Title: Eligibility and implementation of disease-modifying therapy for primary progressive multiple sclerosis in a UK cohort

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Abstract

Background: As disease-modifying therapies become approved for primary progressive multiple sclerosis (PPMS), services must be aligned in readiness.

Methods: In this paper we use population and clinic-based data to estimate eligibility rates for ocrelizumab, and the extent of additional service requirements necessary to ensure its widespread introduction in PPMS.

Results: Overall population estimates for the incidence and prevalence of people with PPMS who are eligible for ocrelizumab are 1.6 and 4.2 per 100,000 respectively. The majority (87%) of incident cases of PPMS satisfied clinical eligibility criteria for ocrelizumab but lacked radiological evidence of disease activity due to a historical tendency not to routinely monitor using MRI in this group. The majority of prevalent patients did not satisfy clinical eligibility criteria for ocrelizumab, mainly because of advanced disease duration or disability.

Conclusions: These findings illustrate the fact that there has been a tendency for people with PPMS not to receive routine clinical and radiological monitoring. Additional planning or resources will be required to facilitate contemporary disease re-evaluation and surveillance at a population level.

Introduction

Primary progressive multiple sclerosis (PPMS) accounts for around 10-15% of prevalent MS.(1) Ocrelizumab, a humanised monoclonal antibody to CD20, recently became the first drug to be licensed for the treatment of adults with PPMS. The European marketing authorisation for ocrelizumab is for early PPMS, Extended Disability Status Scale (EDSS) ≤6.5, with imaging features characteristic of inflammatory activity.

As we enter a new era of DMTs for PPMS, healthcare providers must align resources in readiness. In this paper we report ocrelizumab eligibility rates within a population-based PPMS cohort and test their validity within a clinic-based cohort, to inform on service provisions required for the widespread introduction of DMTs in PPMS.

Method

The South Wales MS registry hosts data from a population-based cohort in Cardiff, Vale of Glamorgan and Cwm Taf (combined population mid-2018: 941,603),(2) identified using prevalence surveys and maintained using prospective data collection methods,(1) and a clinic-based cohort from Royal Gwent Hospital, Newport (estimated catchment population: 591,225).(2) The population-based cohort differs from a clinic cohort in two main ways: it was identified using several data sources, and therefore includes individuals who may not routinely attend clinics, and individuals are followed up systematically including annual EDSS assessment.(1) We screened both cohorts for individuals who had received a diagnosis of PPMS between January 2004 and March 2019 according to contemporary diagnostic criteria of the time,(3–7) (incident) and identified people with a diagnosis of PPMS who were alive and resident within the catchment area on 1st April 2019 (prevalent).

We reviewed medical records of each case to evaluate the rates of clinical eligibility criteria for ocrelizumab defined by: (i) fulfilment of contemporary MS diagnostic criteria,(7) (ii) EDSS score ≤6.5,

(iii) disease duration < 15 years. We also evaluated the proportion of patients who had ever undergone contrast-enhanced or interval MRI of the brain or spinal cord.

Data from the population-based cohort was used to estimate eligibility rates for ocrelizumab, which were then tested for consistency within the clinic-based cohort. Comparisons were made using unpaired t-tests (continuous variables), Mann-Whitney test (EDSS) and chi-squared (categorical variables). Prevalence data was used to calculate the service requirements for drug introduction. Incident data was used to predict on-going annual service requirements. The study of data from this cohort has been approved by the South East Wales Research Ethics Committee (ref no.05/WSE03/111).

Results

Incident cohort

We identified 134 individuals who received a diagnosis of PPMS between 2004-2019. Two were excluded from analysis (clinic cohort) due to lack of EDSS data. Clinico-demographic features are shown in table 1. Overall, 115 out of 132 (87%) fulfilled clinical eligibility criteria for ocrelizumab at the time of diagnosis (figure 1A). Failures to meet criteria were the result of: EDSS (6%), insufficient evidence to fulfil contemporary diagnostic criteria (5%) and disease duration (3%).

MRI brain +/- spinal cord data was available for 130 out of 132 patients (98%). Only 48 (36%) had had adequate MR imaging to evaluate disease activity (either interval or contrast-enhanced MRI), of whom 22 (46%) had radiological evidence of disease activity. Overall, 21 out of 132 (16%) fulfilled all eligibility criteria for ocrelizumab.

