

Oral fumarate for relapsing-remitting multiple sclerosis

Approved therapies for relapsing-remitting multiple sclerosis include interferon beta and glatiramer acetate as first-line, and natalizumab and mitoxantrone as second-line.¹ The first-line drugs reduce disease activity and progression only moderately, and the more efficacious second-line drugs have serious adverse effects. Further, all approved drugs for the treatment of multiple sclerosis require frequent subcutaneous or intramuscular injections, or intravenous infusions in outpatient clinics. Hence there is a great need for oral drugs that match the first-line injection therapies in efficacy and safety.

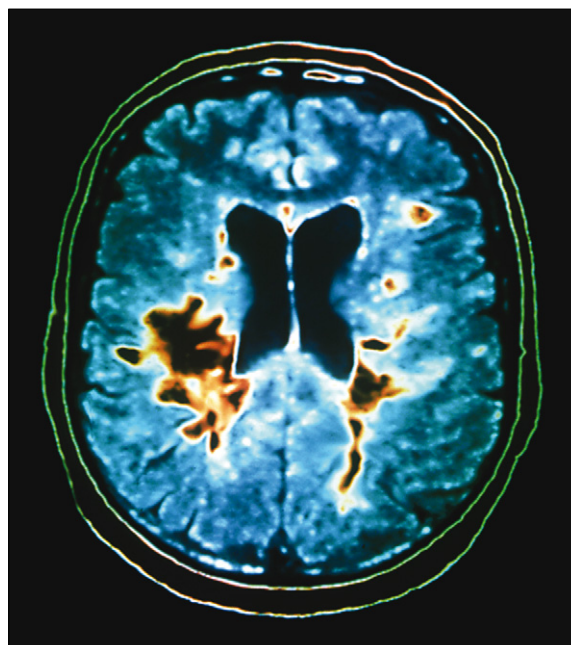
In today's *Lancet*, Ludwig Kappos and colleagues report that an oral formulation of dimethyl fumarate (BG00012), up to 240 mg three times daily, reduced new inflammatory lesions (serial MRI) in patients with relapsing-remitting multiple sclerosis.² The study was a 24-week placebo-controlled dose-finding trial, with the mean total number of new gadolinium-enhancing (GdE) lesions from weeks 12 to 24 as the primary outcome measure. The highest dose reduced the number of GdE lesions by 69% compared with placebo, and gave significant reductions in several other MRI outcomes; the two lower doses had no effect on any of the MRI outcomes. This result raises the question whether 240 mg three times daily is the most effective dose, or whether higher doses, if tolerable, could have a stronger effect. The study was not powered to show superiority over placebo in clinical outcomes, but a non-significant 32% relative reduction in the annualised relapse rate was observed. The drug seemed safe, but was associated with adverse effects, especially flushing and gastrointestinal symptoms. However, it is worrying that 25% of patients receiving BG00012 at 240 mg three times daily withdrew from the 24-week study.

Fumaric acid has been used for psoriasis³ and an open-label trial indicated that BG00012 could be beneficial in relapsing-remitting multiple sclerosis.⁴ The mechanism by which BG00012 works in multiple sclerosis is not known; dimethyl fumarate and its active metabolite methylhydrogenfumarate may be immunomodulatory and neuroprotective. By activating the transcription factor nuclear-factor-E2-related factor 2 (Nrf2), fumarates induce expression of endogenous antioxidative factors in rat brain cells in vitro,⁵ which may protect the CNS from

the detrimental effect of reactive oxygen intermediates released as part of the inflammatory process in multiple sclerosis. Indeed, Nrf2 knockout mice develop a leuco-encephalopathy with astrogliosis, suggesting a role of Nrf2 in the maintenance of myelin.⁶ Fumarates also inhibit the transcription factor nuclear-factor κ B, which is important for the expression of several inflammatory cytokines, chemokines, and adhesion molecules.⁷ In experimental autoimmune encephalomyelitis, an animal model of multiple sclerosis, fumarate inhibited the disease course, inhibited macrophage activation in the spinal cord, and increased expression of interleukin 10.⁸

Recently, a phase II trial of laquinimod, another oral treatment for multiple sclerosis, was reported.⁹ The higher of two doses showed a 40% reduction in the number of GdE lesions, compared with placebo. Phase II studies of other oral preparations have been reported,^{10,11} and phase III studies of at least four other new oral drugs (cladribine, fingolimod, teriflunomide, and laquinimod) for relapsing-remitting multiple sclerosis are in progress.¹² Hence, within the next 4–5 years neurologists may be able to choose between up to five new oral drugs for relapsing-remitting multiple sclerosis, although perhaps not all will be marketed after the phase III results.

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MRI scan of brain of patient with multiple sclerosis

Destruction of myelin sheaths around axon fibres of brain is seen in large demyelinated lesions (black/orange).

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The balance between efficacy, safety, and convenience will be decisive for the choice of drug. Oral formulations have advantages in convenience and will be preferred by most patients, as long as efficacy and safety are similar to that of injectable alternatives. Although comparison of drugs tested in different placebo-controlled trials is difficult and should be done cautiously, BG00012 might have a favourable benefit-to-risk profile compared with its oral competitors and the currently available first-line injectable drugs. However, we will have to await the results from the ongoing large phase III trials to establish the place of BG00012 and other oral drugs in the treatment of relapsing-remitting multiple sclerosis.

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JAK2—a new player in acute lymphoblastic leukaemia

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Acute lymphoblastic leukaemia is the commonest paediatric malignancy, and, genetically, has long been one of the best characterised tumours.¹ In today's *Lancet*, Dani Bercovich and colleagues² add mutations of the tyrosine kinase JAK2 to the growing list of genetic alterations implicated in the pathogenesis of acute lymphoblastic leukaemia.

Acute lymphoblastic leukaemia is characterised by chromosomal abnormalities, such as gains and losses of whole chromosomes, and recurring chromosomal translocations, which include t(12;21) *ETV6-RUNX1*, t(1;19) *TCF3-PBX1*, t(9;22) *BCR-ABL1*, and rearrangement of *MLL*. Identification of these abnormalities is important for clinical management, and has provided crucial insights into normal and leukaemic haemopoiesis. Children with Down's syndrome develop a unique range of haematological disorders with important differences from those seen in children without this syndrome.³ In about 10% of infants with Down's syndrome,

haemopoietic progenitors acquire mutations in the transcription factor GATA1 (figure), and give rise to a transient myeloproliferative disorder that resolves spontaneously in most cases. A fifth of cases subsequently evolve into acute myeloid leukaemia.

Overall, children with Down's syndrome have up to a 40-fold increased risk of acute myeloid leukaemia, which is often of megakaryocytic lineage and is highly sensitive to cytotoxic chemotherapy. Such children are also at increased risk of acute lymphoblastic leukaemia, but unlike myeloid leukaemia associated with Down's syndrome, leukaemic cells in lymphoblastic leukaemia associated with Down's syndrome are not more sensitive to chemotherapy and outcome is often poor.⁴ The nature of the genetic abnormalities underlying acute lymphoblastic leukaemia in Down's syndrome is poorly understood. Bercovich and colleagues' finding that JAK2 is mutated in a substantial proportion of acute lymphoblastic leukaemia cases is notable for two reasons: it is one of