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REVIEW ARTICLE

Role of disease-modifying oral drugs in multiple sclerosis: A systematic review with meta-analysis

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Abstract

The purpose of the study was to evaluate the efficacy and safety of cladribine tablets compared with all oral therapies used in patients with relapsing-remitting multiple sclerosis (RRMS). A systematic review of the literature was conducted to identify published clinical trials about RRMS and a network meta-analysis was performed to determine the efficacy and safety of available treatments. We identified seven relevant studies, which were selected based on three criteria that allowed us to construct comparisons of efficacy and safety. Regarding the annualized relapse rate (ARR), there were no significant differences with respect to the decrease of this between cladribine tablets, dimethyl fumarate and fingolimod; although teriflunomide and cladribine tablets showed a significant difference. In relation to the mean number of gadolinium-enhanced T1 lesions, dimethyl fumarate showed a lower number of lesions (–0.85 [–1.21; –0.48]), as did cladribine tablets versus placebo. No statistically significant differences were identified between cladribine tablets and fingolimod (–0.08 [–0.35; 0.19]) and cladribine versus teriflunomide (–0.28 [–0.64; 0.08]). While comparing adverse events that caused discontinuation, cladribine tablets showed an adequate safety profile, which was quantitatively similar to the compared drugs. Cladribine tablets demonstrated efficacy in terms of decrease of ARR and gadolinium-enhanced T1 lesions; although there is no significant difference between cladribine tablets, fingolimod and teriflunomide, the ARR is a stronger measure of efficacy compared to the number of T1 lesions made in contrast with long-term RRMS. Cladribine also demonstrated an adequate safety and tolerability profile promoting therapeutic adherence.

Key words: *Relapsing-remitting multiple sclerosis. Cladribine tablets. Disease-modifying treatments.*

Papel de los fármacos orales modificadores de la enfermedad en la esclerosis múltiple: una revisión sistemática con metanálisis

Resumen

El propósito del estudio fue evaluar la eficacia y seguridad de las tabletas de cladribina en comparación con todas las terapias orales utilizadas en pacientes con EMRR. Se realizó una revisión sistemática de la literatura para identificar ensayos clínicos publicados sobre EMRR y un metanálisis de red para determinar la eficacia y seguridad de los tratamientos disponibles. Identificamos 7 estudios relevantes, que se seleccionaron en base a 3 criterios que nos permitieron construir

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comparaciones de eficacia y seguridad. En cuanto a la tasa de recaída anualizada, no hubo diferencias significativas con respecto a la disminución de ésta entre las tabletas de cladribina, dimetilfumarato y fingolimod; aunque las tabletas de teriflunomida y cladribina mostraron una diferencia significativa. En relación con el número medio de lesiones T1 potenciadas con gadolinio, dimetilfumarato mostró un menor número de lesiones (–0.85 [–1.21; –0.48]), al igual que las tabletas de cladribina frente a placebo. No se identificaron diferencias estadísticamente significativas entre las tabletas de cladribina y fingolimod (–0.08 [–0.35; 0.19]) y cladribina vs teriflunomida (–0.28 [–0.64; 0.08]). Al comparar los eventos adversos que causaron la suspensión, las tabletas de cladribina mostraron un perfil de seguridad adecuado, que fue cuantitativamente similar a los medicamentos comparados. Las tabletas de cladribina demostraron eficacia en términos de disminución de la tasa de recaída anualizada y lesiones T1 potenciadas con gadolinio; Aunque no existe una diferencia significativa entre las tabletas de cladribina, fingolimod y teriflunomida, la tasa de recaída anualizada es una medida más fuerte de eficacia en comparación con el número de lesiones T1 realizadas en contraste con la EMRR a largo plazo. Cladribina también demostró un perfil adecuado de seguridad y tolerabilidad que promueve la adherencia terapéutica.

