Cladribine vs other drugs in MS
Merging randomized trial with real-life data

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Abstract

Objective
Cladribine tablets were tested against placebo in randomized controlled trials (RCTs). In this study, the effectiveness of cladribine vs other approved drugs in patients with relapsing-remitting MS (RRMS) was compared by matching RCT to observational data.

Methods
Data from the pivotal trial assessing cladribine tablets vs placebo (CLARITY) were propensity score matched to data from the Italian multicenter database i-MuST. This database included 3,150 patients diagnosed between 2010 and 2018 at 24 Italian MS centers who started a disease-modifying drug. The annualized relapse rate (ARR) over 2 years from treatment start and the 24-week confirmed disability progression were compared between patients treated with cladribine and other approved drugs (interferon, glatiramer acetate, fingolimod, natalizumab, and dimethyl fumarate), with comparisons with placebo as a reference. Treatment effects were estimated by the inverse probability weighting negative binomial regression model for ARR and Cox model for disability progression. The treatment effect has also been evaluated according to baseline disease activity.

Results
All weighted baseline characteristics were well balanced between groups. All drugs tested had an effect vs placebo close to that detected in the RCT. Patients treated with cladribine had a significantly lower ARR compared with interferon (relapse ratio [RR] = 0.48; $p < 0.001$), glatiramer acetate (RR = 0.49; $p < 0.001$), and dimethyl fumarate (RR = 0.6; $p = 0.001$); a similar ARR to that with fingolimod (RR = 0.74; $p = 0.24$); and a significantly higher ARR than

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Go to Neurology.org/NN for full disclosures. Funding information is provided at the end of the article.

The Article Processing Charge was funded by Merck.

Glossary

ARR = annualized relapse rate; **DMD** = disease-modifying drug; **DMF** = dimethyl fumarate; **EDSS** = Expanded Disability Status Scale; **FS** = functional system; **FTY** = fingolimod; **GA** = glatiramer acetate; **HAD** = high disease activity; **HR** = hazard ratio; **IFN** = interferon; **IPW** = inverse probability weighting; **NMA** = network meta-analysis; **NTZ** = natalizumab; **PS** = propensity score; **RRMS** = relapsing-remitting MS; **SC** = subcutaneous; **TERI** = teriflunomide.

natalizumab (RR = 2.13; p = 0.014), confirming results obtained by indirect treatment comparisons from RCTs (network meta-analyses). The relative effect of cladribine tablets 10 mg (cumulative dose 3.5 mg/kg over 2 years) was higher in patients with high disease activity vs all treatments except fingolimod and natalizumab. Effects on disability progression were largely nonsignificant, probably due to lack of power for such analysis.

Conclusion
In patients with RRMS, cladribine tablets showed lower ARR compared with matched patients who started interferon, glatiramer acetate, or dimethyl fumarate; was similar to fingolimod; and was higher than natalizumab. The beneficial effect of cladribine tablets was generally amplified in the subgroup of patients with high disease activity.

Classification of evidence
This study provides Class III evidence that for patients with RRMS, cladribine-treated patients had lower ARR compared with interferon, glatiramer acetate, or dimethyl fumarate; similar ARR compared with fingolimod; and higher ARR compared with natalizumab.

Relapsing-remitting MS (RRMS) is characterized by periodic exacerbations of disease symptoms followed by periods of remission, in which symptoms are either partially or completely absent. Disease-modifying drugs (DMDs) are able to decrease the frequency and duration of relapses and sometimes to slow the progression of the disease.[1]

Cladribine tablet is hypothesized as an immune reconstitution therapy that targets specific subsets of the adaptive immune system.[2] As demonstrated in the CLARITY phase 3 randomized controlled study, a short-course treatment (8–20 d/y) with cladribine tablets provided a sustained treatment benefit for patients with RRMS.[3] In particular, the 2 tested doses of cladribine (3.5 and 5.25 mg/kg [3.5 mg/kg is the approved dose]) were superior to placebo in suppressing relapse activity and increasing the probability of remaining relapse-free. In the CLARITY extension, the clinical benefits of 2 years of treatment with cladribine tablets were shown to be sustained, without the need for retreatment.[4]

In this study, we conducted a propensity score (PS)-matched analysis of observational data from the CLARITY trial data set and the Italian multicenter database i-MuST, which includes 3,150 patients diagnosed between 2010 and 2018 at 24 Italian MS centers who started a DMD.

We aim to fill in the gap in the current RRMS treatment landscape, as no direct head-to-head comparisons of cladribine with other common immunotherapies have yet been conducted. In particular, we try to define the role of cladribine tablets in the context of the other available therapies for MS by an individual-level comparative efficacy analysis of cladribine tablets vs other common immunotherapies, such as interferon beta (IFN β-1a and β-1b), glatiramer acetate (GA), fingolimod (FTY), natalizumab (NTZ), dimethyl fumarate (DMF), and teriflunomide (TERI), as first-line therapies for RRMS in Italy.

Methods

Patients
This is an observational retrospective study merging 2 data sets. Details on the study design of the CLARITY data set can be found in the article reporting the clinical trial results,[3] and details about the i-MuST database collection can be found in previous publications.[5] This study takes advantage of the availability of the placebo arm of the CLARITY study, thus providing a reference to which each treatment can be compared.

