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MILESTONE 7

The story of cladribine reaches its climax

In June 2017, the European Medicines Agency (EMA) approved oral cladribine for the treatment of relapsing–remitting multiple sclerosis (RRMS). However, cladribine is not a new drug, and its efficacy in RRMS had already been demonstrated in 2010, but safety concerns prevented its approval. The eventual approval was a landmark because cladribine is the most effective of the oral therapies and is the only oral option for pulsed immune reconstitution, which otherwise requires monoclonal antibodies. Additionally, cladribine's mechanism of action differs from that of other current MS treatments that target lymphocyte function.

Cladribine, or 2-chloro-2′-deoxyadenosine, is a synthetic adenosine analogue that is activated in cells when it is phosphorylated by deoxycytidine kinase. The triphosphorylated active form is cytotoxic, resistant to breakdown by adenosine deaminase and disrupts DNA synthesis and repair, thereby inducing apoptosis. In most cell types, the drug is inactivated through dephosphorylation by 5′-nucleotidase, but in lymphocytes, and particularly B cells, the kinase:phosphatase ratio is high, so the drug remains active and preferentially depletes these cells, leaving other cell types unaffected.

In 2010, the efficacy of oral cladribine for the treatment of RRMS was tested in the 96-week phase III CLARITY trial. Patients with RRMS were randomly assigned to receive placebo or cladribine at a dose of 3.5 mg/kg or 5.25 mg/kg body weight administered over 1–2 weeks at the start of each year. Cladribine at both doses reduced the annual relapse rate at 96 weeks by more than 50% compared with placebo, increased the proportion of patients who were relapse-free (~79% versus 61%) and reduced the risk of 3-month sustained progression of disability by >30% and the mean lesion number detected by MRI by >70%.

Despite these highly encouraging clinical benefits, development of solid tumours, as well as the expected adverse effects of lymphopenia and infections, in a small number of cladribine-treated patients meant that approval for cladribine was denied by the FDA and EMA and the drug did not come to market (although ongoing trials were completed). However, concerns about the safety of cladribine have since been ameliorated by a meta-analysis in which the cancer risk associated with cladribine was found to be similar to that associated with other disease-modifying drugs.

In 2014, the results of the 96-week phase III ORACLE MS trial were reported. This trial tested the effect of cladribine on the time to conversion from a first demyelinating event to clinically definite MS. The trial was terminated early, but both 3.5 mg/kg and 5.25 mg/kg cladribine increased the time to MS diagnosis and reduced numbers of MRI lesions compared with placebo. Importantly, adverse events occurred at a similar rate in all patient groups, confirming the safety of cladribine.

> "cladribine has finally arrived as an effective and unique oral therapy for MS"

In 2018, the results of the CLARITY Extension study were published. In this study, patients from the placebo group in the original CLARITY trial received low-dose cladribine, whereas recipients of cladribine in the original trial were randomly assigned to receive cladribine or placebo. This study design enabled assessment of the effects of long-term cladribine treatment and early versus late treatment, and of the durability of cladribine's clinical effects. Long-term dosing did not increase efficacy, but later treatment was associated with a shorter time to first relapse. Crucially, among patients who received cladribine in CLARITY but placebo in CLARITY Extension, the proportion who were free from relapses and disease progression was unchanged, indicating a durable clinical response.

The short duration of cladribine dosing in the 1-year treatment cycles (allowing haematological recovery during the rest of the year), together with the durable clinical response, suggests that cladribine has potential as an induction therapy. The durability of cladribine's clinical effects also suggests that it 'resets' the immune system, thereby enabling long-lasting disease remission without the need for maintenance therapy.

Despite a long and, at times, uncertain route to regulatory approval, cladribine has finally arrived as an effective and unique oral therapy for MS.

Grant Otto, Associate Editor, Nature Reviews

ORIGINAL ARTICLES Giovannoni, G. et al. A placebo-controlled trial of oral cladribine for relapsing multiple sclerosis. *N. Engl. J. Med.* **362**, 416–426 (2010) | Leist, T. P. et al. Effect of oral cladribine on time to conversion to clinically definite multiple sclerosis in patients with a first demyelinating event (ORACLE): a phase 3 randomised trial. *Lancet Neurol.* **13**, 257–267 (2014) | Giovannoni, G. et al. Safety and efficacy of cladribine tablets in patients with relapsing-remitting multiple sclerosis: results from the randomized extension trial of the CLARITY study. *Mult. Scler.* **24**, 1594–1604 (2018)
FURTHER READING Hohlfeld, R. et al. Cladribine — a contentious therapeutic contender for MS. *Nat. Rev. Neurol.* **7**, 425–427 (2011) | Wiendl, H. et al. Cladribine — an old newcomer for pulsed immune reconstitution in MS. *Nat. Rev. Neurol.* **13**, 573–574 (2017)