Palabras claves: *Esclerosis múltiple recurrente-remitente. Tabletas de cladribina. Tratamientos modificadores de la enfermedad.*

Introduction

Multiple sclerosis (MS) is a chronic degenerative autoimmune disease of the central nervous system characterized by inflammatory demyelination resulting in axonal and neuronal damage. Relapsing-remitting MS (RRMS) being the most common type (85-90%)[1,2]. Patients with RRMS suffer episodes that can cause fainting, this clinical condition can be disabling[3]. In Mexico, the prevalence reports ranges from 12 to 30 cases per 100,000 people[4].

Various therapies for MS require regular long-term self-injection that can result in patient dissatisfaction, which can severely affect therapeutic adherence and cause a secondary efficacy reduction[5]. Considering that the worldwide rate of non-adherence for MS is at 44%, which is similar to that of chronic diseases[6], oral medications have been introduced to improve adherence and, therefore, have an impact on therapeutic efficiency[7]. Oral cladribine (2-chloro-2'-deoxyadenosine) is an analog of adenosine deaminase resistant to deoxyadenosine[8,9]. It is a prodrug that requires intracellular phosphorylation, with a chlorine substitution in the purine ring. This protects it from degradation and increases its intracellular time[10].

In treatment with cladribine tablets, patients in the 3.5 and 5.25 mg group had fewer magnetic resonance imaging (MRI) lesions[11] than those patients in the placebo group, for gadolinium-enhanced T1 lesions (mean 0.11 and 0.12, respectively, vs. 0.91 in placebo) and T2 lesions (mean 0.38 and 0.33, respectively, vs. 1.43 in placebo)[12]. There is not enough information to directly compare the oral therapeutic strategies available for RRMS in Mexico. The aim of this study was to evaluate the efficacy and safety of cladribine tablets compared to oral therapies currently used in patients with RRMS by means of a systematic review and a network meta-analysis, considering the annualized relapse rate (ARR), T1 lesions, and adverse events that cause discontinuation of treatment.

Methods

Search method

In accordance with the Cochrane methodology, the authors searched for data from 1980 to March 1, 2019, under the criteria of the population, intervention, control, and outcomes question "Evaluate the efficacy and safety of cladribine tablets in patients diagnosed with RRMS compared with dimethyl fumarate, fingolimod, and teriflunomide," on PubMed, Cochrane, ScienceDirect, Web of Science, the Health Economic Evaluations Database, EMBASE databases, and regional databases such as LILACs, Scielo Citation Index, Medigraphic, REDALYC, Imbiomed, and Artemisa. The MeSH terms used were "MS," "RRMS," "cladribine," "dimethyl fumarate," "fingolimod hydrochloride," and "teriflunomide," both in English, Spanish, and Portuguese, limited to controlled clinical that included oral disease-modifying therapies.

Inclusion and exclusion criteria

Primary data sources were articles from randomized controlled clinical trials (RCTs). To avoid bias, study selection and data extraction were performed by two independent reviewers. RCTs assessing the effect of cladribine tablets and dimethyl fumarate, fingolimod, or teriflunomide in direct comparison with placebo for the

treatment of MS or RRMS were included, and a third reviewer provided consensus when there was disagreement on the inclusion of an article.

Data extraction information

Information was recorded on study design, selection criteria, population, patient characteristics, ARR, T1 lesions, and adverse events.

Quality assessment

The process of rating the quality of the best available evidence in the clinical studies was assessed following the approach proposed by the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) Working Group and in accordance with the GRADE Handbook.

Outcomes

Efficacy evaluation was performed based on the decrease of ARR and the change in the mean number of gadolinium-enhanced T1 lesions in the MRI. The safety profile was assessed by the number of patients who discontinued treatment due to adverse events.

Statistical analysis

Indirect comparisons were calculated using a network meta-analysis, since this is the most appropriate way of summarizing data to provide a series of unbiased effects obtained from direct and indirect comparisons. A random effects model was used as this is more appropriate than fixed effect models when there is heterogeneity between patient populations and between trials. To ensure a closed network, a placebo was used as a common point. Three interventions were used as comparators: dimethyl fumarate, fingolimod, and teriflunomide versus cladribine tablets; each study had both an intervention and a placebo. Direct evidence of the defined outcomes of each study was incorporated. Statistical significance was determined as $p > 0.05$. All calculations were performed with the software R version 3.5.2.

