Causes of death in patients with multiple sclerosis from a large US insurance database

AUTHORS

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Introduction

- Multiple sclerosis (MS) is a chronic disease of the central nervous system[1]
  - Data suggest that patients with MS have a life expectancy that is decreased by about 5 to 10 years compared with the general population[2-7]
  - Limited data are available regarding the causes of death (CODs) that account for the excess mortality found in the MS population
- Death certificates typically record up to 4 sequential conditions for categorizing a death in Part I, with the expectation that the immediate COD (the condition that led directly to the death) would be listed first and the underlying COD would be listed last[8]
  - Part II of the death certificate is reserved for conditions that contributed to the death but did not directly lead to the underlying COD[8]
- Death certificate data are not always straightforward to interpret when determining COD for patients with MS because of a lack of uniformity in the way that CODs are recorded
  - MS is frequently listed as the underlying cause, which provides no insight into whether a particular complication of end-stage MS may have actually led to the death
  - Many physicians list cardiorespiratory arrest as the immediate COD; however, this is the final common pathway of all deaths and therefore not informative when attempting to understand what conditions actually led directly to the death
- In many cases, the information provided by the immediate or the underlying COD might not be translatable into increased physician vigilance and improved patient care and therefore an analysis of diseases or injuries that more directly lead to death could be valuable to improve care for patients with MS
- Results from a retrospective cohort study in which survival and mortality patterns in patients with MS drawn from the OptumInsight Research (OIR) database were recently presented[9]
  - Using a matched cohort design, the study showed that mortality rate among patients with MS in the United States (US) was approximately twice that observed among non-MS comparators (899 vs 446 per 100,000 person-years)[9]

Objectives

- The goal of the present study was to gain insight into which CODs contributed to the excess mortality seen in these patients with MS relative to the general insured population
- To accomplish this goal, a novel algorithm for the identification of the condition most directly leading to death on the death certificate (the principal COD) was employed

Methods

Selection of subjects and determination of mortality

- Subjects were drawn from the OIR healthcare claims database
  - OIR is a geographically diverse database of billing claims for >39 million commercially insured individuals in the US
- Patients with MS were selected for inclusion if they met the following criteria:
  - Inclusion in the database for ≥3 months and during the period from 1996–2009
  - ≥2 ICD9-340 diagnosis codes (the code for MS) ≥30 days apart or ≥1 ICD9-340 code and ≥1 billing code for MS disease modifying treatment (DMT)
  - Age ≥18 years at the time of their first ICD9-340 diagnostic code
- Up to 3 non-MS comparators were selected for inclusion if they met the following criteria:
  - Inclusion in the database for ≥3 months and during the period from 1996–2009
  - Same age, sex, and residence region during the year of the first MS/DMT code of the matched patient with MS

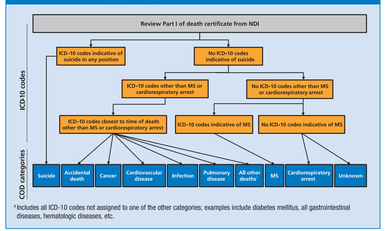
Determination of COD

- Deaths among the selected subjects were identified by linkage with the National Death Index (NDI) and the Social Security Administration Death Master File
  - COD was determined based on the information provided on death certificates for those subjects whose death was identified by linkage with the NDI. All deaths without death certificate information were categorized as being due to an unknown cause

Methods (cont)

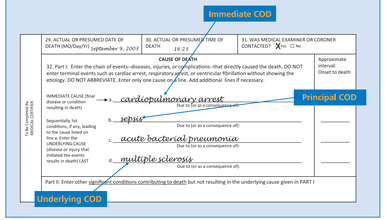
- An expert panel (including a neurologist with MS experience and a physician with death certificate completion experience) identified 8 commonly used primary disease/injury categories into which CODs would be grouped
  - An algorithm to identify the principal COD from death certificate information was developed in order to fit patients into these categories (Figure 1)
  - 2 categories were created for uninformative CODs: cardiorespiratory arrest and unknown
  - The principal COD algorithm used the ICD-10 code closest to the time of death on Part I of the death certificate (Figure 2), with the following exceptions:
    - ICD-10 codes indicative of suicide were always considered the principal COD, regardless of their position on the death certificate
    - MS was considered the principal COD if the only other ICD-10 codes on the death certificate were those indicative of cardiorespiratory arrest or if it was the only COD mentioned in Part I
    - ICD-10 codes indicative of cardiorespiratory arrest were only considered the principal COD if no other codes (including MS) appeared on Part I of the death certificate

Figure 1. Algorithm for determining principal COD and primary disease/injury categories



[a] Includes all ICD-10 codes not assigned to one of the other categories; examples include diabetes mellitus, all gastrointestinal diseases, hematologic diseases, etc.

