Projected Worldwide Disease Burden from Giant Cell Arteritis by 2050

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ABSTRACT. ***Objective.*** To estimate and project the number of people affected worldwide by giant cell arteritis (GCA) by 2050. Modeling the number of people visually impaired as a result of this disease will help establish the projected morbidity and resource burden.

Methods. A systematic literature review up to December 2013 was conducted using PubMed and ISI Web of Science. Studies reporting an incidence rate for GCA were used to model disease incident cases at regional and national levels. United Nations Population Prospect data were used for population projections. Morbidity burden was established through rates of visual impairment. The associated financial implications were calculated for the United States.

Results. The number of incident cases of GCA will increase secondary to an aging population. By 2050, more than 3 million people will have been diagnosed with GCA in Europe, North America, and Oceania. About 500,000 people will be visually impaired. By 2050, in the United States alone, the estimated cost from visual impairment due to GCA will exceed US$76 billion. Inpatient care for patients with active GCA will total about US$1 billion. Management of steroid-related adverse events will increase costs further, with steroid-induced fractures estimated to total US$6 billion by 2050.

Conclusion. Projecting disease burden for GCA on a global scale allows for optimization of healthcare planning and prioritization of research domains. Additional population-based studies are required to more accurately project worldwide disease burden. Our work highlights the future global disease burden of GCA, and illustrates the associated financial implications. (J Rheumatol First Release Nov 1 2014; doi:10.3899/jrheum.140318)

Key Indexing Terms:

GIANT CELL ARTERITIS | INCIDENCE | PREVALENCE
DISEASE BURDEN | BLINDNESS | COSTS

Giant cell arteritis (GCA) is the most common chronic systemic inflammatory vasculitis affecting people aged over 50 years[1]. It has a predilection for medium- and large-sized vessels of the head and neck. Obliteration of the arterial lumen leads to its ischemic complications, such as scalp necrosis, jaw claudication, and optic neuropathy. GCA is associated with significant morbidity, mostly through its detrimental effect on vision. Visual manifestations affect about 30% of patients, though prompt treatment can prevent permanent, irreversible vision loss[1].

The pathoetiology of this disease is not currently fully understood, though it is likely the culmination of both genetic and environmental stressors. There is no pathognomonic laboratory test or marker to identify this disease[2]. The current gold standard to confirm the diagnosis is a temporal artery biopsy (TAB). However, the diagnosis can be made clinically despite a negative biopsy result[3], and although merely a classification criteria for GCA, the 1990 American College of Rheumatology (ACR) criteria are widely used by physicians to help make the diagnosis of GCA[3], as well as frequently used as inclusion criteria in GCA studies.

Despite the availability of new disease-modifying drugs, the mainstay of treatment of GCA involves corticosteroids, which have side effects. More than half of all patients with GCA experience at least 1 adverse effect commonly associated with corticosteroid treatment[4], thereby adding further to the morbidity experienced from this disease.

There are high costs associated with managing GCA, not only because of the social costs attached to visual impairment. Being a relapsing and remitting disease, GCA

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requires frequent followup for disease activity monitoring and in severe cases may require hospitalization. The added costs associated with managing the side effect and complications of immunosuppressive treatment must also be considered when determining the disease cost burden.

This aim of our review is to investigate and model the increase in disease burden of GCA over the next 35 years. United Nations (UN) data suggest that in 2050, more than a third of people living in the developed world will be over the age of 60 years[5]. Thus the global burden of diseases associated with aging, such as GCA, is also set to dramatically increase.

MATERIALS AND METHODS

A systematic review of all publications up to December 2013 was performed using the PubMed and ISI Web of Science databases. The search criteria included "giant cell arteritis OR temporal arteritis OR Horton's disease" and "prevalence OR incidence." Articles written in English, French, or Dutch were reviewed for relevance. Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines were followed[6].

