New drugs may improve, complicate treatment for multiple sclerosis

Treatments are limited for people with multiple sclerosis. Interferon, for instance, only modestly decreases the chances of a relapse and, like other drugs for the disease, must be injected. Two drugs already in use for other conditions now offer hope for a more effective therapy that can be taken as a pill. Cladribine, developed for leukemia, and fingolimod, developed for transplant rejection, both put a big dent in the rate of relapse, according to three new studies[1–3]. Cladribine results in the selective long-term depletion of $CD4^+$ and $CD8^+$ T cells, and fingolimod prevents antigen-activated lymphocytes from leaving the lymph nodes. Both drugs target inflammation, the key driver of injury in multiple sclerosis—but this mechanism of action also raises concerns about side effects, say the experts.

Hans Link:

That cladribine and fingolimod, compared to placebo, reduce the relapse rate by about 60% and the risk of disability progression is gratifying news for people with multiple sclerosis. But this does not mean that a cure for multiple sclerosis has emerged.

First, both studies include only relapsing-remitting multiple sclerosis (RRMS), comprising about a third of the about 2 million people with multiple sclerosis worldwide. Whether people with other forms of the disease—such as secondary progressive multiple sclerosis (SPMS), the most prevalent form—will benefit from oral cladribine or fingolimod is not known (although a 1996 trial showed that intravenous cladribine stabilized or even slightly improved SPMS). Second, a substantial proportion of the treated patients in both studies continued to have relapses, increasing disability or both.

The studies also leave several unresolved questions. These include determining the risk of long-term side effects, including the possible development of progressive multifocal leukoencephalopathy (PML) due to reactivation of latent JC virus and increased prevalence of cancers with increasing length of immunomodulating therapy; defining the lowest possible effective dose for each compound; and identifying possible combination therapies with enhanced beneficial effects.

When cladribine and fingolimod become available for treatment of multiple sclerosis, the neurologist's choice of best possible therapy for the individual patient will become more challenging. The dictum "first, do no harm" should be kept in mind. The currently used drugs interferons and glatiramer acetate have acceptable side effect profiles but lower the relapse rate by only 30%, do not substantially influence disability progression and are not effective in SPMS or primary progressive multiple sclerosis. Natalizumab (Tysabri) is used in severe RRMS and lowers the relapse rate by 60%, but the risk of developing PML increases with number of natalizumab infusions, and reports of 31 confirmed cases of PML had been received by the FDA, with about 10 deaths.

Although cladribine and fingolimod had similar clinical effects in these studies, whether cladribine has a more benign side effect profile remains an open question. I bet that access to both cladribine and fingolimod, for administration in low oral doses, will mean a great leap forward for people with multiple sclerosis, but expanded and comparative trials need to be done.

Professor of Neurology, Karolinska Institute, Stockholm, Sweden.

COMPETING INTERESTS STATEMENT

The author declares competing financial interests: details accompany the full-text HTML version of the paper at http://www.nature.com/naturemedicine/.

> "The dictum "first, do no harm" should be kept in mind.—Hans Link"

Roland Martin:

Neurologists have prescribed the first-line therapies for multiple sclerosis, interferon-β and glatiramer acetate, for more than 15 years. Although these drugs are only moderately effective and need to be injected, they are well tolerated.

The newly tested oral agents, fingolimod and cladribine, may suffer from the opposite problem. The new studies show that these agents are more effective than the old ones, as was directly shown for fingolimod, but it is clear that their adverse event profiles are not trivial.

Side effects observed during these relatively short trials range from reduced blood cell counts to serious infections and neoplasms for both drugs and macular edema, hemorrhagic encephalitis and cardiovascular events for fingolimod. Even though the frequency of these events was low in the reported large trials, their risk should not be underestimated, as the 'prototypical' patient with multiple sclerosis is in his or her early to mid-20s and is looking at long-term therapy. Moreover, the best dose with respect to efficacy has not been identified; for both new drugs, the lower dose was as effective or more effective than the higher one. New trials testing whether lower doses are safer, but also effective, should therefore be considered.

The availability of these drugs will potentially also greatly increase the complexity of disease management. For instance, cladribine acts over very long periods of time and may raise the risk of infectious complications such as progressive multifocal leukoencephalopathy if a treatment such as natalizumab is started too early after stopping cladribine. Another issue is whether cladribine may affect fertility, as it is incorporated into DNA and causes DNA strand breaks.

Oral agents are eagerly awaited by people with multiple sclerosis and their physicians, and fingolimod and cladribine represent a major step forward in treating this disease. But outstanding questions clearly remain.

Institute for Neuroimmunology and Clinical Multiple Sclerosis Research, University Medical Center-Eppendorf, Hamburg, Germany.

1. Kappos, L. *et al.* A placebo-controlled trial of oral fingolimod in relapsing multiple sclerosis. *N. Engl. J. Med.* **362**, 387–401 (2010).
2. Cohen, J.A. *et al.* Oral fingolimod or intramuscular interferon for relapsing multiple sclerosis. *N. Engl. J. Med.* **362**, 402–415 (2010).
3. A placebo-controlled trial of oral cladribine for relapsing multiple sclerosis. *N. Engl. J. Med.* **362**, 416–426 (2010).