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Title:
Effectiveness of cladribine compared to fingolimod, natalizumab, ocrelizumab and alemtuzumab in relapsing-remitting multiple sclerosis

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ABSTRACT

Background:
Comparisons between cladribine and other potent immunotherapies for multiple sclerosis are lacking.

Objectives:
To compare the effectiveness of cladribine against fingolimod, natalizumab, ocrelizumab and alemtuzumab in relapsing-remitting multiple sclerosis.

Methods:
Patients with relapsing-remitting multiple sclerosis treated with cladribine, fingolimod, natalizumab, ocrelizumab or alemtuzumab were identified in the global MSBase cohort and two additional UK centres. Patients were followed for >=6/12 and had >=3 in-person disability assessments. Patients were matched using propensity score. Four pairwise analyses compared annualised relapse rates and disability outcomes.

Results:
The eligible cohorts consisted of 853(fingolimod), 464(natalizumab), 1131(ocrelizumab), 123 (alemtuzumab), or 493(cladribine) patients. Cladribine was associated with a lower ARR than fingolimod (0.07vs0.12, p=0.006), and a higher ARR than natalizumab (0.10vs0.06, p=0.03), ocrelizumab (0.09vs0.05, p=0.008), and alemtuzumab (0.17vs0.04, p<0.001). Compared to cladribine, the risk of disability worsening did not differ in patients treated with fingolimod (HR1.08, 95%CI 0.47-2.47) or alemtuzumab (0.73, 0.26-2.07), but was lower for patients treated with natalizumab (0.35, 0.13-0.94) and ocrelizumab (0.45, 0.26-0.78). There was no evidence for a difference in disability improvement.

Conclusion:
Cladribine is an effective therapy that can be viewed as a step-up in effectiveness from fingolimod, but is less effective than the most potent intravenous multiple sclerosis therapies.

INTRODUCTION

Cladribine triggers lymphocyte apoptosis by inhibiting DNA synthesis and repair.[1] The superiority of cladribine over placebo in the treatment of relapsing-remitting multiple sclerosis (MS) was shown in the CLARITY randomised clinical trial, where 3.5mg/kg over two years reduced the frequency of relapses by 57%, and disability worsening by 33%.[2]

Since the CLARITY trial was placebo controlled, the comparative effectiveness of cladribine has not been studied in a randomised setting. In the absence of evidence from randomised trials, carefully designed observational studies can be used to compare the effectiveness of therapies, and subsequently guide treatment decisions.[3] A recent study from the MSBase registry concluded that cladribine was superior to other oral MS therapies (fingolimod, dimethyl fumarate and teriflunomide) in reducing relapses, and in treatment persistence.[4] A small number of head-to-head comparisons were of insufficient duration or power to evaluate disability outcomes, used merged data from registries and randomised trials, or did not compare cladribine to highly-effective therapies.[5-7] In particular, no generalisable information exists about the effectiveness of cladribine compared with ocrelizumab or alemtuzumab. In practice, cladribine is viewed as a highly-effective therapy suitable for patients with highly active MS who are at risk of accumulating disability.[8-10] Benchmarking cladribine against the most effective available therapies is therefore an unmet need essential for guiding evidence-based treatment selection.

In this study, we have emulated a trial comparing relapse activity, disability accumulation, and disability improvement among MS patients treated with cladribine and four other highly-effective and widely used MS therapies: fingolimod, natalizumab, ocrelizumab and alemtuzumab.

METHODS

Database and population

Longitudinal patient data were extracted from MSBase[11], an international observational MS registry, and from two non-MSBase centres in the United Kingdom (Cambridge and Cardiff). The study was approved by the Melbourne Health Human Research Ethics Committee and local ethics committees in all centers. Written informed consent was obtained from all patients.

Patients with relapsing-remitting MS[12-14] who had been treated with cladribine, fingolimod, natalizumab, ocrelizumab or alemtuzumab between January 2018 and March 2023 were assessed for study inclusion. Inclusion criteria were: no prior treatment with haematopoietic stem cell transplantation, alemtuzumab or cladribine; no treatment with mitoxantrone in the preceding 3 years or anti-CD20 therapy in the preceding 12 months; minimum recorded follow-up (6-months before, and at least two disability scores ≥6 months apart after, treatment start); a minimum data set including sex, age, MS symptom onset, relapse dates, MS course and disability score at treatment start (within 6-months before and 1-month after starting therapy). Only in-person disability assessments were included.