Included studies fulfilled the following criteria: (1) incidence rates were calculated for the studied reference population, (2) a diagnosis of GCA was defined as either having positive TAB, a clearly established clinical definition, or meeting the ACR classification clinical criteria for GCA, and (3) dates of the study period were clearly stated. Articles were excluded if they did not distinguish between GCA and polymyalgia rheumatica. When studies were updates of previous cohorts, the most recent study was used and the most current data were incorporated for calculations.

The UN Department of Economic and Social Affairs World Population Prospect data were used for reference population projections[7]. Annual estimated population size for people over the age of 50 years between 2014 and 2050 was extracted for each country. Incident data from available studies were used to model national trends. Provided there was similar demography, incident rates for provincial regions were extrapolated to represent their reference country and were assumed not to change over time. In world regions, as defined by the UN, where multiple country data were available, median (as well as upper and lower limit) incident case estimates were calculated based on the corresponding incidence data of regional countries. Given the differences in methodology and recruitment design between studies, a weighted metaanalysis was not performed. When only 2 studies were available within a region or continent, the mean rate was used. Incident cases were calculated on an annual basis and then added to provide the total number of cases predicted to be diagnosed with GCA by 2050.

To calculate the projected number of people with visual impairment secondary to GCA, a conservative event rate of 15% was used[1]. This is an acceptable average of the potential permanent visual impairment quoted in different papers. Visual manifestations are usually among the presenting symptoms or develop shortly after the diagnosis in about 30% of patients and range from transient visual symptoms to permanent visual loss, the latter affecting nearly 15% of patients[1]. Our work attempts to model the costs associated with permanent visual impairment from GCA, hence the reason for using this figure.

To determine the likely financial effect of visual impairment from GCA, data from the United States were used as an example. In 2007, the total annual costs associated with visual impairment in the United States was calculated to be US$53,896 per person[8]. Between 1980 and 2004, the mean age at diagnosis of GCA for people in the United States was found to be about 75 years of age[9] and mean life expectancy is predicted to be 83.8 years by 2050[7]. Therefore, by the year 2050, a patient with GCA and visual impairment is expected to live for about 9 to 10 years following diagnosis. Generally, GCA is not thought to alter life expectancy, so this was not incorporated into our model[10]. Hence our method for estimating visual impairment-related costs from GCA in the United States over the next decades consisted of using 15% of the total calculated number of GCA-affected individuals in the United States by 2050, multiplying this figure by US$53,896 to determine the cost burden for 1 year, and then multiplying this further by 10, the average number of years remaining in the lifespan of a GCA-affected individual.

To further highlight the potential financial effect of this disease, an example of a direct cost associated with GCA treatment in the United States was calculated. The quoted cost for managing 44,100 inpatients with GCA in the United States between 1986 and 1990 was estimated to total just over US$355 million[11]. Thus, US$8049 per patient for each admission to the hospital was used for projecting the costs of inpatient care. Projected numbers of inpatient admissions were based on the assumption that those with visual loss, i.e., 15% of the total GCA-affected population in the United States, are likely to require at least 1 episode of inpatient hospital care when diagnosed. Given that GCA generally manifests and is diagnosed well after the age of retirement, no indirect costs (loss of productivity) were considered.

The costs for managing corticosteroid-related complications, an important additional financial burden from GCA, was also calculated. Steroid use in GCA is usually of a prolonged nature. Proven, *et al* suggested that the median time for glucocorticosteroids to be discontinued and permanent remission to occur is 21.6 months[4]. In this paper, in those patients experiencing an adverse event, the median time from initiation of therapy to the first adverse event was 1.1 years. Because most patients with GCA will be undergoing corticosteroid treatment for an average of 1–2 years, there is unfortunately sufficient time for them to experience a complication from the treatment. The incidence of corticosteroid-induced fractures was modeled because it is one of the most common adverse events, occurring in up to 38% of patients with GCA[4]. The cost of managing a corticosteroid-induced fracture for 1 patient was estimated to total US$18,358[12]. Effects of inflation and discounting on healthcare costs were not included in our model and so all figures should be considered in present-day values[13,14].