Main results

Search results

A total of 1034 articles were identified in the systematic review of the included databases. After duplicated removal, 761 papers were considered. Twenty-six of the potentially relevant articles were assessed for eligibility, and finally, seven clinical trials that met the efficacy and safety criteria were included (Chart 1). The characteristics of included studies are summarized in table 1.

Table 2 shows population data by intervention and cladribine dosage groups included in the analysis: cladribine tablets 3.5 mg, dimethyl fumarate 240 mg twice daily, teriflunomide 14 mg, and fingolimod 0.5 mg. The posology of interventions was validated through the Basic Table and Catalogue of Health Sector Inputs (CBCISS) of the General Health Council (CSG) for the Mexican population.

From the seven selected studies, data from the annual relapse rate, the average of gadolinium-enhanced T1 lesions, were extracted when available (gadolinium-enhanced T1 lesions data were not available for the TOWER study); for safety data, adverse events that led to the interruption of the study drug were evaluated; this was presented as a rate (Table 3).

Patient characteristics

Studies were conducted from 2010 to 2014 with similar demographic characteristics, all studies included patients diagnosed with RRMS; as for study design, treatment arms of all studied had the common point a placebo group. All studies included a high percentage (65.9-81%) of female patients (Table 2).

Outcomes report

Comparisons of cladribine tablets with dimethyl fumarate, fingolimod, and teriflunomide were made with efficacy, on the decrease of ARR and the change in the mean number of gadolinium reinforced T1 lesions in the MRI, and safety criteria data extracted through the systematic review.

ARR

Cladribine tablets showed no statistically significant differences with regard to the decrease of ARR compared to dimethyl fumarate and fingolimod, however, a lower relapse rate is shown with cladribine tablets when compared to placebo and teriflunomide (Chart 2).

Gadolinium-enhanced T1 lesions

In relation to the mean number of gadolinium-enhanced T1 lesions, treatment with cladribine reported a

