Conditional marketing authorisation: based on very little data

Since the beginning of the 20th century, several mechanisms have been put in place to allow more rapid commercialisation of drugs in the European Union. One notable example is so-called conditional marketing authorisation, in which marketing authorisation (MA) is granted early, with a requirement for evaluation to be completed subsequently (1).

Not much data before marketing authorisation... The European Medicines Agency (EMA) has published a report on the first ten years of its experience with conditional marketing authorisation, from 2006 to 2016 (1). During this period, 30 drugs were the subject of conditional marketing authorisation, mainly in the fields of cancer and infection. They were granted on the basis of the results of 58 clinical trials in total (1).

Only 15 of the 30 drugs were authorised on the basis of results of at least one so-called phase III clinical trial, and sometimes with only preliminary results. More than half of the 58 trials were so-called phase I or II, i.e. exploratory trials which usually serve to generate hypotheses to be tested subsequently in much larger trials (1-3).

Only 34 trials were randomised and comparative; 20 had no comparator. Of the 37 comparative trials (of which 3 were non-randomised), only 2 included a comparator other than placebo or absence of treatment (1).

Were these methodological limitations compensated by trials carried out after marketing authorisation?

...and scarcely more after marketing authorisation. The EMA asked firms to carry out 77 clinical trials after marketing authorisation to complete the evaluation of these 30 drugs. 25 of these trials were again of an exploratory nature, and 28 were not comparative (1). Researchers at the Italian Mario Negri Institute of Pharmacological Research are highly critical of these marketing authorisations and deplored the fact that only 9 out of 77 trials included overall survival as a primary outcome measure (4).

Of the 30 conditional marketing authorisations, 17 were still conditional in 2016, 11 had been converted to classical marketing authorisations, after a median duration of 4 years, and 2 had been withdrawn at the request of the company (1).

The EMA welcomes the fact that conditional marketing authorisation has brought drugs to market around 4 years earlier than classical marketing authorisation, as a result of which patients have had earlier access to new drugs (1). But access with what therapeutic benefit and with what adverse effects? Such questions will remain unanswered unless the EMA is more demanding, with the risk of leaving patients exposed for a long time to drugs with an unfavourable harm-benefit balance.

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