RESULTS

The search yielded a total of 702 articles in PubMed and 430 in ISI Web of Science database. All relevant publications identified through the ISI Web of Science search had been identified through PubMed. After abstract and full-text review, 14 (2.0%) met the inclusion criteria (Table 1). All of the included studies were retrospective, and detailed their calculated incidence rate for the region within the country of origin. All studies used either primary care databases or hospital medical records to identify the number of people diagnosed with GCA over a particular period, and/or searched histopathology databases to record the number of positive TAB (Table 1).

Data from included studies were used to model the effect of incident cases of GCA (Appendix 1), and summary results for corresponding world regions are displayed in Table 2. There were sufficient country data to calculate the projected number of GCA cases likely to be diagnosed by 2050 within Europe (including Denmark, France, Iceland, Italy, Norway, Spain, Sweden, and the United Kingdom), North America (Canada and the United States), and the Oceania region (Australia and New Zealand). At least 3 million people are expected to be diagnosed with GCA by 2050 in these world regions alone. About half a million

Table 1. Profile of studies reporting annual incidence of giant cell arteritis.

Study, Yr	Country (region/city)	Method of Diagnosis	Study Period	Population Incidence > 50 Yrs of Age (per 100,000 people/yr)
Haugeberg, et al (2003)[15]	Norway (North & West)	ACR criteria	1992–1996	32.4
Baldursson, et al (1994)[16]	Iceland (Nationwide)	ACR criteria	1984–1990	27.0
Nordborg, et al (2003)[17]	Sweden (Gothenburg)	Biopsy proven	1976–1995	22.2
Smeeth, et al (2006)[18]	UK (Nationwide)	Clinical criteria	1990–2001	22.0†
Elling, et al (1996)[19]	Denmark (Nationwide)	Biopsy proven	1982–1994	20.4
Kermani, et al (2010)[9]	USA (Minnesota)	ACR criteria	2000–2004	18.9
Gonzalez-Gay, et al (2007)[20]	Spain (Lugo)	Biopsy proven	2001–2005	12.9
Abdul-Rahman, et al (2011)[21]	New Zealand (Otago)	Biopsy proven	1996–2005	12.7
Bas-Lando, et al (2007)[22]	Israel (Jerusalem)	Biopsy proven or ACR criteria	1980–2004	11.3
Ramstead and Patel (2007)[23]	Canada (Saskatoon)	Biopsy proven	1998–2003	9.4
Barrier, et al (1982)[24]	France (Loire-Atlantique)	Biopsy proven or clinical features	1970–1979	9.4‡
Salvarani, et al (1991)[25]	Italy (Reggio Emilia)	Biopsy proven or clinical features	1980–1988	6.9
Dunstan, et al (2014)[26]	Australia (South Australia)	Biopsy proven	1992–2011	3.2
Pamuk, et al (2009)[27]	Turkey (Northwest)	ACR criteria	2002–2008	1.1

† Reported for people over age 40 years. ‡ Reported for people over age 55 years. ACR: American College of Rheumatology.

Table 2. Regional number of people predicted to be diagnosed with or sight-impaired as a result of giant cell arteritis by 2050.

World Region	Countries Used in Model	No. People Diagnosed, Mean (LL–UL)	No. People Visually Impaired, Mean (LL–UL)
Oceania	Australia and New Zealand	44,229 (17,769–70,689)	6634 (2665–10,603)
North America	Canada and USA	793,836 (527,354 –1,060,318)	119,075 (79,103–159,048)
Europe	France, Norway, Sweden, Iceland, UK, Denmark, Spain, Italy	2,442,274† (794,891–3,732,532)	366,341† (119,234–559,880)
Total	—	3,280,339 (1,340,014–4,863,539)	492,051 (201,002–729,531)

† Calculated as median. LL: lower limit; UL: upper limit.

people are predicted to have permanent visual loss from GCA over the next 35 years (Table 2). The number of incident cases of GCA in these 3 regions is predicted to increase secondary to the increase in population aged over 50 years (Appendix 2). However, in Europe, the peak of incident cases is predicted to occur in 2040, after which the overall population is expected to decline.

