

First oral MS drugs effective in phase III trials

The first two oral agents for multiple sclerosis, cladribine (Movectro; Merck Serono) and fingolimod (Novartis), effectively reduce the annual relapse rate in patients with relapsing-remitting multiple sclerosis, according to three recent phase III trials (*New England Journal of Medicine*, early online publication, 20 January 2010).

First, a 96-week, double-blind, placebo-controlled, multicentre trial of cladribine compared two doses of cladribine (3.5mg/kg and 5.25mg/kg, short-course oral tablet therapy) with placebo (total n=1326). Patients who received cladribine had a significantly lower annual relapse rate than patients in the placebo group (0.14 and 0.15 for 3.5mg/kg and 5.25mg/kg, respectively, versus 0.33; $p<0.001$).

Second, a 24-month, double-blind, randomised, placebo-controlled trial of fingolimod compared two doses of fingolimod (0.5mg and 1.25mg, once daily) with placebo (total n=1272). Patients who received fingolimod had a significantly lower annual relapse rate than patients in the placebo group

(0.18 and 0.16 for 0.5mg and 1.25mg, respectively, versus 0.40; $p<0.001$).

Third, a 12-month, multicentre, randomised, double-blind, double-dummy, parallel-group trial compared fingolimod (0.5mg and 1.25mg, once daily) with intramuscular interferon beta-1a (weekly dose of 30µg) (total n=1292). The annual relapse rate was significantly lower in patients receiving fingolimod than in those receiving interferon (0.16 and 0.20 for 0.5mg and 1.25mg, respectively versus 0.33; $p<0.001$).

Other parameters, such as the risk of disability progression and MRI measures of disease, also improved with the oral agents.

Charles Tugwell, specialised clinical pharmacist in neurology/neurosurgery at Barts and The London NHS Trust, commented: "The results of these three trials are very encouraging and take us a step further towards the next significant advance in the treatment of MS. Not only will treatments that can be taken orally be more acceptable and convenient for patients, but evidence from these studies

suggests the outcomes in clinical terms are at least as effective, if not superior to those achieved with beta-interferon."

Adverse events led to discontinuation in 7.9% of patients who received 5.25mg cladribine and 3.5% of patients who received 3.5mg, compared with 2.1% of patients who received placebo; 14.2% who received 1.25mg fingolimod and 7.5% who received 0.5mg, compared with 7.7% of those who received placebo; and 10% of patients who received 1.25mg fingolimod and 5.6% who received 0.5mg, compared with 3.7% of those who received interferon beta-1a.

Mr Tugwell said: "At this early stage of experience there is limited information on the long-term adverse effects of these drugs. When they become available for use it will be crucial to build in mechanisms for appropriate monitoring of adverse effects, and set up a robust post-marketing surveillance programme."

He added: "I wait with interest to see what NICE will decide about these drugs. This will clearly be important in determining their status within the NHS."

Pazopanib shows positive effect in renal cell carcinoma

Pazopanib (GlaxoSmithKline) improves progression-free survival in treatment-naïve and cytokine pre-treated patients with advanced and/or metastatic renal cell carcinoma, according to a recent study (*Journal of Clinical Oncology*, early online publication, 25 January 2010).

The randomised, double-blind, global, multicentre, placebo-controlled phase III trial evaluated the safety and efficacy of pazopanib monotherapy in 435 patients (placebo n=145; pazopanib n=290) who had advanced and/or metastatic renal cell carcinoma.

Treatment with pazopanib significantly prolonged progression-free survival compared with placebo (median progression free survival 9.2 versus 4.2 months; hazard ratio 0.46, 95% CI 0.34–0.62; $p<0.001$). This effect was seen in both the treatment-naïve subgroup (total n=233) and the cytokine pre-treated subgroup (total n=202).

The tumour response rate for pazopanib treated patients in the overall study population was 30% compared with 3% in the placebo group ($p<0.001$), following a median of 58.7 weeks' treatment.

The most commonly reported adverse events were diarrhoea, hypertension, hair colour changes and nausea (>20% of patients).

Anne Hines, lead pharmacist at Merseyside and Cheshire Cancer Network, told *The British Journal of Clinical Pharmacy*: "Since the control group was split roughly half and half between patients who were treatment-naïve and those who had progressed on one prior cytokine therapy, these two groups should be considered separately. This is what the National Institute for Health and Clinical Excellence will be doing later this year."

Ms Hines pointed out that in the treatment-naïve group, pazopanib showed

a progression free survival of 11.1 months, which is similar to that seen with sunitinib (11 months). "The comparator arms between the trials of pazopanib and sunitinib (Sutent; Pfizer) are different, but these results show roughly equivalent outcomes. There is a head-to-head trial in progress of pazopanib versus sunitinib, which should show if there is a difference between these two treatments for first-line therapy. In the end, whether this new agent enters the UK formulary as a first-line alternative to sunitinib will probably come down to cost, although pazopanib shows a favourable side-effect profile with a very low rate of reported grade 3/4 cytopenias," she added.

Pazopanib is an oral angiogenesis inhibitor, targeting vascular endothelial growth factor receptor, platelet-derived growth factor receptor, and c-Kit.