Figure 2. Sample death certificate[10] indicating different methods of assigning COD



Results

Description of the study population

- Deidentified data for 30,402 cases with MS and 89,818 non-MS comparators were available for analysis (Table 1)
- A total of 1579 deaths (5.2%) were observed in the MS cohort, with 2332 deaths (2.6%) in the non-MS comparators (Table 2)
  - The overall mortality rate among the patients with MS was approximately double that of non-MS comparators (899 vs 446 per 100,000 person-years)
  - The difference in mortality rate between patients with MS and non-MS comparators was an excess of 453 deaths per 100,000 person-years

Table 1: Distribution of patients with MS and non-MS comparators

		OIR Database		
		MS (n=30,402)	Comparator (n=89,818)	%[a]
Sex	Female	23,364	69,102	77
	Male	7,038	20,716	23
Mean (SD) years of age at index		44 (10.8)	44 (10.8)	-
Region	Northeast	3,546	10,395	12
	Midwest	9,822	28,816	32
	South	13,333	39,627	44
	West	3,701	10,980	12
Birth year	1920–1929[b]	335	964	1.1
	1930–1939	979	2,836	3.2
	1940–1949	4,578	13,381	15
	1950–1959	9,436	27,848	31
	1960–1969	8,998	26,727	30
	1970–1979	5,000	14,855	17
	1980–1989	1,060	3,159	3.5
	1990–1999	16	48	0.05
Mean insurance coverage interval	Total[c]	1,510	1,837	-
	Post-index[c]	1,071	610	-
	% time covered	92	86	-
DMT usage		19,359	-	64

[a] Due to the matching, the MS and comparator cohorts had the same distribution of demographic factors.
[b] The birth year for patients born before 1920 was set to 1920 to protect privacy.
[c] Includes gaps in coverage.

Cause-specific mortality rate in the MS cohort using principal, underlying, and immediate COD

- The principal COD approach indicated the highest mortality rate (in descending order of rate) due to cardiovascular disease, infection, MS, and cancer (Table 2)
- According to the underlying COD, the highest mortality rate was attributed to MS, cardiovascular disease, and cancer
  - In contrast to the principal COD, the underlying COD indicated a high mortality rate due to MS (133 vs 286 deaths per 100,000 person-years)
  - Mortality rate due to infections (56 deaths per 100,000 person-years) according to the underlying COD was less than half of that attributed to infections by the principal COD (134 deaths per 100,000 person-years)

Table 2. Number of deaths and mortality rate/100,000 person-years (95% confidence interval) by major disease/injury category according to principal, underlying, and immediate COD

The 3 CODs with the highest mortality rate in the MS cohort are shown in red.

	Principal COD				Underlying COD				Immediate COD			
	MS		Non-MS comparators		MS		Non-MS comparators		MS		Non-MS comparators	
	n	Mortality rate	n	Mortality rate	n	Mortality rate	n	Mortality rate	n	Mortality rate	n	Mortality rate
Cardiovascular disease	325	185 (165, 206)	652	125 (115, 135)	284	162 (143, 182)	595	114 (105, 123)	259	147 (130, 167)	531	101 (93, 110)
Cancer	183	104 (90, 120)	557	106 (98, 116)	221	126 (110, 144)	686	131 (121, 141)	166	95 (81, 110)	486	93 (85, 102)
Infection[a]	236	134 (118, 153)	206	39 (34, 45)	99	56 (46, 69)	130	25 (21, 30)	180	102 (88, 119)	156	30 (25, 35)
Pulmonary disease[a]	136	77 (65, 92)	162	31 (26, 36)	51	29 (22, 38)	126	24 (20, 29)	100	57 (46, 69)	103	20 (16, 24)
MS	234	133 (117, 151)	1	0.2 (0.0, 1.1)	502	286 (261, 312)	1	0.2 (0.0, 1.1)	224	128 (111, 145)	1	0.2 (0.0, 1.1)
Accidental death	76	43 (34, 54)	126	24 (20, 29)	70	40 (31, 50)	140	27 (23, 32)	90	51 (41, 63)	184	35 (30, 41)
Suicide	30	17 (12, 24)	66	13 (9.8, 16)	30	17 (12, 24)	69	13 (10, 17)	2	1.1 (0.1, 4.1)	1	0.2 (0.0, 1.1)
All other deaths[b]	217	124 (108, 141)	342	65 (59, 73)	187	106 (92, 123)	369	71 (64, 78)	169	96 (82, 112)	278	53 (47, 60)
Unknown[c]	129	73 (61, 87)	208	40 (34, 46)	128	73 (61, 87)	207	40 (34, 45)	129	73 (61, 87)	208	40 (34, 46)
Cardiorespiratory arrest	13	7.4 (3.9, 13)	12	2.3 (1.2, 4.0)	7	4.0 (1.6, 8.2)	9	1.7 (0.8, 3.3)	260	148 (131, 167)	384	73 (66, 81)
Overall	1579	899 (855, 945)	2332	446 (428, 464)	1579	899 (855, 945)	2332	446 (428, 464)	1579	899 (855, 945)	2332	446 (428, 464)