If current treatment regimens remain unchanged, over 140,000 patients diagnosed with GCA in the United States will present with acute visual symptoms and receive hospital admission for treatment, such as administration of intravenous corticosteroid (Appendix 3). By 2050, US$1.13 billion is expected to have been spent on inpatient management of visual impairment associated with GCA in the United States. Between 2014 and 2050, the estimated cumulative cost from visual impairment for patients diagnosed with GCA will be US$70.63 billion in the United States alone.

There are significant treatment-related side effects resulting from the use of corticosteroid medication in patients with GCA. Up to 80% of patients with GCA requiring longterm corticosteroids to achieve disease remission will develop a steroid-related adverse event[4]. By 2050, just under 360,000 patients in the United States with GCA are expected to have developed a steroid-induced fracture, at a total estimated cost of management mounting to over US$6.58 billion (Appendix 3).

DISCUSSION

To our knowledge, there have been no previous estimates of the global effect of GCA. Our work highlights the significant morbidity, including visual impairment, and financial effect that GCA is likely to cause in the future. Using currently available incidence data, we have provided a detailed estimate of the projected effect of GCA. It was possible to calculate the projected number of people who are likely to be diagnosed with GCA across North America, Europe, and Oceania. GCA is primarily a disease of whites of European origin and hence, by addressing those world regions, the findings reflect the areas most affected by the disease.

Our work highlights the increasing socioeconomic burden from GCA over the next 35 years, assuming that there are no major breakthroughs in disease screening,

prevention, or treatment. By 2050, an average of 3 million people will have been diagnosed with GCA (Table 2). In the Oceania region, the number of GCA incident cases is predicted to double over the next 35 years.

About 500,000 people will have permanent visual loss from GCA by 2050. Given the variation in reported rates of visual impairment, this figure is likely to underestimate the actual number. Prompt treatment significantly reduces the risk for visual loss. In addition, treatment is expected to mitigate some of these adverse sequelae. However, until prevention or screening for GCA becomes available, early recognition and prompt treatment will remain the main way of mitigating devastating visual complications. Opticians and doctors within all fields of medicine should be aware of the symptoms and signs of GCA and refer appropriately for urgent management.

There are considerable socioeconomic consequences for sudden visual loss secondary to GCA[28]. Many elderly patients who are visually impaired require extensive social support. Across France, Germany, the United Kingdom, and Italy, the rates of institutionalization for visually impaired persons are reported to range from 7.8% to 10.9%[29]. Visual impairment and blindness have important implications for resource allocations, causing marked economic burden[30]. Although cost implications are clearly country-dependent, we found that the total projected cost related to visual impairment from GCA in the United States alone is US$76 billion. The financial implications globally will certainly be much greater.

Additionally, should prolonged steroid treatment remain the primary treatment modality in GCA, there will be additional costs from managing side effects and associated complications. We calculate that, in the United States alone, over 800,000 people with GCA will develop complications from treatment. While the cost of corticosteroids is low, their total costs may be considerably higher when the costs of managing short- and longterm adverse events are considered[12]. In a recent Australian study, about 90% of patients with GCA reported side effects from corticosteroids[26]. This is supported by a Brazilian study that showed a similar proportion (91.1%) of patients with GCA developed a steroid-related complication[31]. In the United States, at least 1 side effect from corticosteroids was identified in 86% of patients with GCA, while 2 or more side effects were reported in just under 60% of patients[4]. We calculated that by 2050, over 350,000 patients will have sustained a steroid-induced fracture in the United States alone. This will cost the US healthcare system an estimated US$6 billion. Again, although costs inevitably vary between countries, this figure puts into perspective the implications of current GCA treatment and potential future global effects.