Briefly, in the CLARITY study 1,326 patients were randomly assigned in a 1:1:1 ratio to receive 1 of 2 doses of cladribine tablets (either 3.5 mg or 5.25 mg/kg of body weight) or placebo. Patients randomized to the 3.5 mg/kg cumulative dose received a first treatment course at weeks 1 and 5 of the first year and a second treatment course at weeks 1 and 5 of the second year. Patients were eligible if they had received a diagnosis of RRMS (according to the McDonald criteria, 2001[6]), had lesions consistent with MS on MRI, had had at least 1 relapse within 12 months before study entry, and had a score of ≤5.5 on the Expanded Disability Status Scale (EDSS).

The i-MuST data set is a multicenter, retrospective database, involving 24 Italian MS centers. The data set used for this analysis included 3,006 patients with RRMS. From these,

patients satisfying the same inclusion/exclusion criteria as CLARITY were extracted. Inclusion criteria were age over 16 years, diagnosis of RRMS (2001 International Panel Diagnostic Criteria and the 2010 revision[6,7]), and initiating a DMD between January 2010 and June 2017. There were no exclusion criteria. The EDSS score[8] was collected for all patients at therapy start; at therapy switch (if any); every 6–12 months, depending on the center; and at the last follow-up.

Only treatment-naive patients were selected in the CLARITY data set because all the patients enrolled in i-MuST were at their first therapy. As a consequence, the study population was defined as all enrolled patients in CLARITY who did not receive any prior DMD and all the patients enrolled in i-MuST who satisfied the inclusion criteria of CLARITY.

The following variables were common to the 2 data sets and were merged: age at treatment start, disease duration since onset, baseline EDSS score, presence of gadolinium-enhancing (active) lesions at baseline, sex, relapses in the previous year, first therapy, and date of first therapy start. First relapse, time to first relapse, time to a progression event confirmed at 3 months, and time to a progression event confirmed at 6 months were also extracted from CLARITY and calculated in the i-MuST data set.

The study population was split into the following treatment groups: placebo, cladribine 3.5 mg/kg, cladribine 5.25 mg/kg, IFN β-1a (subcutaneous [SC]), IFN-1a (SC), IFN β-1b, GA, FTY, NTZ, DMF, and TERI. For treatment comparisons, the IFNs were merged in a single IFN group and the 2 cladribine tablets arms in a single cladribine-treated group. Therefore, unless differently specified, the term IFN indicates the 3 IFNs pooled together, and the term cladribine tablets indicates the 2 cladribine arms pooled together.

Standard protocol approvals, registrations, and patient consents
The study was approved by the Ligurian Region ethical committee (258REG2016). All the centers involved in the study asked for written permission of the use of anonymized personal clinical data for research purposes, and written informed consent was obtained from all study patients included in this study. CLARITY registration—ClinicalTrials.gov number NCT00213135.

Outcomes
The primary end point for the Class III comparative effectiveness analysis was annualized relapse rate (ARR) over 2 years. The secondary end point was time to onset of 24-week sustained disability progression over 2 years. Patients in i-MuST were censored at their treatment switch or at year 2, whichever happened first.

Definition of relapses in i-MuST followed clinical trial criteria: change in the EDSS score, with an increase of ≥0.5 points on the total score, or an increase of 1 point on 2 functional systems (FSs) or 2 points on 1 FS, excluding changes involving bowel/bladder or cerebral FS. In CLARITY, the definition of relapses

closest to those defined in i-MuST was identified to be that of "qualifying relapses," and this variable was used for the analysis.

The ARR for each treatment group was calculated as the total number of relapses experienced in the group divided by the total number of patient-years on study.

The time to onset of 24-week confirmed disability progression is defined as the time from baseline to the first disability progression that is confirmed at the next visit ≥24 weeks after the initial disability progression. Disability progression was defined by 1 of the following: an EDSS score increase of ≥1.5 points from a baseline EDSS score of 0 that is sustained for ≥12 weeks and an EDSS score increase of ≥1.0 point from a baseline EDSS score of 1.0–5.5 (inclusive) for ≥24 weeks.

The date of the initial EDSS assessment at which the minimum increase in the EDSS score is met was the date of onset of the progression. The progression was defined as confirmed when this minimum EDSS change was present on the next study visit occurring after 24 weeks or longer from the onset of the progression. EDSS assessments ≤30 days after a protocol-defined relapse were not used for confirmation of disability progression. If a patient met the defined criteria of confirmed progression and was also having a relapse, the patient was required to meet the defined minimum criteria at the subsequent visit.

Patients without a confirmed progression based on the above rules were censored. The censor date was the date of last EDSS assessment in the study. Patients who withdrew from the study after the baseline visit but before the first clinical evaluation scheduled visit were censored at baseline.

Statistical methods
Baseline was defined for the i-MuST database as the start of therapy date and for the CLARITY database as the randomization date. Baseline disease and demographic characteristics were summarized by group and overall before any adjustment, using descriptive statistics, and were compared between treatment groups using the standardized mean difference as calculated according to Cohen d effect size. A Cohen d effect size >0.1 denotes meaningful imbalance in the baseline covariates.[9–14]

To mitigate the baseline differences between compared groups, the inverse probability weighting (IPW) approach based on PS was used. The weights correspond to the inverse of the conditional PS of receiving the treatment. The PS was calculated by modeling on the baseline characteristics the probability of receiving each treatment vs another one by a logistic regression model applied to each treatment group in the i-MuST study vs the overall CLARITY study population (since the assignment to cladribine tablets or placebo was randomized). The logistic regression model had treatment group as the dependent variable (placebo/cladribine tablets vs other drug) and the following baseline variables as independent covariates: age,

disease duration since onset, baseline EDSS score, sex, and relapses in the previous year.