For each pairwise treatment comparison, patients who received the comparator therapy before study inclusion were excluded.

Procedures

Treatment protocols for cladribine (1.75mg/kg in year 1; 3.5mg/kg over two years), fingolimod (0.5mg daily), natalizumab (300mg monthly), ocrelizumab (600mg 6-monthly) and alemtuzumab (12–24 mg intravenous once per day for 5 days [cycle 1] or for 3 days [subsequent cycles]), are described elsewhere.[2, 15-18] Baseline was the first commencement of a study therapy after January 2018. Patients were censored at the last recorded EDSS score, irrespective of change in treatment status (intention-to-treat contrast of interest).

Data were entered into the MSBase data entry system or local data entry systems as part of routine clinical practice and mostly at tertiary MS centres. The data entry procedures were consistent across both MSBase and non-MSBase centers. MRI data were included as reported by local radiologists based on local protocols. An MRI brain performed within 12 months before, and 1 month after, baseline was considered the baseline MRI. Missing baseline MRI data were addressed through multiple imputation.[19, 20]

A rigorous data quality assurance procedure was followed (eTable 1).[21]

Study endpoints

The primary study outcome was annualised relapse rate (ARR); secondary study outcomes were cumulative hazards of relapses, disability accumulation events, and disability improvement events.

Relapses were defined as new symptoms, or exacerbation of existing symptoms, for at least 24 hours in the absence of a concurrent illness or fever, and occurring ≥30 days after a previous relapse.[22]

Disability was quantified using the Expanded Disability Status Scale (EDSS). Disability accumulation was defined as an increase in EDSS by ≥1 step (1.5 step if EDSS 0, or 0.5 step if EDSS>5.5), confirmed over ≥6 months (in the absence of a relapse in the preceding 30 days), and sustained until the end of follow up. Disability improvement was defined as a decrease in EDSS by ≥1 step (1.5 steps if EDSS 1.5, or 0.5 step if EDSS>6) confirmed over at least 6 months.[23]

Statistical analysis

Four separate matched analyses of cladribine versus fingolimod, natalizumab, ocrelizumab or alemtuzumab were performed. Individual patients were matched, at baseline, on their propensity of being treated with cladribine conditional on clinicodemographic characteristics. Propensity scores were calculated using a multivariable logistic regression model containing the following baseline variables: age, sex, EDSS, MS duration from first symptom, number of relapses in the prior 12 months, disease activity in the prior year (relapses/ disability progression/both relapses and disability progression/no activity), number of prior MS immunotherapies, the most effective previously used treatment (categorised as high-efficacy [natalizumab, rituximab, ocrelizumab, ofatumumab, mitoxantrone], moderate-efficacy [fingolimod, dimethyl fumarate], low-efficacy [interferons β, glatiramer acetate, teriflunomide] or no therapy), presence/absence of new T2 or contrast-enhancing brain MRI lesions, MRI T2-lesion burden (1-2, 3-8, or ≥9 lesions), registry and country.[24]

In the absence of a baseline MRI brain, missing values were imputed using a multiple imputation with an expectation maximisation with bootstrapping algorithm based on treatment group, age, MS duration, EDSS, pre-baseline disease activity, pre-baseline therapy and time since preceding therapy.[19, 25] A sensitivity analysis was conducted after loosening the assumption of missingness-at-random. Normalised weights were used to estimate inferences within the dataset assuming MRI missingness not at random.[26] The relationship between clinical and demographic variables and the absence of MRI data was assessed using multivariable logistic regression, with selection of δ guided by a published algorithm.[27]

Patients were matched, without replacement, in a variable (3:1 to 5:1) matching ratio by nearest neighbour matching within 0.1 standard deviations of the propensity score.[28] The matching ratio specifies the maximum allowed number of control units in each matched pair. Covariate balance was assessed using standardised mean differences. All subsequent analyses were performed using paired models, weighted to account for variable matching ratio. Within each matched patient pair, follow-up was censored at the shorter of the two follow-up periods (pairwise censoring) to mitigate differential treatment persistence and attrition bias. The last eligible timepoint for 6-month confirmed disability outcomes was 6-months before the censor date to ensure adequate follow-up for confirmation. ARRs were compared using a marginal negative binomial model with cluster term for matched patient set. Cumulative hazards of relapses, disability accumulation, and disability improvement events were analysed with weighted conditional proportional hazards models for recurrent events, adjusted for visit frequency for disability outcomes. Schoenfeld's global test was used to evaluate the proportionality assumption. The robustness of our findings to unidentified confounders was calculated using Rosenbaum sensitivity test for Hodges-Lehmann Γ.[29]