INCIDENT COHORT			
	Clinic-based (n=39)	Population-based (n=93)	p value
Mean age at diagnosis (y)	50.2	53.4	0.10
Mean disease duration at	4.3	4.7	0.96

diagnosis (y)			
Median EDSS at diagnosis	5.5	5.5	0.71
Median interval from diagnosis to baseline EDSS (months)	15.3	7.9	**0.02**
CSF performed (n, %)	37 (95%)	85 (91%)	0.62
OCB positive (n, %)	32 out of 37 (86%)	77 out of 85 (91%)	0.80
Clinically eligible for ocrelizumab (n, %)	34 (87%)	81 (87%)	0.58
MRI performed (n, %)	38 (97%)	92 (99%)	0.52
Radiological evaluation of disease activity (n, %)	10 (26%)	38 (41%)	0.10
MRI active (n, %)	5 out of 10 (50%)	17 out of 38 (45%)	0.44
Fully eligible for ocrelizumab (n, %)	5 (13%)	16 (17%)	0.53
PREVALENT COHORT			
	Clinic-based (n=53)	Population-based (n=116)	p value
Mean age at censor date (y)	62.2	63.9	0.37
Mean disease duration at censor date (y)	18.6	16.8	0.21
Median EDSS at censor date	6.5	6.5	0.78
Mean interval from most	51.7	13.7	**<0.0001**

recent EDSS to censor date (months)			
CSF performed (n, %)	42 (80%)	100 (86%)	0.25
OCB positive (n, %)	35 out of 42 (83%)	90 out of 100 (90%)	0.11
Clinically eligible for ocrelizumab (n, %)	11 (21%)	39 (34%)	0.09
MRI performed (n, %)	50 (94%)	106 (91%)	0.61
Radiological evaluation of disease activity (n, %)	14 (26%)	39 (34%)	0.33
MRI active (n, %)	6 out of 14 (43%)	18 out of 39 (46%)	0.47
Fully eligible for ocrelizumab (n, %)	2 (4%)	6 (5%)	0.69

Table 1. Clinical and demographic features of the clinic and population-based cohorts. **CSF** cerebrospinal fluid examination, **EDSS** Expanded disability status scale, **OCB** oligoclonal bands.