We used stabilized trimmed weights (weights that exceeded a specified threshold are each set to that threshold[15]) to mitigate the impact of extremely higher or lower weights on the variability of the estimated treatment effect.[15] The threshold was based on the quantiles of the distribution of the weights (1st to 5th and 95th to 99th percentiles).[15,16] For each treatment pair, we choose to trim the weights at the percentile giving the highest reduction of standardized Cohen d differences.

An IPW negative binomial regression model was used to assess differences between treatments on relapse rate over 2 years. The relapse count was used as a dependent variable, the treatment group as an independent variable, and the log of follow-up duration as an offset variable.

The semiparametric IPW Cox regression model was used to assess treatment effect differences on time to disability progression. Cumulative probability to be progression-free during follow-up was calculated and graphically displayed by mean of Kaplan-Meier survival curves. The estimates of treatment effect were expressed as hazard ratios (HRs) and reported with 95% CIs and p values. Stata (v.14; StataCorp., College Station, TX) was used for the computation.

Subgroup analyses

A subgroup analysis assessed the relative treatment effect of each drug vs cladribine tablets in subgroups of patients defined according baseline disease activity. The definition of patients with high disease activity (HDA) at baseline was the one used in a previous article,[4] as patients with ≥2 relapses during the year before study entry, whether on DMD. The definition including patients with previous relapses while on treatment was not applied here because only naive patients were included in the analyzed cohorts.

All the analyses run on the overall population were rerun on subgroups of patients with and without HDA at baseline. The significance of the difference in treatment effects between subgroups was assesses by interaction tests. The results were displayed by forest plots.

Sensitivity analyses

The following sensitivity analyses were run: (1) analyses with a PS and IPW calculated including baseline MRI information, run on a reduced sample; (2) analyses including patients treated with cladribine tablets 3.5 mg/kg only; (3) analyses adjusted by a 1:1 PS matching and a variable ratio ≤3:1 PS matching; and (4) analysis contrasting cladribine tablets vs each IFN separately.

Data availability

CLARITY and i-MuST data would be available on reasonable request.

Results

Descriptive analysis

A total of 2,204 patients from i-MuST and 945 patients from CLARITY were included in the final analysis. Supplementary figure e-1 (links.lww.com/NXI/A298) presents the flowchart for selecting patients from the i-MuST and CLARITY data sets.

In the i-MuST data set, a total of 1,168 patients were treated with IFN, 402 with GA, 113 with FTY, 149 with NTZ, 295 with DMF, and 77 with TERI. In the CLARITY data set, 305 were in the placebo arm, 322 received the cladribine 3.5 mg/ kg dose, and 318 received the cladribine 5.25 mg/kg dose.

The unweighted characteristics of all patients included in the analysis, according to the treatment group in the i-MuST database and in CLARITY, are presented in table e-1 (links.lww. com/NXI/A298). In CLARITY, patients were randomized among treatment arms; therefore, data are presented here for the overall CLARITY study, according to the IPW approach used. The baseline characteristics detailed for each treatment arm are reported in table e-2.

Patients included in i-MuST were generally younger (excluding patients treated with GA, who were in the same age range, and patients treated with TERI, who were older) than patients included in CLARITY. EDSS levels were generally well balanced (small standardized differences in range of 0.20–0.37) between CLARITY patients and patients treated with FTY, NTZ, and TERI, whereas patients treated with IFN, GA, and DMF had lower EDSS baseline scores. Disease duration was generally lower in i-MuST compared with CLARITY patients with mild to moderate differences. Patients enrolled in i-MuST (especially FTY, NTZ, and DMF) showed a higher frequency of active lesions at baseline compared with trial data. Follow-up duration was lower in i-MuST for patients treated with FTY, DMF, and TERI. The mean time between visits with the EDSS was 157 days with a median of 109 days. Baseline characteristics for each treatment and for CLARITY study after IPW are presented in table 1. The 3 arms of CLARITY are shown separately and compared with each treatment in tables e-3 to e-8 (links.lww.com/NXI/A298).

The weighted characteristics were well balanced between each treatment group from the i-MuST and CLARITY data sets. A residual unbalance persisted for the EDSS in the IFN and GA arms (with standardized difference in range of 0.25–0.34).

Comparative effectiveness analyses

Annualized relapse rate

The IPW-adjusted ARR for each treatment arm is reported in table 2. Treatment with cladribine tablets was associated with a statistically significant reduction in ARR of 52% vs IFN, 51% vs GA, and 40% vs DMF. The reduction of ARR vs FTY was not statistically significant (p = 0.24); NTZ was superior to cladribine tablets, and the ARR ratio of cladribine vs NTZ was