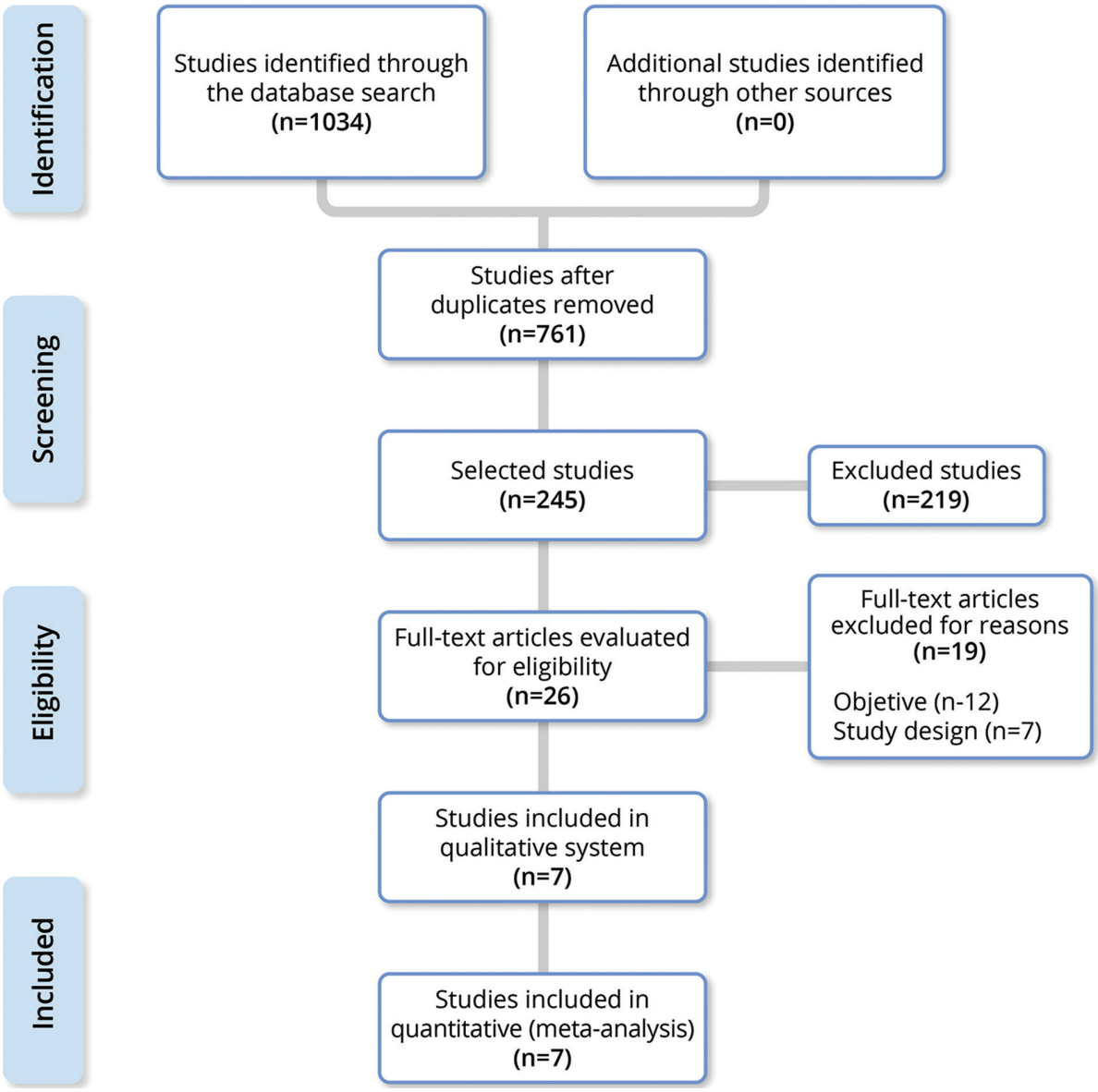

Chart 1. Flowchart summarizing the systematic review adapted to the PRISMA statement.

lower number of lesions when compared against dimethyl fumarate or placebo (Chart 3). This difference was statistically significant. On the other hand, no statistically significant differences were identified when comparing treatment with cladribine with fingolimod (–0.08 [–0.35; 0.19]) and teriflunomide (–0.28 [–0.64; 0.08]).

Adverse events that lead to a discontinuation of study drugs

No significant differences were found between cladribine tablets and the other evaluated treatments (Chart 4). In this case, the null effect is represented by the number one.

Discussion

In the absence of randomized clinical studies comparing all interventions for RRMS, a network meta-analysis is a plausible alternative for obtaining relative efficacy estimators. In Mexico, there are very few studies evaluating the efficacy and safety of treatments for MS.

A network meta-analysis by Siddiqui et al. (2018) in patients with RRMS showed that oral cladribine is among

