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Hospitalized Infections in Giant Cell Arteritis - a Population Based Retrospective Cohort Study

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Abstract

Objective—We aimed to assess the occurrence of infections requiring or acquired during hospitalizations in patients with giant cell arteritis (GCA).

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

Results—We identified 245 patients in the GCA cohort and 245 patients in the non-GCA cohort. 74 GCA (134 episodes) and 79 non-GCA (153 episodes) subjects had infections requiring, or acquired during hospitalizations [Rate ratio (RR) 0.94; 95% confidence interval (CI) 0.74, 1.18]. 67 subjects (107 episodes) in 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, skin and soft tissue infections accounted for the majority of infections requiring hospitalizations and had similar occurrence in both cohorts. Urinary tract infections 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 two cohorts was noted in overall infections acquired during hospitalizations [RR 0.68; CI (0.41, 1.08)].

Conclusion—There is no overall increased risk of infections requiring or acquired during hospitalizations in patients with giant cell arteritis on glucocorticoid therapy. There may be an increased risk of infections requiring hospitalization, especially of the urinary tract in the first six months after GCA incidence although this did not achieve statistical significance in our study.

Keywords

Giant cell arteritis; infection; hospitalization; cohort studies

Introduction

Giant cell arteritis (GCA) is the most common primary systemic vasculitis which typically affects large and medium-size arteries (1, 2). Glucocorticoids (GC) have been the mainstay of treatment for GCA since 1950s. While some patients are treated with GC for 1-2 years,

others experience recurrent disease relapses and require long term 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 is lacking. We aimed to assess the occurrence of infections requiring or acquired during hospitalizations in patients with GCA.

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 Mayo Clinic, Olmsted Medical Center and their affiliated hospitals, local nursing homes, and the few private practitioners in Olmsted County, MN. The patient identifiers from all medical providers are linked together for each resident of Olmsted County. Persons enter the REP when they first become residents of Olmsted County, Minnesota, 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 has been previously 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 ascending aorta and its branches. The medical charts of all the patients included in the GCA cohort were manually reviewed by one 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 age, sex and calendar year matched cohort from Olmsted County, Minnesota 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 was collected on all documented episodes of infection requiring or acquired during hospitalization after the GCA incidence/index date.

Various infections were defined as physician diagnosis confirmed by the following features as documented in the medical records. Septic arthritis: positive microbiologic culture from joint aspirate fluid. Bacteremia/septicemia: isolation of a pathogenic microorganism from one or more blood cultures, with fever ($>38.0^{\circ}\text{C}$). 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

(LRTI): presence of new infiltrates, consolidation, or effusion seen in chest radiography. 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 gastro-enteritis, colitis, acute cholecystitis, ascending cholangitis, appendicitis, diverticulitis or peritonitis. Other infections such as episodes of meningitis, acute viral illness, herpes zoster, 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. Confidence intervals (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 for patient. Statistical analyses were performed using SAS (SAS Institute, Cary, NC) and R (R Foundation for Statistical Computing, Vienna, Austria).

Results

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

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; 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; 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; 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; 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 confidence intervals for the rates and the rate ratios are large. Due to 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 rate ratios comparing GCA to non-GCA ($p=0.5$).

No difference between the two cohorts was noted in overall infections acquired during hospitalizations [RR 0.69; CI (0.42, 1.09)] (Table 5). Sub-group analysis of the subjects by follow-up duration showed that among those with greater than 20 years of follow-up, GCA subjects had more infections requiring hospitalizations than non-GCA subjects [RR 3.04; 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 hospitalizations.

Discussion

No difference was noted between GCA and non-GCA cohorts in our study in terms of overall infections requiring or acquired during hospitalizations 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 the period 1950-1991, infection was reported in 31% of the GCA patients in an uncontrolled observational study (4). In a French GCA cohort without a comparison cohort, infection rate was found to be even lower at about 16% though the definition of infections is not clear in these studies (8). In our study, the overall rate of infections (including only episodes which required or acquired during hospitalization) was 5.8% in the GCA cohort. It has to be mentioned that none of the above mentioned past 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 that of a registry-based observational study conducted in United Kingdom (UK) in which GCA was found to be a risk factor for increased incidence of UTI and URTI including episodes which 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 GCA patients

who experienced at least one 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 common in GCA cohort in the UK study which is in contrary to other GCA cohorts including ours (11-13). 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 sub-group analysis in our study according to diabetes mellitus status and still did not find any significant difference in the results with respect to 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-wise 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 for infection in our GCA cohort unlikely explains our findings, as our GCA patients were age and sex-matched to the non GCA cohort.