Table 1 Inverse probability-weighted demographic and clinical characteristics

Panel A: IFN, GA, and FTY vs CLARITY study

	CLARITY (n = 945)	IFN (n = 1,168)	Standardized mean difference IFN vs CLARITY	CLARITY (n = 945)	GA (n = 402)	Standardized mean difference GA vs CLARITY	CLARITY (n = 945)	FTY (n = 113)	Standardized mean difference FTY vs CLARITY
Age, y, mean (SD)	37.3 (10.1)	36.6 (10.7)	0.071	38.8 (10.2)	39.5 (11.8)	0.07	38.4 (10.3)	38.1 (11.6)	0.025
Females, n (%)	629 (66.5)	768 (65.7)	0.018	629 (66.5)	269 (66.9)	0.008	614 (65)	69 (61.1)	0.08
EDSS score, mean (SD); median (IQR)	2.46 (1.25); 2 (1.5–3.5)	2.11 (1.17); 2 (1–3)	0.29	2.71 (1.28); 2.5 (2–3.5)	2.28 (1.32); 2 (1–3)	0.33	2.86 (1.28); 2.5 (2–4)	2.81 (1.23); 2.5 (2–3.5)	0.04
Disease duration, mean (SD); median (IQR)	2.46 (4.45); 0.52 (0.2–2.6)	2.75 (4.68); 0.7 (0.2–2.9)	0.062	3.38 (5.05); 1.2 (0.3–4.6)	3.10 (5.57); 1.00 (0.17–3)	0.052	4.08 (5.36); 1.95 (0.5–5.8)	3.90 (6.11); 1.79 (0.3–5.6)	0.03
ARR in previous year, mean (SD)	1.32 (0.56)	1.33 (0.58)	0.013	1.33 (0.58)	1.32 (0.56)	0.024	1.35 (0.6)	1.36 (0.57)	0.01
Active lesions, n (%)	306 (32.4)	435/1,023 (42.5)	0.21	290 (30.7)	146/376 (38.7)	0.17	294 (31.1)	48/90 (53.3)	0.46

Panel B: NTZ, DMF, and TERI vs CLARITY study

	CLARITY (n = 945)	NTZ (n = 149)	Standardized mean difference NTZ vs CLARITY	CLARITY (n = 945)	DMF (n = 295)	Standardized mean difference DMF vs CLARITY	CLARITY (n = 945)	TERI (n = 77)	Standardized mean difference TERI vs CLARITY
Age, y, mean (SD)	37.9 (10.4)	36.6 (10.9)	0.12	38.3 (10.3)	38.1 (10.2)	0.015	39.1 (10.4)	39.3 (11.8)	0.019
Females, n (%)	609 (64.4)	84 (56.4)	0.17	617 (65.3)	197 (66.8)	0.03	614 (65)	45 (58.4)	0.13
EDSS score, mean (SD); median (IQR)	2.87 (1.28); 3 (2–4)	2.74 (1.10); 2.5 (2–3.5)	0.10	2.68 (1.30); 2.5 (1.5–3.5)	2.38 (1.23); 2.5 (1.5–3)	0.23	2.87 (1.28); 3 (2–4)	2.56 (1.34); 2 (1.5–3.5)	0.24
Disease duration, mean (SD); median (IQR)	3.87 (5.19); 1.8 (0.5–5.3)	3.28 (5.10); 0.95 (0.17–4.58)	0.11	3.84 (5.12); 1.79 (0.51–5.5)	3.59 (5.61); 0.76 (0.3–4.4)	0.045	4.23 (5.50); 2.06 (0.57–5.97)	3.76 (5.88); 1.05 (0.54–3.98)	0.08
ARR in previous year, mean (SD)	1.36 (0.61)	1.42 (0.66)	0.089	1.32 (0.57)	1.29 (0.53)	0.068	1.33 (0.58)	1.32 (0.57)	0.017
Active lesions, n (%)	299 (31.7)	89/128 (69.5)	0.82	293 (31)	134/276 (48.6)	0.36	287 (30.4)	19/72 (26.4)	0.088

Abbreviations: ARR = annualized relapse rate; DMF = dimethyl fumarate; EDSS = Expanded Disability Status Scale; FTY = fingolimod; GA = glatiramer acetate; HDA, high disease activity; IFN = interferon β; IQR = interquartile range; NTZ = natalizumab; TERI = teriflunomide.

