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The effect of cladribine on T_1 'black hole' changes in progressive MS

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Abstract

We compared the changes of the volumes of T_1-hypointense lesions seen on the magnetic resonance imaging scans of the brain from 159 progressive multiple sclerosis (MS) patients who were enrolled in a double-blind, placebo-controlled trial assessing the efficacy of two doses of cladribine. Although in patients treated with cladribine there was a tendency to have a lower increase of T_1-hypointense lesion volumes than those treated with placebo, no statistically significant effect of cladribine on T_1-hypointense lesion accumulation was found over the one-year double-blind phase. Furthermore, no significant treatment effect was also detected in a subset of 22 patients who received placebo during the double-blind phase of the study and cladribine during the subsequent one-year open-label phase. We conclude that cladribine does not have a major impact on the mechanisms leading to severe tissue destruction in progressive MS.

Keywords: MS; MRI; T_1-hypointense lesions; Cladribine

1. Introduction

Cladribine (2-chlorodeoxyadenosine; 2-CdA) is a purine nucleoside analogue resistant to the action of adenosine deaminase, which results in preferential lymphocytoxicity. In cells with a high ratio of deoxycytidine kinase to deoxynucleotidase (e.g. lymphocytes and monocytes), cladribine is phosphorylated into the active triphosphate deoxynucleotide which damages DNA and promotes cell death [1]. Preliminary trials [2,3] reported that the long-lasting lymphocytotoxic activity of cladribine has the potential for modifying the evolution of progressive multiple sclerosis (MS). In a recent multicenter, randomized, double-blind, placebo-controlled trial of patients with progressive MS [4], it was shown that cladribine had a dramatic effect on the volume and number of active lesions (≥90% reduction) seen on enhanced magnetic resonance imaging (MRI) scans of the brain, a modest effect on the accumulation of T_2 lesion volume and no effect on the accumulation of disability.

As discussed in the previous paper [4,5], the discrepancy between the effect of cladribine on disability and MRI measures of MS activity and burden can be explained by the relatively short duration of the trial and the clinical characteristics of the patients studied. However, an alternative explanation might be that cladribine does not influence factors, such as severe demyelination and axonal loss, which are likely to be responsible for the accumulation of irreversible disability in MS. MRI enhancing lesions reflect the transiently increased blood–brain barrier permeability and inflammation [6] and T_2-weighted imaging provides non-specific information about the pathological substrate of MS lesions [7]. On the other hand, hypointense MS lesions on T_1-weighted scans ('black holes') represent areas with severe tissue disruption [8], and, in patients with secondary progressive MS, T_1-weighted hypointense lesion load correlate strongly with physical disability [9]. To investigate the effect of two

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doses of cladribine (0.7 mg/kg and 2.1 mg/kg) on the accumulation of 'black holes' in the same cohort of patients with progressive MS [4], we measured the volume of hypointense lesions at study entry and after one-year follow up. At the end of the double-blind phase, patients entered an open-label phase. Here we report the results of the analysis of 'black hole' changes during the double blind phase and the first year of the open-label phase.

2. Patients and methods

One hundred and fifty-nine patients with progressive MS were enrolled in a randomized, double-blind, parallel-group, placebo-controlled study to assess the safety and efficacy of 0.7 mg/kg and 2.1 mg/kg of cladribine administered by subcutaneous injection. The study included a four-week screening phase, a one-year double-blind phase, and a six-year open label phase. Patients were assigned to one of three parallel treatment groups (2.1 mg/kg cladribine; 0.7 mg/kg cladribine; or placebo). After all patients at a study site completed the double-blind phase, the blind was broken, and patients who fulfilled the hematologic dosing criteria were permitted to receive open-label cladribine treatment during the extension phase, provided at least 12 months had elapsed since the last dose of cladribine and there was evidence of disease progression. Further details about study population and design have been reported previously [4].

At study entry and at months 6, 12, 18 and 24, dual-echo and enhanced T_1-weighted scans (five to 10 min after the injection of 0.1 mmol/kg gadolinium–DTPA) were obtained from all patients. For T_1-weighted images, slices were axial, contiguous, 3 mm thick with a matrix size of 256×256 mm and a field of view of 250×250 mm. We used T_1-weighted images obtained at study entry, at month 12 (end of the double-blind phase) and at month 24 to measure the volumes of T_1-hypointense lesions. T_1-hypointense lesions were considered those areas with a signal intensity between that of the gray matter and that of the cerebro-spinal fluid and with corresponding lesions on both echoes of the dual-echo images. A single experienced observer, unaware of the treatment regime and scan acquisition order, identified such lesions and marked the corresponding areas on transparent sheets superimposed over the T_1-weighted hardcopies. Then, a trained technician, also unaware of the treatment regime and scan acquisition order, measured the T_1-hypointense lesion volumes using a segmentation technique based on local thresholding [4] and the marked hardcopies as a reference. Further details regarding scan acquisition and post-processing have been reported previously [4].

