

UPDATE ON NEW TREATMENTS IN MULTIPLE SCLEROSIS: ORAL CLADRIBINE

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Multiple sclerosis (MS) is a chronic condition that, in many cases, requires administration of disease-modifying therapies. However, all of the currently approved therapies for MS must be administered parenterally at regular intervals over the long term. Injections or infusions may cause difficulties, particularly for patients who are needle-phobic or those who lead active lifestyles. The difficulties associated with parenteral therapies can result in patients not taking their treatment regularly (poor adherence) or, indeed, refusing treatment; this lowers the effectiveness of the therapy, causing patients to lose faith in the therapy and become less likely to adhere to the drug regimen. There is, therefore, a clear unmet need for an oral MS therapy that could ease initiation of treatment, and enhance long-term treatment adherence, convenience and overall patient satisfaction. MS is considered to be a heterogeneous autoimmune disease with no single therapeutic target, so there is also a need for treatments with different mechanisms of action, as some patients do not respond adequately to current treatment options.

An oral tablet formulation of cladribine has been developed as an investigational treatment option intended to fulfil both of these goals. Cladribine (2'-chloro-2'-deoxyadenosine) is a purine nucleoside analogue with preferential and sustained lymphocyte-depleting properties.¹ It has a more significant effect on CD4+ T-cells than CD8+ T-cells, with relative sparing of other haematological and immune cells, including B-cells, and is able to cross the blood-brain barrier to act on the central nervous system.^{1, 2} Cladribine also reduces levels of proinflammatory cytokines and chemokines.^{3, 4} In MS, the novel mechanism of action of cladribine is expected to reduce inflammation, autoimmune effects and autoreactive cell damage, thereby improving the integrity of the blood-brain barrier. Thus, the effects of cladribine may target some of the key events that are central to the pathophysiology of MS.

A parenteral formulation of cladribine is approved in many countries for the treatment of hairy cell leukaemia and other lymphoid malignancies. The safety profile of cladribine has been well characterized from over 15 years of clinical experience in non-MS indications.

Several preliminary randomized, double-blind, placebo-controlled clinical trials of parenteral cladribine have already been performed in patients with various forms of MS.⁵ A total of 2292 patients with either chronic progressive or relapsing forms of MS were treated with cladribine in the MS-Scripps, MS-001 and Scripps-C studies. Results showed that parenteral cladribine therapy was associated with a consistent and marked reduction in the development of gadolinium-enhancing T1 lesions.^{1, 6, 7} Patients with relapsing-remitting MS (RRMS) also showed a significant reduction in relapse rate (51%; $p < 0.01$) and relapse severity between month 7 and month 18 (end of study) in the cladribine treatment arm compared with placebo.⁷ Cladribine was generally well tolerated at the doses now proposed for use in MS, with a mild and manageable side-effect profile that was similar to placebo.^{1, 6, 7} There were no reports of neurotoxicity, nephrotoxicity or cardiotoxicity.

The safety and efficacy of parenteral cladribine has also been studied in a 2-year, placebo-controlled crossover study in patients with active RRMS conducted in Poland. Parenteral cladribine achieved a marked reduction in relapse rate.⁸ Furthermore, patients had a statistically significant lower requirement for steroids during periods of cladribine treatment compared with placebo, which supports a reduction in the severity of relapses. Mean Expanded Disability Status Scale scores remained stable during the study. This therapeutic efficacy was associated with a sustained reduction in lymphocyte count, reflecting the therapeutic mechanism of action of cladribine. Treatment was generally well tolerated.

Following the promising efficacy data obtained from studies of the parenteral formulation in MS, Phase III clinical studies of an oral tablet formulation of cladribine in patients with RRMS are now underway. One of these studies is the CLARITY (CLAdRibine tablets Treating multiple sclerosis orally) study, a 96-week, double-blind clinical trial that aims to evaluate the safety and efficacy of oral cladribine tablets in patients with RRMS.⁹ A 2-year extension to the CLARITY study will provide information on the long-term safety, tolerability and efficacy of extended administration of oral cladribine tablets.¹⁰ Data should be available in 2009.

The unique mechanism of action of cladribine with its sustained immunological effects, together with a suitable pharmacokinetic profile, permit oral cladribine tablets to be dosed once daily for 1 week per month for 2 or 4 consecutive months per year. Such short-course oral dosing is expected to be convenient for patients and could impact positively on quality of life.

Cladribine promises to revolutionize the MS treatment paradigm with its oral administration, low frequency of administration and potential for a favourable tolerability profile. Existing efficacy and safety data are encouraging, and, assuming positive results from the ongoing clinical programme, it is hoped that oral cladribine tablets may contribute to a high level of treatment adherence and overall patient satisfaction from the start of therapy, which could, in turn, have a beneficial effect on treatment outcomes over the long term.

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