idebenone (RAXONE®) and Leber hereditary optic neuropathy

Unacceptable risks, in the absence of proven efficacy

- Leber hereditary optic neuropathy leads to marked and rapid vision loss. Vision usually remains profoundly altered, even though some cases resolve spontaneously. The initial manifestations usually appear in early adulthood. In mid-2016, there is no curative treatment.

- Idebenone (Raxon®, Santhera Pharmaceuticals), an antioxidant, was granted EU marketing authorisation for this indication in 2015, two years after an initial rejection by the European Medicines Agency.

- Clinical evaluation of idebenone is based on a randomised, double-blind, placebo-controlled trial in 82 patients. Idebenone was no more effective than placebo in terms of visual acuity. The company then presented additional data that were no more convincing.

- Idebenone can cause gastrointestinal disorders, nasopharyngitis and dizziness, and its role has been discussed in two cases of severe liver injury.

- Idebenone may provoke spontaneous abortion.

NOT ACCEPTABLE

In patients with Leber hereditary optic neuropathy, the only available clinical trial of idebenone showed no efficacy in terms of visual acuity beyond the placebo effect. Leber hereditary optic neuropathy is a serious disease with no effective treatment in 2016, but this is no reason to expose patients to the potentially severe adverse effects of idebenone.

Regulators’ failings

For the past several decades, the randomised double-blind trial design has been universally accepted as the best way of obtaining reliable data on the clinical effects of a treatment. The marketing application that drug companies submit to regulatory agencies often contains data from this type of trial. Unfortunately, the results are often undermined by bias or difficult to extrapolate to many of the patients who might otherwise qualify for the treatment in question (for example, see the sacubitril + valsartan combination (see p. 33). Worse yet, regulatory agencies are sometimes satisfied with data that do not come from true comparative trials, as is the case with sonidegib (see issue 178 p. 14).

However, the case of idebenone in Leber hereditary optic neuropathy is particularly shocking. In the comparative trial reported by the company, idebenone was no more effective than placebo. The European Medicines Agency therefore had valid grounds for refusing to recommend marketing authorisation. The company was undeterred, however, and resubmitted the application, adding non-comparative data which were no more convincing. The agency finally ended up issuing a positive opinion, despite the total lack of proven efficacy (beyond the placebo effect...) but with clear adverse effects!

Faced with drug companies’ persistence in pursuing their commercial goals by any means, and with the inability of regulatory agencies and policy makers to hold steady under pressure, patients and healthcare professionals must be as persistent in demanding properly evaluated medications that provide a tangible therapeutic advance for the patients concerned.