Table 2 ARR after IPW adjustment in all the analyzed treatment groups

	IPW clinical variables			IPW clinical + MRI variables		
		ARR ratio (95% CI)			ARR ratio (95% CI)	
	ARR (95% CI)	IFN vs placebo	Cladribine vs IFN	ARR (95% CI)	IFN vs placebo	Cladribine vs IFN
Placebo	0.321 (0.275–0.367)	0.76 (0.64–0.91); *p* = 0.002	0.48 (0.41–0.57); *p* < 0.001	0.319 (0.273–0.365)	0.79 (0.66–0.95); *p* = 0.011	0.46 (0.38–0.55); *p* < 0.001
Cladribine	0.118 (0.101–0.134)			0.116 (0.099–0.132)		
IFN	0.246 (0.222–0.269)			0.252 (0.226–0.279)		
		GA vs placebo	Cladribine vs GA		GA vs placebo	Cladribine vs GA
Placebo	0.318 (0.254–0.382)	0.78 (0.57–1.08); *p* = 0.13	0.49 (0.36–0.68); *p* < 0.001	0.318 (0.254–0.383)	0.79 (0.57–1.09); *p* = 0.14	0.49 (0.36–0.68); *p* < 0.001
Cladribine	0.123 (0.099–0.147)			0.122 (0.098–0.147)		
GA	0.249 (0.187–0.311)			0.250 (0.187–0.313)		
		FTY vs placebo	Cladribine vs FTY		FTY vs placebo	Cladribine vs FTY
Placebo	0.320 (0.257–0.383)	0.54 (0.32–0.89); *p* = 0.016	0.74 (0.45–1.22); *p* = 0.24	0.321 (0.257–0.385)	0.47 (0.28–0.79); *p* = 0.005	0.84 (0.50–1.41); *p* = 0.51
Cladribine	0.127 (0.103–0.150)			0.127 (0.103–0.150)		
FTY	0.171 (0.091–0.252)			0.151 (0.078–0.223)		
		NTZ vs placebo	Cladribine vs NTZ		NTZ vs placebo	Cladribine vs NTZ
Placebo	0.326 (0.261–0.391)	0.18 (0.10–0.34); *p* < 0.001	2.13 (1.17–3.88); *p* = 0.014	0.329 (0.265–0.394)	0.17 (0.09–0.32); *p* < 0.001	2.28 (1.23–4.24); *p* = 0.009
Cladribine	0.128 (0.104–0.152)			0.128 (0.104–0.152)		
NTZ	0.060 (0.026–0.094)			0.056 (0.023–0.089)		
		DMF vs placebo	Cladribine vs DMF		DMF vs placebo	Cladribine vs DMF
Placebo	0.312 (0.246–0.377)	0.65 (0.44–0.97); *p* = 0.036	0.60 (0.41–0.89); *p* = 0.001	0.322 (0.256–0.387)	0.64 (0.43–0.94); *p* = 0.024	0.63 (0.43–0.93); *p* = 0.02
Cladribine	0.123 (0.099–0.147)			0.129 (0.104–0.154)		
DMF	0.204 (0.135–0.272)			0.204 (0.136–0.273)		

Abbreviations: ARR = annualized relapse rate; DMF = dimethyl fumarate; FTY = fingolimod; GA = glatiramer acetate; IFN = interferon β; IPW = inverse probability weighting; NTZ = natalizumab.
Results are presented after IPW adjustment with clinical variables (left columns) and with clinical variable + MRI variables (right columns).

Figure 1 ARR ratio of cladribine vs other treatments
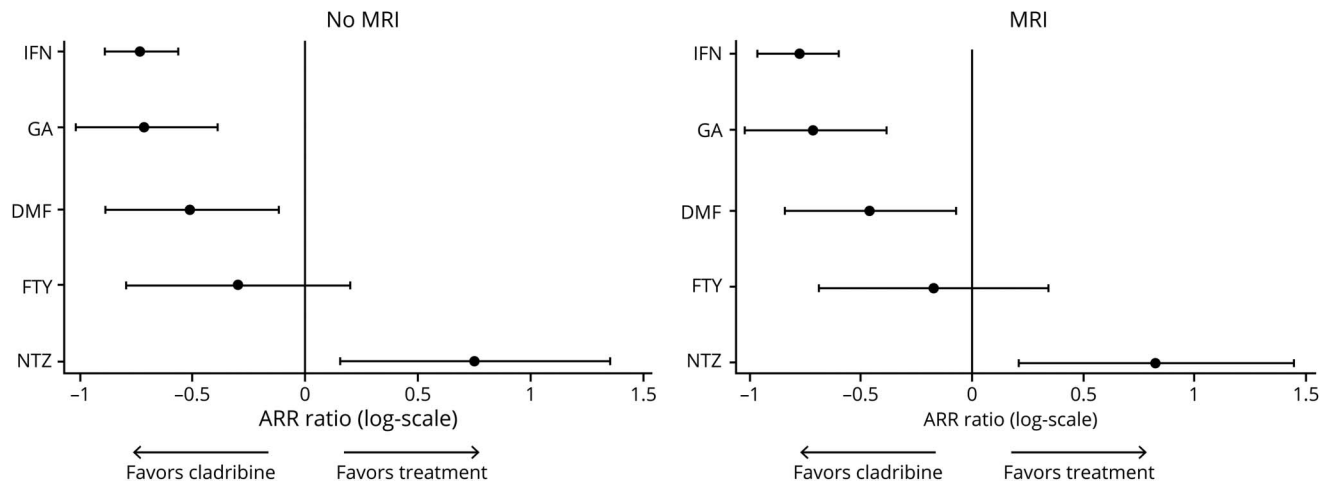
ARR = annualized relapse rate; DMF = dimethyl fumarate; FTY = fingolimod; GA = glatiramer acetate; IFN = interferon β; NTZ = natalizumab.

2.13 (p = 0.014) (table 2). Cladribine tablets compared with TERI was not analyzed because the TERI arm was too small (n = 77) to draw meaningful conclusions. The treatment effects vs placebo were close to those observed in randomized controlled trials and estimated in previous network meta-analyses (table e-9 and figure e-2, links.lww.com/NXI/A298)[17–19] with largely overlapping CIs for all the drugs. In this study, NTZ showed a reduction in the ARR vs placebo of 82% (with very large CIs)—higher than that observed in the AFFIRM study (ARR ratio vs placebo = 68%) and reestimated in the network meta-analyses, but with overlapping CIs. Similar results were obtained for the analysis including baseline MRI activity in the PS calculation on the subgroup of patients with available MRI information at baseline (table 2, second column). Forest plots for these 2 analyses are presented in figure 1. Similar results were obtained when considering the 2 different doses of cladribine tablets separately (table e-10).