Sub-group analysis of the subjects by follow-up duration showed that among those with greater than 20 years of follow-up, GCA subjects had more infections requiring hospitalizations than non-GCA subjects. However, the numbers of infections were few to draw any conclusions from this observation. Gastrointestinal infections were higher in GCA cohort in our study. Also, UTIs were noted to be significantly higher in the GCA cohort in the first six month post GCA incidence date. This may be explained by the fact that the highest doses of glucocorticoid therapy are used in the first six months following GCA diagnosis (14). We did not find any difference in infections rates between the GCA and non-GCA cohort by sex or calendar year of GCA incidence. We did not have enough subjects in our GCA cohort to examine whether infection rates differed for GCA patients on glucocorticoids alone versus glucocorticoids in combination with methotrexate/other immunosuppressive therapy.

The strengths of this study are that it is population-based and that complete medical record information is available for all subjects. With the exception of a higher proportion of the working population employed in the health care industry, and correspondingly higher education levels, on the whole, results of this study utilizing the population of Olmsted County, Minnesota are generalizable to the populations of interest elsewhere (15). This is the only study to date that has evaluated the occurrence of infections in patients with GCA over such a prolonged period (six decades). Patients aged 50 years of age with chest imaging studies suggestive of inflammation in vessel walls and elevated inflammatory markers were also included in the study. Since 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, MN may not have been included; however such events are usually captured at 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 due to the small sample size of our cohorts. Vaccination data was not collected in our study, and so analysis

based on vaccination status was not done. Non-hospitalized infections were not included in our study as complete information on outpatient infection episodes is incomplete.

To conclude, there is no overall increased risk of infections requiring or acquired during hospitalizations in patients with GCA on glucocorticoid therapy though there may be an increased risk specifically for gastrointestinal infections. There also may be an increased risk of infections requiring hospitalization, especially of the urinary tract in the first six 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. We believe that the conclusions of this study provide useful background information for discussion of chronic glucocorticoid therapy in patients with GCA.

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Table 1

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

	GCA (N=245)	Non-GCA (N=245)	p value
Age, years (SD)	76.2 (8.3)	75.9 (8.5)	0.74
Females	194 (79%)	194 (79%)	1.0
Length of follow-up, years (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
Body mass index, 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

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 *	Non-GCA rate *	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, 49.43)
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 urinary tract infection	27	31	33	48	1.39 (0.96-1.95)	1.89 (1.39-2.50)	0.74 (0.47, 1.14)
Gastrointestinal	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)

** Other infections include osteomyelitis, meningitis, viral influenza, acute viral illness, herpes zoster, presumed viral illness, acute febrile illness of unknown etiology, influenza B

* Rates are reported per 100 person-years

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 *	Non-GCA rate *	Rate Ratio (95% CI)
Overall	67	63	107	110	4.51 (3.7-5.4)	4.32 (3.6-5.2)	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 urinary tract infection	16	18	18	24	0.76 (0.45-1.20)	0.94 (0.60-1.40)	0.81 (0.43, 1.47)
Gastrointestinal	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)

* Rates are reported per 100 person-years

** other infections include meningitis, osteomyelitis, viral influenza, acute viral illness, herpes zoster, presumed viral illness, acute febrile illness of unknown etiology

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-years (95% CI)	Non-GCA Rate per 100 person-years (95% CI)	Rate ratio
0-6 months	7.3 (3.5-13.9)	4.1 (1.3-9.6)	1.79 (0.74-4.81)
7-12 months	3.5 (0.9-8.9)	5.0 (1.8-10.9)	0.72 (0.19-2.39)
>12 months	4.2 (3.3-5.1)	4.1 (3.3-5.0)	1.02 (0.77-1.36)

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)
Gastrointestinal	1	2	1	2	0.042	0.079	0.64 (0.04, 5.00)
Pyelonephritis and/or Urinary Tract Infection	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