[a] Includes pulmonary infection
[b] Excludes pulmonary infection
[c] Includes all ICD-10 codes not assigned to one of the other categories; examples include diabetes mellitus, all gastrointestinal diseases, hematologic diseases, etc.
[d] Includes 333 deaths that did not have death certificate information because they were identified from Social Security records, but not from the NDI, plus a small number of individuals identified from the NDI whose death certificate data were insufficient to assign a COD.

Results (cont)

- The immediate COD indicated the highest mortality rate due to cardiorespiratory arrest, cardiovascular disease, MS, and infection
  - Unlike the principal COD method, the immediate COD indicated the highest rate of mortality as a result of cardiorespiratory arrest (7.4 vs 148 deaths per 100,000 person-years)
  - Morality rate owing to MS was similar using the principal and immediate COD approaches (133 vs 128 deaths per 100,000 person-years)

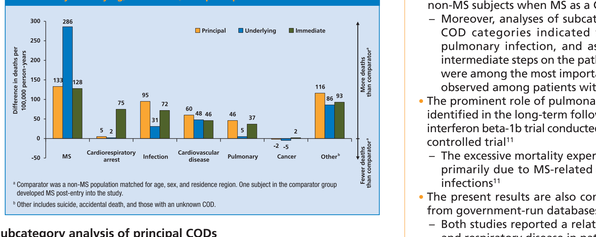
Cause-specific mortality rate in the comparator cohort

- Among the non-MS comparators, the principal COD categories with the highest mortality rate were cardiovascular disease, cancer, infection, and pulmonary disease

Differences in cause-specific mortality rate between the MS and comparator cohorts

- Based on the principal COD algorithm, the largest contributors (other than MS) to the 453 per 100,000 person-years excess in mortality rate between patients with MS and non-MS comparators were: infection (21.0% [95/453 deaths per 100,000 person-years]), cardiovascular disease (13.2% [60/453 deaths per 100,000 person years]), and pulmonary disease (10.2% [46/453 deaths per 100,000 person years]) (Figure 3)
  - Together these 3 principal COD categories accounted for 44.4% of the total difference in mortality (201/453 deaths per 100,000 person-years)
  - Although MS was still the largest category of principal COD, only 29.4% of the overall difference in mortality (133/453 deaths per 100,000 person-years) was attributed to MS
  - Notably, cancer did not contribute to the excess mortality in the MS cohort
- According to the underlying COD, the differences in mortality rate between patients with MS and non-MS comparators were primarily attributed to MS, which accounted for 63.1% of the difference (286/453 deaths per 100,000 person-years)
- Based on the immediate COD method, the differences in mortality rate between patients with MS and non-MS comparators were attributed to MS in 28.3% of the cases (128/453 deaths per 100,000 person-years), cardiorespiratory arrest in 16.6% of the cases (75/453 deaths per 100,000 person-years), and infection in 16.0% of cases (72/453 deaths per 100,000 person-years)

Figure 3. Difference in mortality rate (per 100,000 person-years) between patients with MS relative to non-MS comparators by underlying, immediate, and principal COD



[a] Comparator was a non-MS population matched for age, sex, and residence region. One subject in the comparator group developed MS post-entry into the study.
[b] Other includes suicide, accidental death, and those with an unknown COD.

Subcategory analysis of principal CODs

- Subcategories of infection, pulmonary disease, and cardiovascular disease were assessed to gain greater insight into the prevailing principal COD categories that were particularly important contributors to the excess mortality in the MS cohort (Figure 4)
  - In the infection category, almost all (90.6% [86/95 deaths per 100,000 person-years]) of the excess mortality was attributed to either pulmonary infections or sepsis
  - In the pulmonary disease category, more than half of the difference in excess mortality (58.7%, 27/46 deaths per 100,000 person-years) was attributed to aspiration
  - No single subcategory of cardiovascular disease stood out as a contributor to the excess mortality in the MS cohort

Figure 4. Contribution of subcategories[a] (within infection, pulmonary disease, cardiovascular disease, cancer, and other) of principal COD to differences in mortality rate between patients with MS relative to non-MS comparators

[a] Subcategories were only derived from the following main categories: infection, pulmonary disease, cardiovascular disease, and other. Cancer is only shown as a main category.
[b] Other principal COD subcategories evaluated but for which excess deaths in the MS cohort were <4/100,000 person years included: accidental falls, asthma, chronic obstructive pulmonary disease, decubitus ulcers, dementia, diabetes, hepatic disease, paralytic disease, and renal disease.

