77 (0.36, 1.57)
Lower respiratory tract infection and/or pneumonia	25	36	38	52	2.04 (1.53–2.68)	1.60 (1.13–2.20)	0.79 (0.51, 1.19)
Pyelonephritis and/or UTI	27	31	33	48	1.39 (0.96–1.95)	1.89 (1.39–2.50)	0.74 (0.47, 1.14)
GI	26	13	31	13	1.31 (0.89–1.85)	0.51 (0.27–0.87)	**2.50 (1.36, 4.99)**
Other infection**	7	10	7	13	0.30 (0.12–0.61)	0.51 (0.27–0.87)	0.60 (0.22, 1.41)

Statistically significant data are in bold face. *Rates are reported per 100 person-years. **Other infections include osteomyelitis, meningitis, viral influenza, acute viral illness, herpes zoster, presumed viral illness, acute febrile illness of unknown etiology, and influenza B. UTI: urinary tract infection; GI: gastrointestinal.

Table 3. Infections requiring hospitalization in patients with giant cell arteritis (GCA) compared to subjects without GCA (non-GCA).

Infection Type	GCA Subjects with Infections	Non-GCA Subjects with Infections	GCA Infections	Non-GCA Infections	GCA Rate* (95% CI)	Non-GCA Rate* (95% CI)	Rate Ratio (95% CI)
Overall	67	63	107	110	4.51 (3.69–5.45)	4.32 (3.55–5.21)	1.04 (0.80, 1.36)
Septic arthritis	2	0	2	0	0.08 (0.01–0.30)	0.00 (0.0–0.14)	5.36 (0.54, 4943.10)
Bacteremia/ septicemia	9	8	9	9	0.38 (0.17–0.72)	0.35 (0.16–0.67)	1.07 (0.42, 2.71)
Skin/soft tissue infection	10	8	10	13	0.42 (0.20–0.78)	0.51 (0.27–0.87)	0.83 (0.36, 1.87)
Lower respiratory tract infection and/or pneumonia	21	31	33	47	1.39 (0.96–1.95)	1.85 (1.36–2.46)	0.76 (0.48, 1.17)
Pyelonephritis or UTI	16	18	18	24	0.76 (0.45–1.20)	0.94 (0.60–1.40)	0.81 (0.43, 1.47)
GI	25	11	30	11	1.26 0.85–1.80)	0.43 (0.22–0.77)	**2.84 (1.50, 6.00)**
Other infection**	5	5	5	6	0.21 (0.07–0.49)	0.26 (0.08–0.60)	0.91 (0.27, 2.90)

Statistically significant data are in bold face. *Rates are reported per 100 person-years. **Other infections include meningitis, osteomyelitis, viral influenza, acute viral illness, herpes zoster, presumed viral illness, and acute febrile illness of unknown etiology. UTI: urinary tract infection; GI: gastrointestinal.

Table 4. Infections requiring hospitalization in patients with giant cell arteritis (GCA) compared to subjects without GCA (non-GCA) according to time since GCA diagnosis/index date.

Time Period	GCA, Rate per 100 Person-yrs (95% CI)	Non-GCA, Rate per 100 Person-yrs (95% CI)	Rate Ratio
0–6 mos	7.3 (3.5–13.9)	4.1 (1.3–9.6)	1.79 (0.74–4.81)
7–12 mos	3.5 (0.9–8.9)	5.0 (1.8–10.9)	0.72 (0.19–2.39)
> 12 mos	4.2 (3.3–5.1)	4.1 (3.3–5.0)	1.02 (0.77–1.36)

No difference between the 2 cohorts was noted in overall infections acquired during hospitalization (RR 0.69; 95% CI 0.42, 1.09; Table 5). Subgroup analysis of the subjects by followup duration showed that among those with greater than 20 years of followup, GCA subjects had more infections requiring hospitalization than did non-GCA subjects (RR 3.04; 95% CI 1.14, 8.12). The median length of hospital stay was 5 days and median duration of antibiotic use was 10 days in each cohort among infection episodes requiring hospitalization.

DISCUSSION

No difference was noted between GCA and non-GCA cohorts in our study in terms of overall infections requiring or acquired during hospitalization after the GCA incidence/index date. Our findings are in line with the available data from the same population revealing that patients with GCA are not at increased risk of herpes zoster compared with the general population, even during the first 6 months of therapy[7]. In the same population in 1950–1991, infection was reported in 31% of the patients with GCA in an uncon-

Table 5. Infections acquired during hospitalizations in patients with giant cell arteritis (GCA) compared to subjects without GCA (non-GCA).