Table 1. Included articles characteristics

Study	Study design	Participants	Intervention and dosing	n	Duration (Months)	Reported outcomes
CLARITY[16] NCT00213135	Multicentric RCT Phase III	Adults. RRMS McDonald criteria, EDSS (0-5.5). At least one relapse in the past 12 months.	Placebo Cladribine 3.5 mg Cladribine 5.25 mg	437 433 456	22	ARR, FRR. Time to first relapse. Mean number of gadolinium-enhanced T1 lesions, weighted active lesions on T2 and combined single lesions. Incidence of treatment emergent adverse events.
FREEDOMS[15] NCT00289978	Double-blind randomized, placebo-CT, Phase 3	Adults. RRMS McDonald criteria, EDSS (0-5.5).	Placebo Fingolimod 0.5 mg Fingolimod 1.25 mg	418 425 429	24	ARR. Time of disability progression. Number of gadolinium-enhanced lesions.
FREEDOMS II[17] NCT00355134	Double-blind randomized, placebo-CT, parallel groups, multicentric Phase 3.	Adults. RRMS McDonald criteria, EDSS (0-5.5).	Placebo Fingolimod 0.5 mg Fingolimod 1.25 mg	355 358 370	22	ARR. Change percentage in brain volume. Time of disability progression. Number and volume of gadolinium-enhanced T1 lesions. Adverse events.
TEMSO[18] NCT00134563	Double-blind randomized, placebo-CT, parallel group, Phase 3	Adults. RRMS McDonald criteria, EDSS (0-5.5). At least two relapses in the previous 2 years or one relapse in the previous year, but not within 60 days before randomization.	Placebo Teriflunomide 7 mg Teriflunomide 14 mg	363 365 358	25	ARR. Disability progression. Total volume of the lesion. Number of unique active lesions. Adverse events.
TOWER[19] NCT00751881	Double-blind randomized, placebo-CT, Phase 3	Adults. RRMS McDonald criteria, EDSS (0-5.5). At least one relapse in the last year or two relapses in the last 2 years and none in the 30 days prior to randomization.	Placebo Teriflunomide 7 mg Teriflunomide 14 mg	389 407 372	11	ARR. Time up to 12 weeks of sustained accumulation of disability. Adverse events.
DEFINE[20] NCT00420212	Double-blind randomized, placebo-CT, Phase 3	Adults. RRMS McDonald criteria, EDSS (0-5.5). At least one relapse the year before randomization.	Placebo Twice daily BG-12 240 mg Three times a day BG-12 240 mg	408 410 416	24	Relapses. Number of gadolinium-enhanced lesions. Time of disability progression. Adverse events.
CONFIRM[21] NCT00451451	Double-blind randomized, placebo-CT, Phase 3	Adults. RRMS McDonald criteria, EDSS (0-5). At least one relapse in the past 12 months or at least one gadolinium-enhanced lesion 0-6 weeks before randomization.	Placebo Twice daily BG-12 240 mg Three times a day BG-12 240 mg Glatiramer acetate 20 mg	363 359 345 350	22	ARR. Number of new T2 hypertensive lesions or increasing number of T2 lesions, T1-enhanced images. Adverse events.

RCT: randomized controlled clinical trial; EDSS: expanded disability status scale; ARR: annualized relapse rate; FRR: free relapse rate.

the most effective disease-modifying treatments and has an adequate safety profile comparable to other treatments, it also presents a significant reduction in relapse rate compared to teriflunomide and even parenteral drugs[13]. In addition to this, Papadopoulos et al. conducted a safety analysis on the likelihood to help or harm, defined as the ratio of number needed to harm to the number needed to treat with respect to adverse events causing discontinuation of treatment (NNTH AE-D), which showed favorable evidence for cladribine (72 [95% CI 27.9 to

Table 2. Population characteristics

Reference	Clinical form of the disease	Study arms	Sample size	Age	% women
Giovannoni et al., 2010[16]	RRMS	Placebo	437	38.7 ± 9.9	288 (65.9)
		Cladribine 3.5 mg	433	37.9 ± 10.3	298 (68.8)
		Cladribine 5.25 mg	456	39.1 ± 9.9	312 (68.4)
Kappos et al., 2010[15]	RRMS	Placebo	418	37.2 ± 8.6	298 (71.3)
		Fingolimod 0.5 mg	425	36.6 ± 8.8	296 (69.6)
		Fingolimod 1.25 mg	429	37.4 ± 8.9	295 (68.8)
Calabresi et al., 2014[17]	RRMS	Placebo.	355	40.1 ±8.4	288 (81)
		Fingolimod 0.5 mg	358	40.6 ± 8.4	275 (77)
		Fingolimod 1.25 mg	370	40.9 ± 8.9	281 (76)
O´Connor et al., 2011[18]	RRMS	Placebo.	363	38.4 ± 9.0	275 (75.8)
		Teriflunomide 7 mg	365	37.4 ± 9.0	255 (69.7)
		Teriflunomide 14 mg	358	37.8 ± 8.2	255 (71.0)
Confavreux et al., 2014[19]	RRMS	Placebo	389	38.1 ± 9.1	273 (70)
		Teriflunomide 7 mg	407	37.4 ± 9.4	300 (74)
		Teriflunomide 14 mg	372	38.2 ± 9.4	258 (69)
Gold et al., 2012[20]	RRMS	Placebo	408	38.5 ± 9.1	306 (75)
		Twice a day BG-12 240 mg	410	38.1± 9.1	296 (72)
		Three times a day BG-12 240 mg	416	38.8 ± 8.8	306 (74)
Fox et al., 2012[21]	RRMS	Placebo	363	36.9 ± 9.2	251 (69)
		Twice a day BG-12 240 mg	359	37.8 ± 9.4	245 (68)
		Three times a day BG-12 240 mg	345	37.8 ± 9.4	250 (72)
		Glatiramer acetate 20 mg	350	36.7 ± 9.1	247 (71)