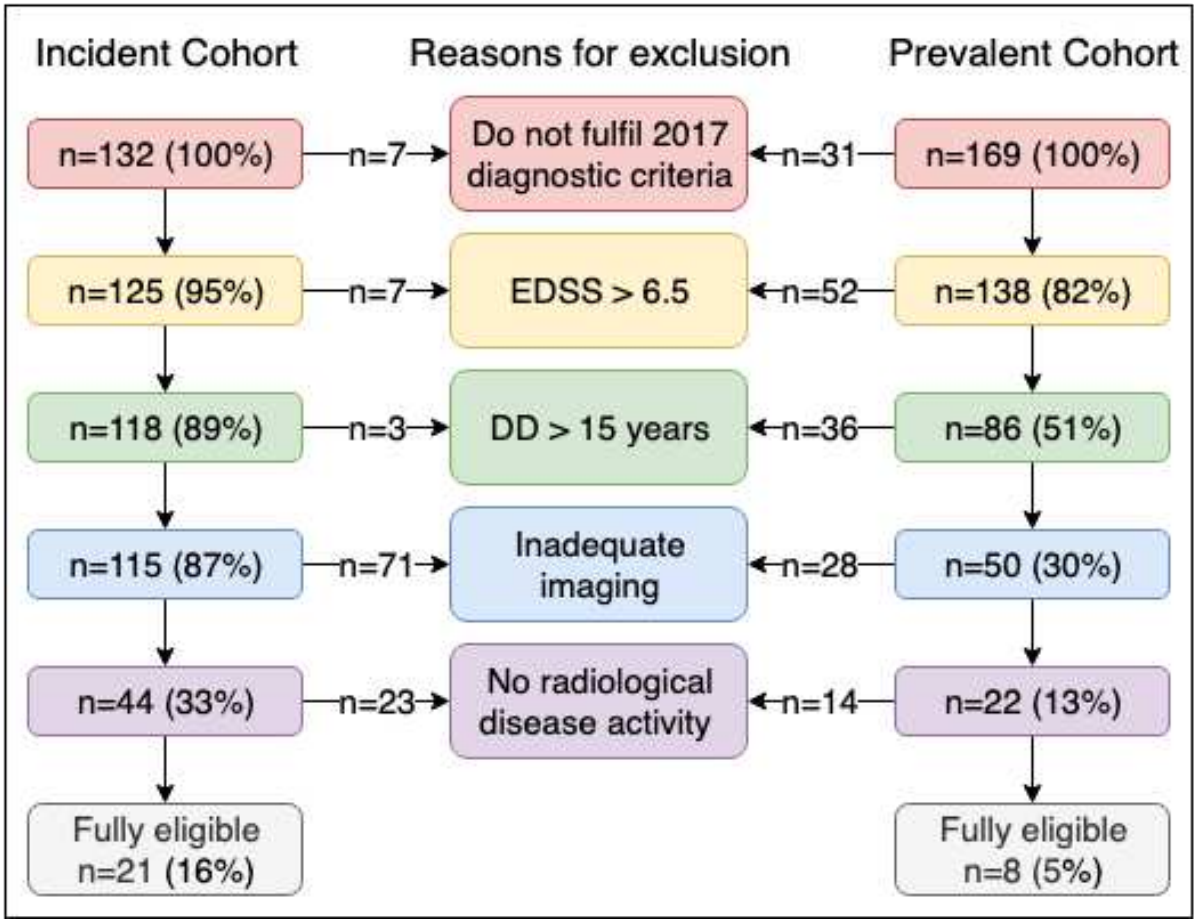
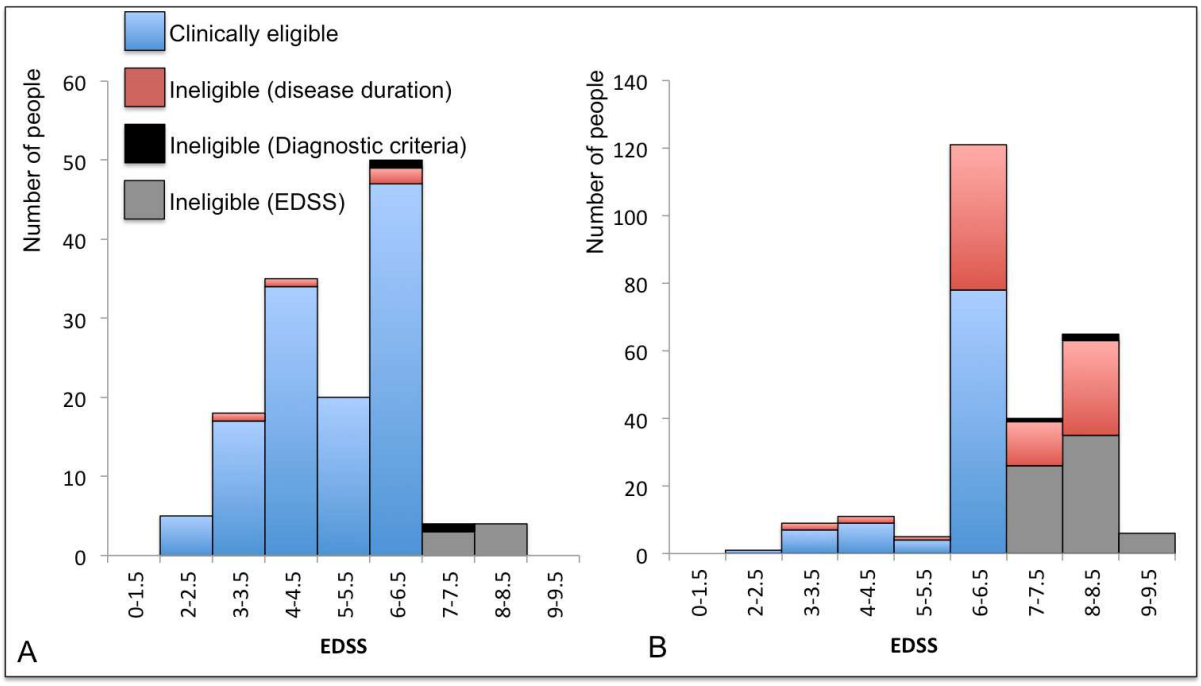


Figure 1. Flow chart illustrating eligibility of the incident and prevalent cohorts for ocrelizumab according to sequential criteria.