Infection Type	GCA Subjects with Infection	Non-GCA Subjects with Infection	GCA Infections	Non-GCA Infections	GCA Rate*	Non-GCA Rate*	Rate Ratio (95% CI)
Overall	19	30	28	44	1.180	1.729	0.69 (0.42, 1.09)
Septic arthritis	0	0	0	0	0.000	0.000	—
Bacteremia/septicemia	1	1	2	1	0.084	0.039	1.79 (0.23, 26.60)
Skin/soft tissue infection	2	4	2	4	0.084	0.157	0.60 (0.09, 2.67)
Lower respiratory tract infection and/or pneumonia	12	17	15	24	0.632	0.943	0.68 (0.35, 1.26)
GI	1	2	1	2	0.042	0.079	0.64 (0.04, 5.00)
Pyelonephritis and/or UTI	12	17	15	24	0.632	0.943	0.68 (0.35, 1.26)
Other infections	2	7	2	7	0.084	0.275	0.36 (0.06, 1.28)

*Rates are reported per 100 person-years. GI: gastrointestinal; UTI: urinary tract infection.

trolled observational study[4]. In a French GCA cohort without a comparison cohort, the infection rate was found to be even lower at about 16%, although the definition of infections is not clear in these studies[8]. In our study, the overall rate of infections (including only episodes that required or were acquired during hospitalization) was 5.8% in the GCA cohort. It has to be mentioned that none of the above- mentioned studies had a primary aim of assessing the occurrence of infections in GCA; hence they have to be interpreted with caution.

Our findings are in contrast to those of a registry-based observational study conducted in the United Kingdom in which GCA was found to be a risk factor for increased incidence of UTI and upper respiratory tract infection (URTI), including episodes that did not require hospitalization[9]. The GCA cases in the UK study were originally identified using diagnostic coding, and a significant number of these patients were excluded for various reasons. The proportion of patients with GCA who experienced at least 1 episode of UTI, URTI, or serious infections was 48%, which is significantly higher than the previously reported infection rates in GCA[4,8,10]. Diabetes mellitus was present more often in the GCA cohort in the UK study, in contrast to other GCA cohorts, including ours[11,12,13]. In contrast to our study, the individual medical records were not reviewed in the UK study; hence there may be a greater possibility for misclassification of GCA and/or infections in the UK study. We did a subgroup analysis in our study according to diabetes mellitus status and still did not find any significant difference in the results regarding infection risk. In the UK study, GCA was associated with an increased risk of infection in younger patients (age < 70 years). There were not enough subjects in our study to do a meaningful age-based subgroup analysis. With a mean age of onset around 70–75 years, GCA affects an older population of patients. We believe that a "healthy cohort bias" favoring less risk of infection in our GCA cohort does not explain our findings, because our patients with GCA were age-matched and sex-matched to the non-GCA cohort.

Subgroup analysis of the subjects by followup duration showed that among those with greater than 20 years of followup, GCA subjects had more infections requiring hospitalization than did non-GCA subjects. However, the numbers of infections were too few to draw any conclusions from this observation. GI infections were higher in the GCA cohort in our study. Also, UTI were noted to be significantly higher in the GCA cohort in the first 6-month post-GCA incidence date. This may be because the highest doses of GC therapy are used in the first 6 months following GCA diagnosis[14]. We did not find any difference in infection rates between the GCA and non-GCA cohort by sex or calendar year of GCA incidence/index date. We did not have enough subjects in our GCA cohort to examine whether infection rates differed for patients with GCA who were taking GC alone versus GC in combination with methotrexate/other immunosuppressive therapy.

The strengths of our study are that it was population-based and that complete medical record information was available for all subjects. With the exception of a higher proportion of the working population employed in the healthcare industry, and correspondingly higher education levels, on the whole, results of this study using the population of Olmsted County are generalizable to the populations of interest elsewhere[15]. This is the only study to date, to our knowledge, that has evaluated the occurrence of infections in patients with GCA over such a prolonged period (6 decades). Patients aged ≥ 50 years with chest imaging studies suggestive of inflammation in vessel walls and elevated inflammatory markers were also included in the study. Because there were only 5 such subjects, subgroup analysis excluding these subjects was not done.

Study limitations are those inherent in the retrospective design. Some hospitalizations that occurred outside Olmsted County may not have been included; however, such events are usually identified at a followup of resident subjects. In any case, it is not likely that these event rates would have been different between GCA and non-GCA cohort. In addition, statistical power to detect significant differences was limited in our study owing to the small sample size of

our cohorts. Vaccination data were not collected in our study, and so analysis based on vaccination status was not done. Infections not requiring hospitalization were not included in our study because information on outpatient infection episodes was incomplete.

There is no overall increased risk of infections requiring or acquired during hospitalization in patients with GCA taking GC therapy, although there may be an increased risk specifically for GI infections. There also may be an increased risk of infections requiring hospitalization, especially of the urinary tract, in the first 6 months after GCA incidence, although this did not achieve statistical significance in our study. Overall length of hospital stay and duration of antibiotic use is not different in patients with GCA requiring hospitalization because of infection. The conclusions of our study provide useful background information for discussion of chronic GC therapy in patients with GCA.

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