A sensitivity analysis required >= 18 months follow-up for all patients. In a further sensitivity analysis data were censored at treatment discontinuation, commencement of subsequent therapy, or the last recorded EDSS, whichever occurred first. For this analysis, the duration of treatment effect was presumed based on pharmacokinetics, or previous evidence: cladribine 4years, alemtuzumab 5years, ocrelizumab 270days, natalizumab 60days and fingolimod 30days. Treatment discontinuation was assessed using weighted conditional proportional hazards models without pairwise censoring. The analysis was also repeated using inverse probability of treatment weighting.

Data were analysed using R, v4.2.1 (R CoreTeam).

RESULTS

Of 30142 patients with MS who were ever treated with a studied therapy, a total of 853 (fingolimod), 464 (natalizumab), 1131 (ocrelizumab), 123 (alemtuzumab) and up to 493 (cladribine) patients fulfilled inclusion criteria (Figure 1; eTable 2). The clinicodemographic details of the included population were similar to those of patients ever received studied therapy but were excluded from the analysis (eTable 3).

Prior to matching, the four treatment groups differed in their baseline characteristics (eTable 4). The probability of being treated with either therapy was calculated using a logistic regression model (eTable 5). Patients treated with cladribine were less likely to have received a high-efficacy therapy than patients treated with alemtuzumab, ocrelizumab or natalizumab, had lower EDSS scores than patients treated with alemtuzumab and ocrelizumab, and were older than patients treated with natalizumab.

Table 1 shows the characteristics of the matched cohorts for all four pairwise primary analyses. Characteristics of patients who were excluded by the matching procedure are in eTable 6. Propensity score matching resulted in 86%-98% improvement in balance between the matched groups, with standardised mean differences of <10% (Table 1; eFigure 1; eFigure 2). Mean pairwise censored follow-up ranged from 1.8 to 2.1 years. Patient numbers allowed assessment of relapses for up to 3years for alemtuzumab, 3.5years for natalizumab, and 4years for fingolimod and ocrelizumab. Disability outcomes were evaluated for up to 2.5 years for fingolimod, natalizumab, and ocrelizumab, and 2years for alemtuzumab.

Effectiveness

Fingolimod vs cladribine

198 cladribine-treated patients were matched with 403 patients treated with fingolimod (Table 1). On average, patients received one prior MS therapy (low-efficacy in 48-52%), and a mean EDSS of 1.8. The mean ARR was higher in patients treated with fingolimod than cladribine (mean [SD], ARR 0.12[0.30] vs 0.07[0.23], Figure 2A). Similarly, the cumulative hazard of relapses was higher for fingolimod than cladribine (HR=1.71, 95%CI 1.12-2.63, Figure 2B). The difference was robust to unmeasured confounding to the magnitude of >100% of the cumulative effect of the measured confounding using Rosenbaum sensitivity test for Hodges-Lehmann Γ. There was no evidence for a difference in disability accumulation (HR=1.08, 0.47-2.47, Figure 2C) or disability improvement (HR=0.38, 0.13-1.1, Figure 2D) between groups.

Natalizumab vs cladribine

220 patients treated with cladribine were matched with 331 natalizumab patients. On average, patients received one prior MS therapy (moderate-efficacy in 45%), and had a mean EDSS of 2.1. The mean ARR was lower in patients treated with natalizumab than cladribine (ARR

0.06[0.22] vs 0.10[0.30], Figure 3A). Furthermore, both the cumulative hazard of relapses (HR=0.55, 0.33-0.93, Figure 3B) and disability accumulation (HR=0.35, 0.13-0.94, Figure 3C) were lower for natalizumab than cladribine. The difference in relapses was robust to the magnitude of 20% of the measured confounding (Hodges-Lehmann Γ). There was no evidence for a difference in disability improvement (HR=0.65, 0.36-1.17).