RRMS: relapsing-remitting multiple sclerosis.

–129.5])[14]. In this context, our findings are consistent with published reports of cladribine and its safety profile.

In relation to the ARR, cladribine tablets had no significant difference in its effect on relapses compared with the other interventions, however, it had a statistically significant when compared to teriflunomide. The CLARITY study reports an effect size with a greater than 50% decrease in annual relapses, a decrease in disability of up to 30%, and the effect was consistent in sub-population analysis.

The analysis for the gadolinium-enhanced T1 lesions outcome found that the effect of cladribine was comparable to those presented with fingolimod[15]. Although there is no significant difference between cladribine, fingolimod, and teriflunomide, it must be taken into to consideration that the reported ARR is a stronger measure of efficacy compared to the number of T1 lesions.

The evidence provided by the therapeutic options individually, allows us to put the agents that are used on a daily basis into context, seen in a broader way. This review of oral administered drugs makes it possible to assess important clinical outcomes, while at the same time taking into account that the difference between the characteristics of each drug may affect the clinical outcome. At present, a range of disease-modifying drugs with different mechanisms of action is available, with simplified dosages and periodicity schedules. Cladribine tablets are a therapeutic option that offers the expected therapeutic effect, with an annualized administration scheme that confers comfort to the

Table 3. Data included in the meta-analysis

	Annualized relapse rate				Gadolinium-enhanced T1 Lesions				Adverse events leading to discontinuation of the study drug			
	Placebo		Intervention		Placebo		Intervention		Placebo		Intervention	
Study	n	Rate	n	Rate	$\bar{\mu}$	SD	$\bar{\mu}$	SD	n	Rate	n	Rate
CLARITY[16]	437	33%	433	14%	0.91	2.10	0.12	2.7	435	2.07%	430	3.49%
FREEDOMS[15]	418	40%	425	18%	1.1	2.40	0.2	0.80	418	7.66%	425	7.53%
FREEDOMS II[17]	355	40%	358	21%	1.2	2.97	0.4	1.84	355	10.42%	358	18.44%
TEMSO[18]	363	54%	358	37%	1.33	2.96	0.26	1.16	360	8.06%	358	10.89%
TOWER[19]	388	50%	370	32%	-	-	-	-	385	6.23%	371	15.63%
DEFINE[20]	408	36%	410	17%	1.8	4.20	0.1	0.60	408	13.48%	410	15.85%
CONFIRM[21]	363	40%	359	22%	2	5.60	0.5	1.70	363	10.47%	359	12.26%

$\bar{\mu}$ average; SD: standard deviation.