Our results of the effects of cladribine tablets vs other drugs on ARR were compared with those reported by a previous network meta-analysis (NMA) (figure e-3, links.lww.com/NXI/A298).[20] All the cladribine effects vs the other DMDs were within the CIs of those estimated in the NMA.[20]

Disability progression
The HRs for comparisons of disability progression are reported in table 3 and displayed in figure e-4 (links.lww.com/NXI/A298). A small proportion of patients had missing data on follow-up EDSS. Excluded patients in each group were 40 (3.42%) for IFN; 23 (5.72%) for GA; 5 (4.4%) for FTY; 15 (10%) for NTZ; and 33 (11.2%) for DMF. A significant difference in favor of cladribine tablets on time to disability progression was observed only for GA (−36%; p = 0.045).

The survival curves for progression-free probability of each treatment vs cladribine tablets 3.5 mg/kg are shown in figure
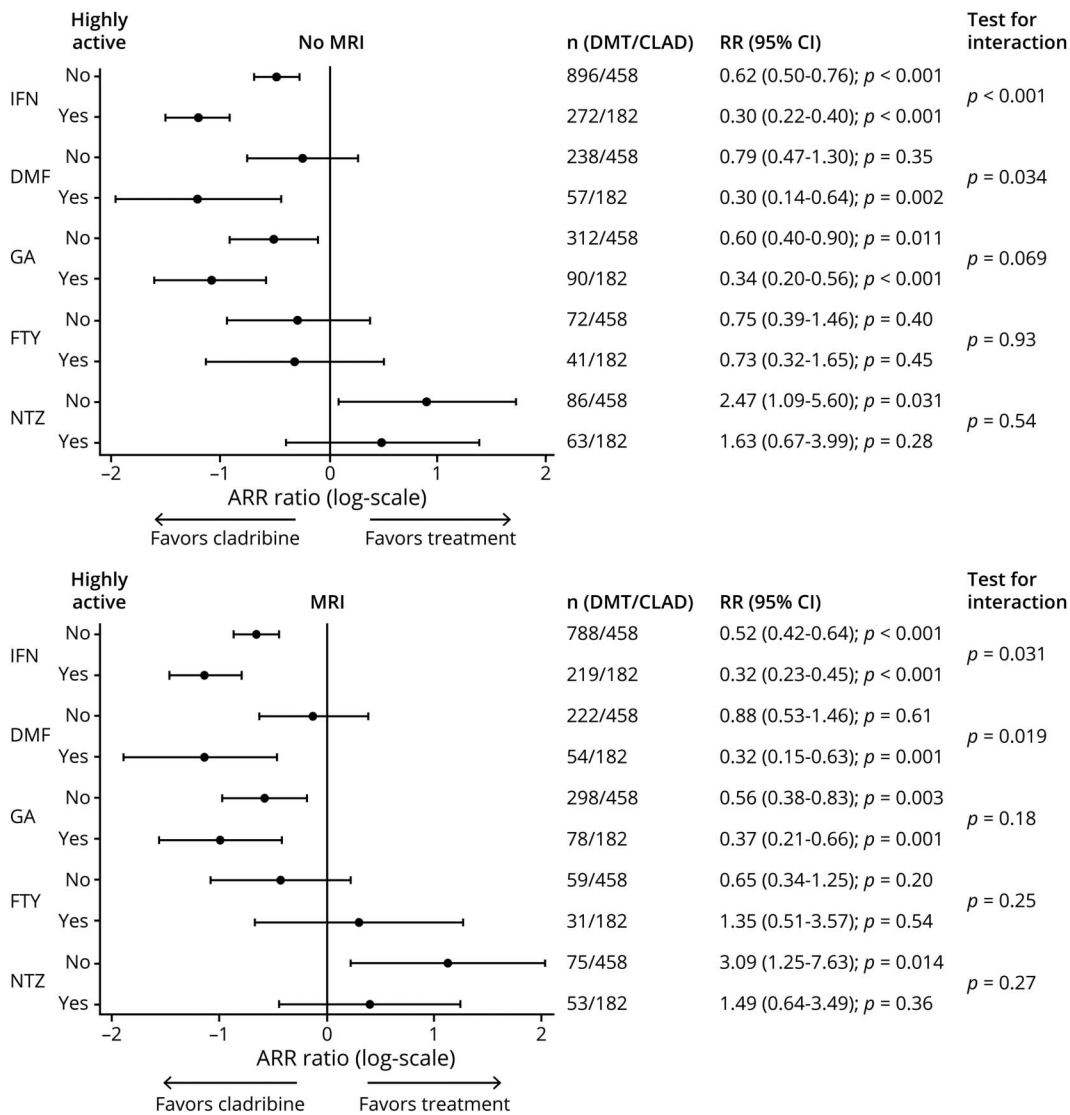
e-5 (links.lww.com/NXI/A298), whereas the HRs for comparisons of disability progression, considering the 2 different doses of cladribine tablets separately, are reported in table e-11.