Ocrelizumab vs cladribine

380 cladribine-treated patients were matched with 667 ocrelizumab patients. The mean age was 42 years, EDSS 2.4, and patients had received 2 previous MS therapies (43% moderate-efficacy, 18% high-efficacy). The mean ARR was lower in patients treated with ocrelizumab than cladribine (ARR 0.05[0.18] vs 0.09[0.27], Figure 4A). Furthermore, both the cumulative hazards of relapses (HR=0.61, 0.42-0.88, Figure 4B), and disability accumulation (HR=0.45, 0.26-0.78, Figure 4C) were lower for ocrelizumab than cladribine. The difference in relapses was robust to unmeasured confounders to the magnitude of 40% of the measured confounding (Hodges-Lehmann Γ). There was no evidence for a difference in disability improvement (HR=0.8, 0.5-1.29, Figure 4D).

Alemtuzumab vs cladribine

173 cladribine-treated patients were matched with 68 alemtuzumab patients with a mean EDSS of 2.8, 2 previous MS therapies (48% moderate-efficacy, 27% high-efficacy), and recent disease activity in 60% of patients indicative of active MS. Both the mean ARR (ARR 0.04[0.19] vs 0.17[0.38], Figure 5A), and cumulative hazards of relapses (HR=0.25, 0.10-0.65, Figure 5B) were lower in patients treated with alemtuzumab than cladribine. The difference was robust to unmeasured confounders to the magnitude of 80% of the measured confounding (Hodges-Lehmann Γ). There was no evidence for a difference in disability

accumulation (HR=0.73, 0.26-2.07, Figure 5C) or improvement (HR=1.3, 0.50-3.38, Figure 5D). The analysis was sufficiently powered to detect a minimum difference of 79% cumulative hazard of disability accumulation, and 73% disability improvement (based on 200 simulations at $1-\beta=0{\cdot}8$).

Sensitivity analyses

Sensitivity analyses (i) where patients were censored at the discontinuation of studied therapy, and (ii) where all patients were followed for >= 18 months after baseline, largely confirmed the results of the primary analysis (eTable 7). Inverse probability of treatment weighting was not superior to matching and provided consisted results. In keeping with the presumed duration of treatment effect, patients treated with cladribine were reported as more persistent on therapy than those treated with fingolimod, natalizumab or ocrelizumab, but not alemtuzumab (eFigure 3). All results were fully replicated with imputation of missing MRI data under the missing-not-at-random assumption.

DISCUSSION

In the expanding MS treatment landscape, understanding of the comparative effectiveness of available therapies is paramount to optimising patient outcomes. In this observational, propensity-score matched analysis of the global observational MSBase registry and two additional UK centres, we have studied the effectiveness of cladribine compared with four therapies commonly used in relapsing-remitting MS. Cladribine was superior to fingolimod, but inferior to natalizumab, ocrelizumab and alemtuzumab in reducing relapse activity. In addition, treatment with cladribine was associated with a greater probability of disability accumulation than natalizumab and ocrelizumab.

A previous inverse probability of treatment-weighted analysis from MSBase including 445 ocrelizumab-treated and 76 cladribine-treated patients suggested lower relapse rates for ocrelizumab than cladribine after cessation of fingolimod.[7] Our present study expands on this initial observation and generalises the conclusions to a broad range of clinical scenarios representative of the prevalent MS population. This study supports treatment with ocrelizumab as a step up in effectiveness compared to cladribine, with superior effect on both relapses and disability accumulation. Furthermore, this study is the first to compare the effectiveness of alemtuzumab and cladribine, describing superiority of alemtuzumab in suppressing relapses. The lack of an observed difference in disability outcomes between these two immune reconstitution therapies may be attributable to the characteristics of the matched cohort, who had moderate baseline EDSS scores (2.8-2.9), a high proportion of patients with a recent relapse/disability accumulation, and a modest follow-up period of 2 years.

The clinical scenarios within which treatments are used can influence the observed differences between compared therapies, and should therefore be carefully considered in study design.[30] For example, patients in the cladribine vs alemtuzumab pairwise comparison had the highest disease activity. The effectiveness of cladribine was compared to interferon-beta, fingolimod and natalizumab in a small, non-overlapping pilot study from MSBase.[5] Patients in this early study received cladribine as part of the Australian Product Familiarisation Program(2011), and outcomes were evaluated over a 1-year period. Cladribine was comparable to fingolimod and inferior to natalizumab in reducing relapses and disability accumulation and was more frequently associated with disability improvement than either fingolimod or natalizumab. Caution is advised in interpreting the pilot study results due to small cohort size, exposure to a single cladribine cycle for many patients, and a follow-up duration too short to draw definitive conclusions about disability. A further study from MSBase, using a more contemporary cohort, also suggested that cladribine is superior to fingolimod in reducing relapse activity.[4] A study that combined data from the Italian MS registry and the CLARITY trial in treatment-naive patients with MS reported relapse outcomes that seemed comparable between fingolimod and cladribine.[6] However, whether treatment groups from registries can be compared to those from randomised trials is unclear.