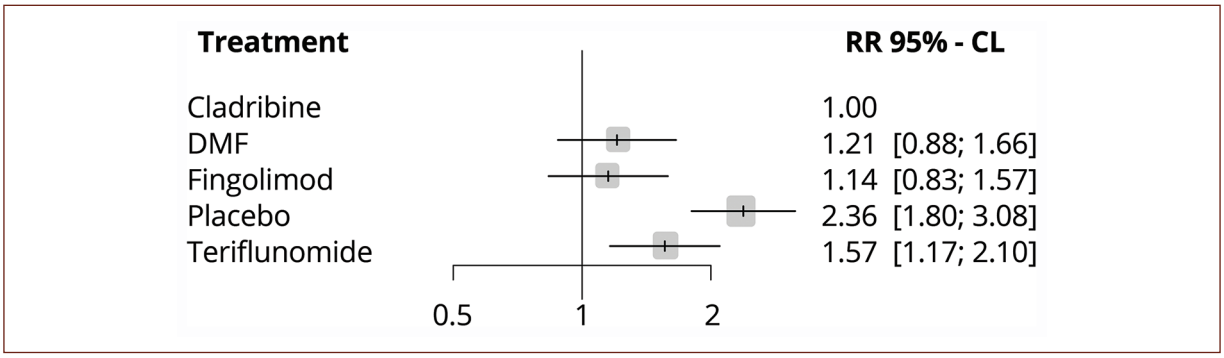

Chart 2. Forest plot in patients with relapsing-remitting multiple sclerosis randomized to receive cladribine tablets, dimethyl fumarate (DMF), fingolimod, teriflunomide, or placebo treatment with 95% confidence level and relative risk for annualized relapse rates (ARRs).

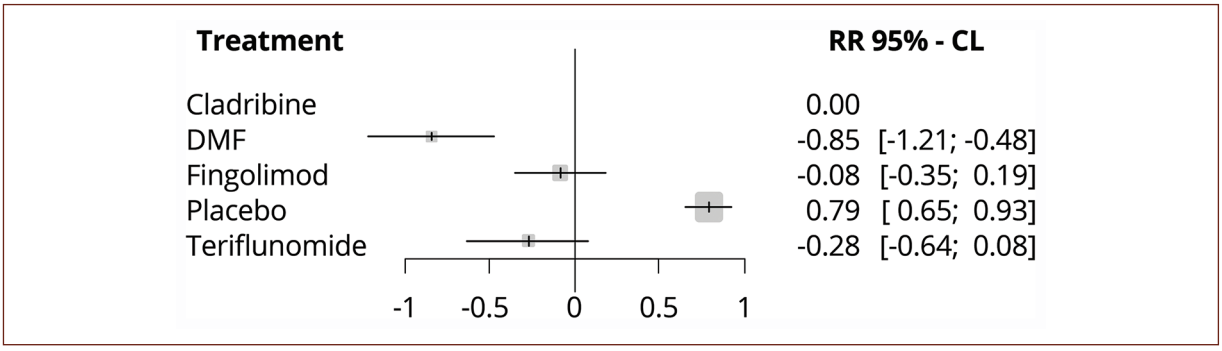

Chart 3. Forest plot in patients with relapsing-remitting multiple sclerosis randomized to receive cladribine tablets, dimethyl fumarate (DMF), fingolimod, teriflunomide, or placebo treatment with 95% confidence level. Difference in gadolinium-enhanced T1 lesions means per patient.

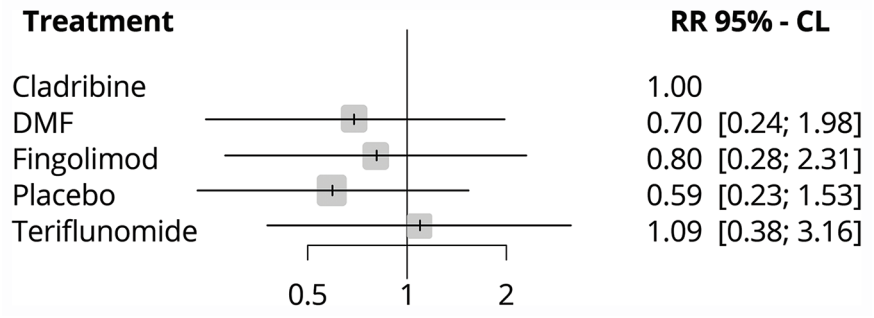

Chart 4. Forest plot in patients with randomized relapsing-remitting multiple sclerosis to receive cladribine tablets, dimethyl fumarate (DMF), fingolimod, teriflunomide, or placebo treatment with 95% confidence level. Relative risk for adverse events causing treatment interruption.