Table 3 Risk of 24-week disability progression of cladribine vs other drugs

	IPW clinical variables	IPW clinical + MRI variables
	HR (95% CI)	HR (95% CI)
IFN (n = 1,128) vs placebo	0.72 (0.55–0.94); p = 0.017	0.75 (0.57–0.99); p = 0.046
Cladribine vs IFN	0.86 (0.68–1.09); p = 0.22	0.81 (0.62–1.05); p = 0.11
GA (n = 379) vs placebo	0.93 (0.58–1.47); p = 0.74	1.00 (0.63–1.59); p = 0.99
Cladribine vs GA	0.64 (0.41–0.99); p = 0.045	0.58 (0.38–0.90); p = 0.015
FTY (n = 108) vs placebo	0.61 (0.30–1.27); p = 0.19	0.65 (0.32–1.30); p = 0.23
Cladribine vs FTY	0.89 (0.44–1.83); p = 0.76	0.84 (0.42–1.67); p = 0.62
NTZ (n = 134) vs placebo	0.45 (0.22–0.92); p = 0.028	0.35 (0.16–0.78); p = 0.01
Cladribine vs NTZ	1.20 (0.59–2.42); p = 0.61	1.51 (0.69–3.33); p = 0.31
DMF (n = 262) vs placebo	0.54 (0.29–1.00); p = 0.051	0.68 (0.38–1.19); p = 0.18
Cladribine vs DMF	1.07 (0.59–1.94); p = 0.83	0.80 (0.46–1.39); p = 0.43

Abbreviations: DMF = dimethyl fumarate; FTY = fingolimod; GA = glatiramer acetate; HR = hazard ratio; IFN = interferon β; IPW = inverse probability weighting; NTZ = natalizumab.

Figure 2 Relapse rate ratio of cladribine vs each other treatment according to HDA subgroups

Highly active	No MRI	n (DMT/CLAD)	RR (95% CI)	Test for interaction
IFN No		896/458	0.62 (0.50-0.76); *p* < 0.001	
IFN Yes		272/182	0.30 (0.22-0.40); *p* < 0.001	*p* < 0.001
DMF No		238/458	0.79 (0.47-1.30); *p* = 0.35	
DMF Yes		57/182	0.30 (0.14-0.64); *p* = 0.002	*p* = 0.034
GA No		312/458	0.60 (0.40-0.90); *p* = 0.011	
GA Yes		90/182	0.34 (0.20-0.56); *p* < 0.001	*p* = 0.069
FTY No		72/458	0.75 (0.39-1.46); *p* = 0.40	
FTY Yes		41/182	0.73 (0.32-1.65); *p* = 0.45	*p* = 0.93
NTZ No		86/458	2.47 (1.09-5.60); *p* = 0.031	
NTZ Yes		63/182	1.63 (0.67-3.99); *p* = 0.28	*p* = 0.54

ARR ratio (log-scale)
Favors cladribine ← → Favors treatment

Highly active	MRI	n (DMT/CLAD)	RR (95% CI)	Test for interaction
IFN No		788/458	0.52 (0.42-0.64); *p* < 0.001	
IFN Yes		219/182	0.32 (0.23-0.45); *p* < 0.001	*p* = 0.031
DMF No		222/458	0.88 (0.53-1.46); *p* = 0.61	
DMF Yes		54/182	0.32 (0.15-0.63); *p* = 0.001	*p* = 0.019
GA No		298/458	0.56 (0.38-0.83); *p* = 0.003	
GA Yes		78/182	0.37 (0.21-0.66); *p* = 0.001	*p* = 0.18
FTY No		59/458	0.65 (0.34-1.25); *p* = 0.20	
FTY Yes		31/182	1.35 (0.51-3.57); *p* = 0.54	*p* = 0.25
NTZ No		75/458	3.09 (1.25-7.63); *p* = 0.014	
NTZ Yes		53/182	1.49 (0.64-3.49); *p* = 0.36	*p* = 0.27

ARR ratio (log-scale)
Favors cladribine ← → Favors treatment

ARR = annualized relapse rate; CLAD = cladribine; DMD = disease-modifying drug; DMF = dimethyl fumarate; FTY = fingolimod; GA = glatiramer acetate; HDA, high disease activity; IFN = interferon β; NTZ = natalizumab; RR = relapse ratio.

Subgroup analyses

The effect of cladribine tablets vs other drugs was tested in subgroups defined according to baseline disease activity. The weighted baseline characteristics for each treatment by subgroup (HDA vs non-HDA) are presented in tables e-12 and e-13 (links.lww.com/NXI/A298). The same characteristics are reported in tables e-14 to e-18 with the 3 arms of CLARITY presented separately. Results on ARR are shown in figure 2. The effect of cladribine tablets was generally amplified in the HDA subgroup and the same was true for cladribine 3.5 mg alone (table e-19). The subgroup analysis run on time to disability progression is presented in tables e-20 and e-21. The same trend for a higher efficacy of cladribine tablets is observable in the HDA subgroup.

Sensitivity analyses

PS matching 1:1

Baseline characteristics of patients after 1:1 PS matching are reported in table e-22 (links.lww.com/NXI/A298). A good balance with standardized differences <0.10 for almost all characteristics and treatments was observed. The ARR ratio between cladribine tablets and single treatment arms after 1:1 PS matching (table e-23) confirmed in general the results observed with the IPW approach.

PS matching 3:1

The characteristics of matched samples after up to 3:1 PS matching are reported in table e-24 (links.lww.com/NXI/A298). Here also a good balance was observed between the

compared groups. The ARR ratio between cladribine tablets and single treatment arms after 3:1 PS matching (table e-25) confirmed the results observed with the IPW approach.