Discussion

- The advantage of the principal COD method was that it decreased the number of uninformative causes (cardiorespiratory arrest and MS) that were reported compared with the underlying and immediate COD methods
  - Although CODs in the MS cohort were likely related to MS in the majority of cases, this categorization cannot be leveraged to improve care of patients with MS
  - Relative to the other methods of determining COD, the principal COD was more effective at reducing the mortality rate attributed to MS than the underlying COD and the rate attributed to cardiorespiratory arrest than immediate COD
  - MS still accounted for the highest mortality rate when using the principal COD, likely due to the limitations of the available data
- Using the principal COD method, infection, cardiovascular disease, and pulmonary disease were the most important contributors to the higher mortality rate seen among patients with MS compared with non-MS subjects when MS as a COD was excluded
  - Moreover, analyses of subcategories of these most frequent principal COD categories indicated that certain disease states (ie, sepsis, pulmonary infection, and aspiration), which seem very likely to be intermediate steps on the pathway leading from advanced MS to death, were among the most important contributors to the excessive mortality observed among patients with MS
- The prominent role of pulmonary infections in patients with MS was also identified in the long-term follow-up of patients with MS from the pivotal interferon beta-1b trial conducted 21 years after the start of the randomized controlled trial[11]
  - The excessive mortality experienced by the original placebo group was primarily due to MS-related causes, especially MS-related pulmonary infections[11]
- The present results are also consistent with retrospective data reported from government-run databases in Denmark[2] and Great Britain[12]
  - Both studies reported a relatively high mortality rate due to infection and respiratory disease in patients with MS[2,12]
- Limitations of the current study include
  - The diagnosis of MS was not based on a review of medical records or an examination of the patient. Death certificate data are most often the result of physician judgment. Consequently, the lack of uniform processes for recording CODs can add variability and lead to errors in the data
  - Because the mean age at the first MS diagnostic code was 44 years, inclusion in this study likely commenced a considerable number of years into the patient's illness.[1] Consequently, this study cannot determine which diseases/illnesses commonly result in early death in patients with MS
  - The use of a commercial insurance claims database may not be fully representative of the general population of the US

Conclusions

- Although in the majority of cases MS is the underlying COD, indicative of MS-related death, the principal COD was an informative method of assessing CODs among individuals with a chronic illness such as MS
- Pulmonary infections, sepsis, pulmonary aspiration, and ischemic heart disease were the principal CODs that accounted for the greatest excess mortality in patients with MS compared with non-MS comparators when MS was not considered as a COD
- Increased awareness of these potentially fatal conditions for patients with MS can improve patient care by increasing physician vigilance and facilitating early intervention

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Disclosures

M Corwin has received personal compensation for activities with Bayer HealthCare Pharmaceuticals as a consultant.

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Howard Golub has received personal compensation for activities with Bayer HealthCare Pharmaceuticals as a consultant.

Gary Cutter has consulted and/or participated in Data and Safety Monitoring Committees (DSMB) for the following companies: Apotek, Biogen, Cleveland Clinic, Eli Lilly, GlaxoSmithKline Pharmaceuticals, Medivation, Merck, Modigenetech, NINDS, NMSS, NICHD, NHLBI (Protocol Review Committee), Ono Pharmaceuticals, Prolor, Sanofi Aventis, and Teva. He has also served on Consulting & Advisory Boards for the following companies: Alexion, Abbott, Allozyne, Bayer, Celgene, Consortium of MS Centers (grant), Coronado Biosciences, Diogenix, Medimmune, Klein-Buendel Incorporated, Novartis, Nuron Biotech, Receptos, Somnus Pharmaceuticals, Spinifex Pharmaceuticals, St. Louis University, and Teva Pharmaceuticals. Dr Cutter is employed by the University of Alabama at Birmingham and President of Pythagoras, Inc. a private consulting company located in Birmingham, Alabama, United States.

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Dirk Pleimes is a salaried employee of Bayer HealthCare Pharmaceuticals. He owns stock in Bayer AG, the owner of Bayer Pharma AG/Bayer HealthCare Pharmaceuticals.

Douglas Goodin has participated (or is currently participating) in several industry-sponsored clinical trials in multiple sclerosis; the sponsoring pharmaceutical companies for these trials have included (or do include) Ares-Serono, Merck Serono, Novartis, Berlex Laboratories, Bayer Schering HealthCare, Biogen Idec, Schering AG, and Teva Neuroscience. He has also lectured at both medical conferences and in public on various aspects of the epidemiology, diagnosis, and management of multiple sclerosis, and in many cases these talks have been sponsored directly or indirectly by one or another of the above listed companies. He has served as a temporary ad hoc consultant to several of these organizations on several occasions.

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