Prevalent cohort

We identified 169 people currently resident with a diagnosis of PPMS. Clinico-demographic features are shown in table 1. Overall, 50 people (30%) fulfilled clinical eligibility criteria for ocrelizumab according to their most recent EDSS (figure 1B); 63 (37%) failed on one criterion and 56 (33%) on 2 or more. Failures were the result of: disease duration (53%), EDSS (41%), and insufficient evidence to fulfil contemporary diagnostic criteria (18%).

MRI brain +/- spinal cord data was available for 157 (93%) people. Only 53 (31%) had had adequate MR imaging to evaluate disease activity, of whom 24 (45%) had radiological evidence of disease



activity. Overall, 8 out of 169 (5%) patients fulfilled all eligibility criteria for ocrelizumab.

Figure 2. Bar charts illustrating rates of clinically eligibility for ocrelizumab within (A) incident and (B) prevalent PPMS population-based cohorts. Clinical eligibility was defined by (i) fulfilment of contemporary MS diagnostic criteria,(7) (ii) EDSS score ≤6.5, (iii) disease duration < 15 years.

<u>Comparison of population-based and clinic-based cohorts</u>

The interval from diagnosis to baseline EDSS and from most recent EDSS to censor date were longer in the clinic-cohort than the population-based cohort. Allowing for this discrepancy, eligibility estimates derived from the population-based cohort appeared to be in line with findings within the clinic-based cohort. Using data from our population-based cohort, we estimate that there are 4.2 per 100,000 (95% CI 2.9-5.5) prevalent cases of PPMS who are clinically eligible for ocrelizumab, up to 45% of whom will be fully eligible based on estimated rates of radiological disease activity. An

additional 0.6 per 100,000 (95% CI 0.3-1.4) clinically eligible incident cases would be expected per year, up to 46% of whom will be fully eligible. Services need to be aligned to provide contemporary re-evaluation of prevalent cases and surveillance of incident cases using clinical and MRI evaluation.

Discussion

In this review of a UK cohort of people with PPMS, we found that 87% of incident cases and 30% of prevalent cases of PPMS fulfilled clinical eligibility criteria for ocrelizumab. However, only 16% and 5% currently fulfil all eligibility criteria for ocrelizumab owing to the low availability of interval or contrast-enhanced MRI in this patient-group. Given that radiological evidence of disease activity was detected in almost half of individuals who had evaluation of radiological disease activity, true eligibility rates for ocrelizumab in incident and prevalent PPMS cohorts could approach 40% and 15% respectively. These data are expected to be of utility in planning service requirements for the widespread introduction of ocrelizumab for PPMS.

Our data, highlight a historical lack of clinical and radiological surveillance, for people with PPMS. Those within the clinic-based cohort had experienced a significantly longer interval since their most recent EDSS evaluation versus a systematically studied population-based cohort, implying that people with PPMS may have a tendency to become detached from routine services. Diagnostic criteria for PPMS have also evolved over time; individuals diagnosed prior to 2001 may need additional tests in order to satisfy more stringent contemporary diagnostic criteria. The need to enhance the amount of clinical and MRI surveillance within the routine care framework for people with progressive MS must be considered when planning services to implement emerging therapies.

We accept that this study is subject to limitations. It is difficult to know the extent to which the population and practice in South Wales reflects other MS centres. We chose to limit our analysis to the eligibility criteria for ocrelizumab, the first drug to reach the market for PPMS. However, we

expect data from this cohort, which is likely to represent the manner in which many contemporary cohorts in developed countries were managed during this period, to have practical relevance in aiding services to plan for the emergence of other DMTs for PPMS. We acknowledge that MRI data in this study was incomplete and that the selection of individuals with PPMS for MRI may have been biased towards a particular subpopulation, e.g. those with more clinical evidence of disease activity. The presence of this potential confounder makes it important to cautiously interpret our estimates of full eligibility.

Conclusions

Up to 40% of incident cases of PPMS may be eligible for ocrelizumab. Resources beyond drug costs must be aligned to enable the recall prevalent PPMS cases, and ensure robust clinical and imaging surveillance of incident cases as DMTs emerge.

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