First Oral Short-course Treatment for Adults with Highly Active Relapsing Multiple Sclerosis Now Approved in Europe

An expert interview with Gavin Giovannoni

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In recent years, a number of novel disease-modifying therapies have been approved for the treatment of patients with multiple sclerosis (MS). Cladribine tablets (Mavenclad™, Merck), a purine nucleoside analogue, has been used for the treatment of several neoplasms[1] and, in the last 15 years, has been developed for the treatment of MS. The clinical development of cladribine tablets has encountered a number of setbacks but in June 2017, the European Commission granted marketing authorisation for cladribine tablets for the treatment of relapsing-remitting MS (RRMS) in patients with high disease activity.[2] Approval was based on more than 10,000 patient years of data with more than 2,700 patients included in the clinical trial programme and more than 10 years of observation in some patients. In September 2017, cladribine tablets became available for patients with MS in the UK and Ireland. In an expert interview, Gavin Giovannoni, discusses this new addition to the treatment armamentarium for RRMS.

Q: What are the advantages of cladribine tablets over other oral disease-modifying therapies for MS?

The most important advantage is in the way in which the tablets are administered. They are not a maintenance treatment and therefore do not have to be given continuously. They are administered in short courses, and cause the immune system to be depleted and reconstituted through a unique mechanism, targeting the lymphocyte population, particularly B lymphocytes. When the immune system is reconstituted, the autoimmune response that underlies MS is suppressed, resulting in an immune system that is competent in terms of fighting infections, immune surveillance for malignancies and for generating immune responses to novel infections and vaccines. The incidence of potential long-term side effects is therefore likely to be low. This minimizes the risk of secondary autoimmune disease when the immune system reconstitutes, unlike alemtuzumab, which has a long-term risk of secondary autoimmune disease in 45–50% of patients; necessitating routine monthly monitoring for up to 4 years after the last course. Since cladribine tablets are given as short courses – 5 days in month 1, 5 days in month 2, repeated a year later – there are up to 20 days of treatment over 2 years. The treatment effect persists into years 3 and 4 in the majority of patients.

Another advantage of cladribine is the fact that it is semi-selective. There are other immunotherapies that deplete the immune system but these tend to affect the entire immune system whereas cladribine selectively targets the lymphocyte population, not affecting innate immunity, so we don't see infections associated with other therapies in this class. The only infection that has been noted is recurrent herpes infections, particularly shingles, because cladribine suppresses the T lymphocyte population. This complication associated with cladribine is seen with almost all immunosuppressive therapies.

The most important advantage of cladribine tablets is their ease of use. The monitoring requirement for liver function tests and other blood tests is lower than other disease-modifying therapies (DMTs). This reduces the pressure on nursing staff. Patients do not need repeated visits to hospital, in contrast with other DMTs such as alemtuzumab where monthly visits are needed for blood and urine tests and possibly treatment modification based on the results of these tests.

Q: What is the mechanism of action of cladribine tablets?

Cladribine affects DNA metabolism. It is a chlorinated purine analogue; the chlorination prevents it from being broken down by adenosine deaminase. It enters the cell and becomes phosphorylated. The triphosphorylated form then becomes incorporated into DNA and kills cells by apoptosis. The intracellular ratio of kinases to phosphatases favours the accumulation of cladribine in lymphocytes. Hence it selectively depletes lymphocytes, particularly B cells,[3] without having a significant impact on leucocytes. In addition, the kinetics of depletion is slow, occurring over months. By contrast, alemtuzumab causes cell lysis within hours, resulting in side effects such as infusion site reaction, temperature and rash.

Q: Could you tell us about the clinical development of cladribine tablets, leading to their recent approval in the UK and Ireland?

Cladribine was originally an oncology product and was classified as a chemotherapy agent. The first submission for regulatory approval in 2011 only included one pivotal trial, the phase III CLAdRIbine Tablets treating MS orallY (CLARITY) trial.[4] This submission was rejected based on a safety signal related to malignancies (4 cases of malignancies occurred in the cladribine study arm versus none in the placebo group). However, when compared with other DMTs, the rate of malignancies was as expected and the rate in the placebo arm was very low. More safety data has emerged since, including a second clinical trial, extension study and registry, which suggest that cladribine does not increase the incidence of malignancies over the expected background rate in the short term.[5,6] In addition, further analysis of clinical data revealed that cladribine tablets are particularly beneficial in patients with highly active disease, having an impact on relapse and disability progression. Another important parameter, which is increasingly used in studies of MS therapies, is no evident disease activity (NEDA). In the CLARITY phase III study, NEDA was 47%, which places cladribine among the DMTs with the highest efficacy.[7–12]

Q: Which patients are likely to benefit most from treatment with cladribine?

The patients who are likely to benefit most are treatment naïve patients with more active disease. The clinical studies involved patients with active MS in terms of having had a relapse in the last 2 years but also an MRI scan that showed high lesion load and/or gadolinium-enhancing lesions at baseline. Cladribine is also beneficial as a second- or third-line treatment in patients who have experienced disease breakthrough on other DMTs.[13,14] ❑

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