Stratification of IFN arms
The IPW-weighted baseline characteristics of the 3 IFN arms split are reported in table e-26 (links.lww.com/NXI/A298). Good balance with standardized differences <0.10 was observed for almost all characteristics across the 3 arms compared with CLARITY. The weighted ARR ratio (table e-27, links.lww.com/NXI/A298) showed a higher effect of cladribine tablets in IFN-1b and IFN-1a SC compared with IFN-1a IM.

Discussion

This study presents a novel approach, matching individual patient data from the CLARITY randomized controlled phase III trial with those included in a large multicenter observational study in newly diagnosed patients. The presence of the placebo arm from CLARITY allowed us to compare, as a first step, the effectiveness of each drug from the observational study vs placebo with the effect reported in randomized clinical trials. The effect of each treatment vs placebo was close to that observed in the clinical trials except for NTZ, where a larger effect in the drug vs placebo was seen (ARR ratio 82% vs 68% reported in the AFFIRM trial[21]), even if the large CIs of the estimate obtained in this study limit the interpretation of such result.

The results from comparative effectiveness showed a superiority of cladribine tablets vs IFN, GA, and DMF on the relapse rate in the first 2 years. No significant differences were observed with FTY, whereas NTZ was shown to be superior.

Similar results were observed in a previous observational study[22] on comparative effectiveness of cladribine conducted in a cohort of patients from the MSBase International Registry. A small cohort of patients treated with cladribine vs FTY, NTZ, and IFN showed a superiority of cladribine vs IFN and a superiority of NTZ on cladribine on hazard of first relapse. On the same outcome, no significant differences between cladribine and FTY were detected. No comparisons vs GA or DMF were performed.

A recent NMA[20] compared the effects of various DMDs on ARR and confirmed disability progression in active and highly active RRMS, including 41 studies. Cladribine was ranked in fourth position on a scale of efficacy for ARR reduction after alemtuzumab, NTZ, and ocrelizumab. In the same NMA, a significant reduction of ARR with cladribine, estimated around 40% vs GA and up to 48% vs IFN, was reported and was close to that observed in our study. When compared with DMF, the ARR reduction due to cladribine was not significant and lower than that observed in our study (22%; 95% CI 43%–7%) in NMA vs 36% in our study; our data are therefore consistent with those reported in NMA). The ARR under cladribine was comparable to FTY and higher than the ARR under NTZ, even if the difference was not significant.

In the NMA,[20] cladribine was statistically similar to the other DMDs on confirmed disability progression. In our study, the superiority of cladribine was detected only vs GA.

Cladribine is approved and indicated mainly for the treatment of patients with highly active RRMS. Having individual patient data, we were able to perform a subgroup analysis, which indicated a higher efficacy of cladribine vs other DMDs in patients with HDA, with ARR reduction close to 70% vs IFN, GA, and DMF in this specific subgroup of patients.

Study limitations
This study carries all the well-known limitations of non-randomized comparisons, with the advantage of a placebo arm giving a benchmark for comparisons.[23] In addition, the sample size for all the comparisons on disability progression was low, giving estimates with large CIs. To mitigate the potential bias due to the lack of randomization, we applied an IPW in the main analysis as well as several sensitivity analyses with different matching algorithms.

With our comparative results, based on a wide national database (i-MuST) and the CLARITY data set, we simulated a scenario representing the complexity of management of patients with MS, which confirms the effectiveness of cladribine tablets in treating RRMS. Our approach let us overcome the lack of direct head-to-head comparisons of cladribine tablets to other common DMDs. We confirmed the superiority of cladribine tablets in reducing relapse rate, during the first 2 years, compared with its major competitors, such as IFN, GA, and DMF; NTZ data were still superior as given in the results. Finally, having individual patient data, we were able to show the higher efficacy of cladribine in the subgroup of patients with HDA.

Appendix Authors

Name	Location	Contribution
Alessio Signori, PhD	University of Genoa	Designed and conceptualized the study; analyzed the data; and drafted the manuscript for intellectual content
Francesco Saccà, MD	University Federico II Naples	Major role in the acquisition of data
Roberta Lanzillo, MD, PhD	University Federico II Naples	Major role in the acquisition of data
Giorgia Teresa Maniscalco, MD	AORN Cardarelli Naples	Major role in the acquisition of data
Elisabetta Signoriello, MD, PhD	University Luigi Vanvitelli, Naples	Major role in the acquisition of data
Anna Maria Repice, MD	Careggi University Hospital, Florence	Major role in the acquisition of data
Pietro Annovazzi, MD Damiano Baroncini, MD	ASST Valle Olona, PO Gallarate	Major role in the acquisition of data
Marinella Clerico, MD, PhD	University of Turin	Major role in the acquisition of data
Eleonora Binello, MD	Turin	Major role in the acquisition of data
Raffaella Cerqua, MD	Marche Polytechnic University, Ancona	Major role in the acquisition of data
Giorgia Mataluni, MD, PhD	Policlinic Tor Vergata, Rome	Major role in the acquisition of data
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Simona Bonavita, MD	University Luigi Vanvitelli	Major role in the acquisition of data
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Appendix (continued)

Name	Location	Contribution
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Andrea Visconti, MD	Merck Serono S.p.A., Rome	Drafted the manuscript for intellectual content
Maria Pia Sormani, PhD	University of Genoa	Designed and conceptualized the study; analyzed the data; drafted the manuscript for intellectual content; and supervised the study

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