Title: **Cladribine controls multiple sclerosis via memory B cell depletion**

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Text: **Background:** Cladribine is a lymphocyte-depleting agent that inhibits relapsing MS. We developed a compassionate-use programme using subcutaneous cladribine in people with MS (pwMS) ineligible for licensed disease modifying drugs (DMT). Drug dose was adapted to individual lymphocyte levels. We hypothesized that (i) cladribine preferentially depletes memory B cells to be consistent with other high-efficacy DMT, and (ii) adapted dosing would avoid severe lymphopenia.

Methods: We obtained the regulatory submission of oral cladribine from the European Medicines Agency. pwMS consented to receive 60-70mg s.c. cladribine and have blood samples immunophenotyped. Expression data of genes associated with cladribine activity were extracted from public databases.

Results: 12 month efficacy of 3.5mg/kg oral cladribine was associated with modest (~40%) depletion of CD4+ and mild (~20%) depletion of CD8+ T cells, however marked (~85%) depletion of CD19+ B cells. 1/57 showed a transient grade 3 lymphocyte toxicity compared to 106/126 people receiving alemtuzumab . Although the number of CD19+ B cells often recovered to normal, both class-switched (IgD-) and non-switched (IgD+) CD19+/CD27+ memory B cells remained significantly below normal limits at all time points analysed (1-12 months post-dosing). High deoxycytidine kinase (DCK) levels, which produce toxic phosphorylated cladribine moieties, were found in B compared to T cells, and in germinal centre B cells, which form memory B cells. High DCK coupled with low levels of adenosine deaminase (ADA) and low adenosine-active cytoplasmic 5' nucleotidases, and the slow repopulation of memory B cells create a molecular mechanism for selective targeting of the memory B cell pool by cladribine.

Conclusions: Cladribine selectively induces marked and long-lasting memory B cell depletion similar to alemtuzumab creating a central unifying mechanism of action for cladribine and other highly effective DMT. Personalized dosing based on individual lymphocyte response may de-risk the use of cladribine further.

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