Finally, our finding that natalizumab is superior to cladribine in reducing relapses concurs with previous reports.[5-7] Unlike the previous studies, however, our present study has found evidence for superiority of natalizumab over cladribine by showing a 65% reduction in the cumulative hazards of disability accumulation over 2.5-years.

Network meta-analyses combine direct and indirect evidence from multiple studies, assuming transitivity and consistency of observations.[31] This offers an alternative analytical approach for comparing treatments in the absence of randomised clinical trials. Our findings align with a network meta-analysis comparing cladribine to various therapies across 41 studies, ranking it fourth in effectiveness, behind alemtuzumab, ocrelizumab and natalizumab.[32] The use of different methodological approaches, each with their own limitations and assumptions, to arrive at similar conclusions provides additional confidence in the findings.

The most significant limitation of this study is its observational nature.[33] We have however performed a carefully designed propensity score matched analysis to minimise treatment indication and attrition bias, informative censoring and ensure that positivity assumption is satisfied. While this approach reduces measured confounding, it doesn’t eliminate it, leaving observational studies vulnerable to potential unmeasured confounding. We have therefore demonstrated that all analyses were robust to unmeasured confounders of a magnitude of >20% of the cumulative measured confounding. We improved homogeneity of disability assessments by excluding telehealth assessments, and ensuring Neurostatus certification at all centres.[34] Despite accessing data from the largest MS registry and two additional centres, the comparison of disability outcomes for alemtuzumab lacked statistical power. We report the effectiveness of cladribine in groups of patients with comparable baseline characteristics treated in common clinical contexts. Results may however not be generalisable to all patient populations, such as patients who are treatment naïve. The current analysis used an 'intention-to-treat' approach to evaluate the effectiveness of 3.5mg/kg cladribine over the available subsequent follow-up. Results were consistent using an 'as-treated' approach, using a presumed 4-year duration of treatment effect. Rigorous evaluation of the duration of treatment effect or the value of additional treatment doses would, be best pursued in a separate study. While treatment safety and patient comorbidities are important components of disease management, these data were not available for inclusion in the present study. Since information about pre-baseline MRI activity was only available for a subset of patients, we utilised multiple imputation. As previously described, this approach produces no difference in outcomes among patients with baseline MRI available.[20, 35] Limited information about MRI activity however precluded the evaluation of radiological outcomes.

Our findings support cladribine as an effective therapy for the treatment of relapsing-remitting MS. While we show a superior effectiveness of natalizumab and ocrelizumab on reducing relapses and disability accumulation compared to cladribine, the magnitude of this difference is small, and equates to a reduction by one relapse every 25 patient-years. Compared to cladribine, alemtuzumab reduced relapses by one relapse every eight patient-years. On the contrary, the effectiveness of cladribine was clearly superior to fingolimod in preventing relapses (reduction by one relapse every 20 patient-years). Clinical application of these findings remains complex, and requires careful consideration of multiple factors, including cost, safety, and convenience. The results however help to place cladribine in the context of other MS therapies and suggest that cladribine can be viewed as a step-up in effectiveness from fingolimod, but less effective than the most potent intravenous therapies.

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T. Kalincik served on scientific advisory boards for MS International Federation and World Health Organisation, BMS, Roche, Janssen, Sanofi Genzyme, Novartis, Merck and Biogen, steering committee for Brain Atrophy Initiative by Sanofi Genzyme, received conference travel support and/or speaker honoraria from WebMD Global, Eisai, Novartis, Biogen, Roche, Sanofi-Genzyme, Teva, BioCSL and Merck and received research or educational event support from Biogen, Novartis, Genzyme, Roche, Celgene and Merck.

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DATA ACCESS, RESPONSIBILITY AND ANALYSIS

IR and TK had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis

DATA AVAILABILITY

The MSBase registry is a data processor and warehouses data from individual principal investigators who agree to share their datasets on a project-by-project basis. External party access to data from either the MSBase centres or two non-MSBase UK centers is subject to reasonable requests and solely at the discretion of the principal investigators. Permission for data access must be sought individually from the respective principal investigators.

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