The effect of cladribine on the T_1-hypointense lesion volumes during the double-blind phase was assessed using an ANOVA model for repeated measures including time (baseline and month 12 scans) as the within subjects factor and treatment (placebo versus 0.7 mg/kg and 2.1 mg/kg cladribine) as the between subjects factor. This analysis was also performed considering primary and secondary progressive MS patients separately. For patients receiving placebo during the double-blind phase and who then were treated with cladribine between months 12 and 24, the changes of T_1-hypointense volumes between the two study periods were compared using a two-tailed Student *t*-test for paired data.

3. Results

Demographic and baseline characteristics of the patients studied as well as the effect of the two doses of cladribine on disability, enhancing lesion number and volume and T_2 lesion volumes have been reported previously [4]. For the whole population studied, the average T_1-hypointense lesion volumes were 4019 mm^3 (S.D. = 6547 mm^3) on the entry scans and 4104 mm^3 (S.D. = 6596 mm^3) on the scans obtained at month 12 (mean absolute change = +84.2 mm, mean percentage change = +2.4%). The average T_1-hypointense lesion volumes, the absolute and percentage volume difference between month 12 and study entry for the three treatment groups are reported in Table 1. T_1-hypointense lesion volumes were similar in placebo and cladribine-treated patients on the baseline scans. Although patients treated with 2.1 mg/kg cladribine showed a

Table 1
Mean (SE) T_1-hypointense lesion volumes at study entry and month 12 in patients treated with placebo, cladribine 0.7 mg/kg and cladribine 2.1 mg/kg

	T_1-hypointense lesion volumes Entry scan (mm^3)	T_1-hypointense lesion volumes Month 12 (mm^3)	Mean absolute change (SE) (mm^3)	Mean percentage change (SE) (%)
Placebo	3980 (1132)	4205 (1184)	+225 (143)	+4.2 (4.5)
Cladribine 0.7 mg/kg	4371 (1012)	4417 (995)	+45 (126)	+1.1 (4.4)
Cladribine 2.1 mg/kg	3711 (754)	3679 (712)	−31 (221)	−1.7 (3.4)

modest reduction of the volume of 'black holes' and patients treated with placebo had a higher increase in the volume of 'black holes' than those treated with 0.7 mg/kg cladribine, no significant difference was found between the placebo and the treatment arms. The same was true when primary and secondary progressive MS patients were considered separately (data not shown). Twenty-two patients who received placebo during the double-blind phase of the study received cladribine during the subsequent open-label phase. These patients had an average absolute increase of T_1-hypointense lesion volume 74 mm^3 ($SE = 107$ mm^3) during the first phase of the study and $= 63$ mm^3 ($SE = 153$ mm^3) during the second 12 months. This difference was not statistically significant.

4. Discussion

The encouraging results of two pilot studies of cladribine in progressive and relapsing–remitting MS [2,3] could not be confirmed in a multicenter, randomized, double-blind, placebo-controlled study of 159 patients with either primary or secondary progressive MS [4]. On the one hand, cladribine dramatically reduced the number of enhancing lesions and had a moderate, but statistically significant, effect on the accumulation of T_2 lesion burden. On the other, however, cladribine did not have any impact on disability accumulation. This clinical/MRI discrepancy is not surprising, considering the clinical characteristics and the relative small size of the patients cohort studied, the relative short duration of the follow up period [5] and the much greater sensitivity of MRI-derived measures compared to clinical measures in detecting MS-related changes [7].

However, this study [4] left unanswered the question whether the ability of cladribine to reduce enhancement and the accumulation of T_2 lesions would have had a subsequent clinical impact. In patients with clinically definite MS, the correlation between changes seen on conventional MRI scans and the long-term clinical evolution of MS is modest indeed [7]. One of the main reasons for this finding is the poor specificity of the abnormalities seen on T_2-weighted and post-contrast T_1-weighted scans to the most destructive aspects of MS, such as severe demyelination and axonal loss. Recent work has shown that T_1-hypointense abnormalities on post-contrast scans correspond to areas with severe tissue damage [8], that their extent correlates strongly with changes in disability in patients with secondary progressive MS [9], and that treatment with interferon beta-1 a slows down the rate of their accumulation in patients with relapsing–remitting MS [10]. Therefore, we measured the volumes of 'black holes' in patients with progressive MS treated with two doses of cladribine in a previous placebo-controlled trial [4] to assess whether cladribine was able to modify the mechanisms leading to tissue destruction within MS lesions. Although cladribine (particularly when given at 2.1 mg/kg) reduces the amount of 'black holes' on follow up scans compared to placebo, this effect is relatively modest and does not reach statistical significance. One might argue that with a longer follow up and a larger and more homogeneous sample of patients, this effect might become statistically significant. However, our results suggest that the magnitude of such an effect is likely to be clinically unimportant and we conclude that cladribine does not have a major impact on the mechanisms leading to severe tissue destruction in lesions of progressive MS patients.

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