Table 4. Safety profile of oral drugs

Drug	Short-term side effects	Long-term efficacy	Long-term side effects	Important safety aspects
Fingolimod	Bradycardia, average of 8 bpm during the first infusion (2.3%). Macular edema. Elevation of liver function enzymes. Mild infections. Herpes zoster infection.	Data to 7 years: 84-96% free of gadolinium lesions, 70% free of T2-weighted lesions. Average PBVC: –2.8 for more than 84 months.	No new aspects to known side effects of crucial tests.	Herpes zoster infection in a small number of patients. PML risk 1/18.000.
Dimethyl fumarate	Flushing or redness. Gastrointestinal irritation. Lymphopenia.	ARR from years 1-5: 0.202, 0.163, 0.139, 0.143, and 0.138.	PML, so far 5 patients > 230,000 who have been treated with DMF, some cases reported with FUMADERM.	PML risk of 1/50,000. In people > 50 years, early lymphocyte reduction is associated with an increased risk of PML.
Teriflunomide	Asymptomatic increase of alanine aminotransferase. Headache. Diarrhea. Hair thinning. Nausea.	9 years of TEMSO follow-up. 55% relapse free. Stable EDSS scale average > 50% without progression.	No pattern of malignancies, especially hematologic cancers such as leukemia or lymphoproliferative tumors.	
Cladribine	Lymphopenia. Herpes zoster infection (< 10%). There is no increased risk of malignant tumors.	Data not available	Data not available	No reported cases of PML in multiple sclerosis.

*PML: progressive multifocal leukoencephalopathy (adapted from Faissner and Gold, 2018)[22].

patient and his caregiver, which undoubtedly favors therapeutic adherence. Cladribine tablets reach quickly and steadily its effect on lymphocytes after an administration, resulting in a good efficacy, safety, and proven tolerability profile.

The specific evidence establishes that all interventions require careful patient selection. According to the safety profile and tolerability of cladribine tablets, in the CLARITY study[16] due to its dose-dependent mechanism action, the most common adverse effect was lymphopenia, increasing the risk of an opportunistic infection; however, there are no reports of progressive multifocal leukoencephalopathy (PML), bradycardia, or macular edema attributable to cladribine tablets on patients with MS (Table 4). In relation to the safety profile, this meta-analysis shows no statistically significant

differences in adverse effects, but simply a different pattern.

Limitations and strengths of the study

The main limitation of the study remains that on Mexican population, regarding this disease, information is poor or scarce; so the results of the analysis must be interpreted with caution. Nevertheless, international literature did not provide randomized clinical trials that would allow direct comparisons, making an indirect comparison an alternative to explore the existent and limited alternatives.

The main strength of the study is the use of a network meta-analysis with a random effects model that allows homogenizing the main biases within the analysis to make indirect comparisons. The selection of the articles was carried out by specialists on the subject and in the event of any lack of concession, a third reviewer intervened.

Conclusion

Cladribine tablets demonstrated efficacy in terms of decrease of ARR and gadolinium-enhanced T1 lesions made in contrast with patients with long-term RRMS, as well as a good safety profile and tolerability that promote therapeutic adherence, becoming an appropriate therapeutic option for patients with RRMS. It is important to evaluate the different therapeutic interventions from a standardized perspective for an appropriate treatment selection that positively delays or modifies the natural course of this disease and can contribute to the quality of life of patients with RRMS.

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Con icts of interest

The authors LRM, GVS, DAO, BLYO, and SMH are responsible for the article content and declare have received honoraria from Merck. GVS, DAO, BLYO, and SMH are employees of HS Estudios Farmacoeconómicos S.A. de C.V., are ISPOR members and declare have received honoraria also from Roche, Novartis, Sanofi, Pfizer, and Biogen as well as have served in a consulting or advisory role for Roche, Celgene, and AstraZeneca. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

Ethical disclosures

Protection of human and animal subjects. The authors declare that no experiments were performed on humans or animals for this study.

Con dentiality of data. The authors declare that they have followed the protocols of their work center on the publication of patient data.

Right to privacy and informed consent. The authors declare that no patient data appear in this article.

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