Our study has highlighted the paucity of available epidemiological data on GCA. It was not possible to predict true global disease burden. While GCA has been most extensively described in European-derived white populations, it is also recognized among people of different ethnic groups (such as Indians, Chinese, Africans, and Latin Americans). In omitting these world regions from our future predicted GCA calculations, especially China and India, which together comprise close to one-third of the world's population, we are substantially underrepresenting the overall effect of this disease worldwide. Prevalence studies in these regions are clearly required to more accurately project the potential global disease burden of GCA.

Case reports and a number of case series have highlighted the fact that GCA can affect people of any racial background. African Americans accounted for 13% of patients with a diagnostic TAB from a hospital-based study in Washington[32]. Similarly, there have been a number of reported cases of GCA among people of Chinese ethnicity[33,34,35]. Interestingly, an increase in prevalence of GCA has been found between 2 Japanese-based studies performed in 1997[36] and 2001–2008[37]. Nonetheless, it has been estimated that the rate of GCA in people of Asian ethnicity is about 20 times less common than their white counterparts[38,39]. There are also reports of GCA in people of Indian descent[40,41].

In Latin America, GCA has been reported among Puerto Rican and Mexican people[42,43]. In a case-control study from Mexico, it was noted that the Mestizo population was more commonly affected compared to Mexican people of white or Spanish ancestry[43]. However, a Brazil-based cohort study found that the vast majority of patients with GCA in their population were of white descent[31]. These differences among Latin American countries illustrate the diversity of ethnic populations within this world region. Given the reported difference in GCA rates between ethnically mixed populations, the projection of the likely number of people affected by GCA in Africa, Asia, and South America could not be undertaken using available white incidence rates.

There are some important caveats to our work. First, the UN population and demographic predictions we used to project incidence may prove to be incorrect. In addition, environmental factors, migration, and globalization of populations add further complexity to calculating future numbers of GCA worldwide. The studies from which the incidence rates were derived used varying methods to identify and define GCA (Table 1). Some were based on clinical diagnosis alone, while others adhered to the ACR classification criteria or histology. The studies identifying GCA only by positive TAB are likely to have underestimated the true incidence rate. GCA cases will have inevitably been missed in some studies and hence our predicted figures will likely be an underestimate of true GCA incident case numbers.

Projecting for countries where only regional study data are available does not take into account variation of the incidence rate within that country and may lead to error.

This is particularly relevant for countries with many different ethnic groups, such as the United States. In California and Tennessee, where there is a larger demographic of Hispanics and African Americans, the incidence rates have been found to be 0.36 per 100,000 and 1.58 per 100,000, respectively[32,44]. For this review, we have used data from the Minnesota study because that is a larger and more frequently repeated study[9]. However, Minnesota has a much larger European-derived white demographic. It is therefore possible that the Minnesota incidence rate is too high to predict GCA for the entire US population. Projecting for world regions, when only data on a few countries within that region are available, assumes similar incidence rates among the countries for which no data are available. We did not project for world regions that lacked sufficient data.

It is well appreciated that women are more commonly affected than men[22]. However, given that only a small number of studies commented on the incidence rate per sex, we were unable to calculate the sex-specific burden of GCA. Nonetheless, this is not likely to dramatically affect the conclusion of our findings.

The reported number of patients with GCA having permanent visual loss varies widely. The literature reports incidence for visual loss anywhere from 6% to 70%[45]. Both the quoted incidence and the definition of visual impairment vary significantly among studies. In addition, information on the degree of visual loss and precise visual defect is often omitted from studies.

We chose to use a recent figure of 15% for the visual loss rate, quoted by Borchers and Gershwin in 2012[1]. This rate is consistent with various current global incidence rates reported in other studies[21,46,47]. The extremely high figures of permanent visual loss from GCA quoted in the earlier literature are probably no longer accurate in view of the early recognition of disease and prompt treatment initiation. Evidence now also suggests that with appropriate and early treatment, vision loss among patients with GCA can improve in about 13% of cases[48].

Although different levels of ocular involvement will result in varying degrees of disability and financial burden, there are cost implications with most forms of visual impairment[49]. Because we were unable to model the costs for the different degrees of visual impairment, we had to make the assumption that all people we predicted to have visual impairment would have some form of permanent visual disability with cost implications. This figure of 15%, although possibly an underestimate of the actual total patient numbers having any form of visual impairment, is likely to represent a fairly accurate percentage of patients who will have a substantial visual deficit with resulting cost burden.

Our study provides an example of the potential cost implications of 1 steroid-induced side effect: steroid-induced fractures. We were unable to model for all potential complications. This cost should only be viewed as an example and not representative of the total costs of steroid-induced side effects in GCA. The risks from corticosteroids are dose, duration, and patient-dependent. Because of the lack of data available, we were unable to account for all these details in our calculations. However, because most patients with GCA will take corticosteroid treatment for an average of 1–2 years, steroid-induced complications are common and hence critical to factor into our disease-burden model.

A factor that could alter our projections is the development of treatment regimens with a more benign side-effect profile. Increases in understanding of the pathogenesis of this disease could lead to more targeted steroid-sparing therapies. There are currently molecules under investigation with many of the beneficial antiinflammatory effects of corticosteroids, but fewer of the adverse effects[50]. However, we are a long way from the use of such agents in GCA. Until a new treatment becomes available, corticosteroids will remain the primary modality of treatment. The aim should therefore be to minimize their potential side effects. This may require a multidisciplinary care approach in which health professionals from various specialist backgrounds monitor the patient as a whole and hence optimize care.

GCA is a potentially devastating disease associated with significant visual morbidity and financial burden. To our knowledge, this is the first paper projecting the likely future disease burden from GCA on a global scale. The elderly population worldwide is increasing, which will likely cause a greater number of GCA incident cases over time. It is estimated that the total number of cumulative incident cases of GCA across Europe and North America alone will exceed 3 million by 2050. Our work highlights the need for further population-based studies to allow for accurate determination of incidence rates. Clearly, additional research into the etiology and treatment of GCA is required. An increased understanding of the mechanisms of this disease could lead to major breakthroughs in disease screening, prevention, and treatment. This would alter the projected disease incidence, visual impairment rates, steroid complications, and hence the overall cost burden associated with this disease.

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APPENDIX 1. Projected change in incident cases of GCA per country and cumulative burden of disease by 2050 in each country.

Country	Proportional Increase in Incident Cases Diagnosed in 2015 and 2050, %	Predicted Total No. Incident Cases by 2050
Australia	169.0	12,488
Canada	147.1	57,840
Denmark	119.9	18,210
France	128.1	98,575
Iceland	167.9	1418
Israel	196.4	12,082
Italy	118.4	74,770
New Zealand	157.9	9282
Norway	149.2	26,833
Spain	140.4	107,725
Sweden	130.1	35,007
Turkey	239.7	11,323
UK	134.3	226,097
USA	142.1	943,690
Total	139.7	1,635,341

GCA: giant cell arteritis.

APPENDIX 2. Projected GCA incident cases for each world region.

Yr	North America	Europe	Oceania
2015	17,643	59,469	866
2020	19,038	62,056	963
2025	20,181	64,323	1065
2030	21,205	66,291	1156
2035	22,238	68,205	1257
2040	23,189	69,628	1355
2045	24,059	69,420	1446
2050	24,711	68,027	1532

GCA: giant cell arteritis.

APPENDIX 3. Projected financial burden associated with 2 possible complications of GCA in the United States by 2050.

Complications from GCA	Projected No. People with GCA Affected in the USA	Total Costs, US$
Visual impairment	141,554	
Initial inpatient costs	—	1,139,364,121
Ongoing support	—	76,291,674,360
Steroid-induced fractures	358,602	6,583,183,327

GCA: giant cell arteritis.