Why drugs should be evaluated in several randomised comparative trials

Every year, the Prescrire Drug Awards are based on the reviews published in the Marketing Authorisations section of Prescrire's French edition over the past year. For the 2024 Prescrire Drug Awards, as in previous years, we chose not to give awards to certain drugs that were evaluated in a single comparative trial, even when the trial showed the drug to represent a therapeutic advance for patients. Examples include: darolutamide, for use in combination with docetaxel in certain metastatic prostate cancers (*Prescrire Int June 2024*); and dostarlimab, for use in combination with first-line chemotherapy in certain endometrial cancers (*Prescrire Int February 2025*). What is the reason for this choice?

It is a fundamental principle of experimental science that the reproducibility of the result of a scientific experiment should be verified, to make sure that the result was not due to chance alone or a flaw in the experiment's design. This principle also applies to the evaluation of a drug's efficacy. There can be rare exceptions, for example when the drug's efficacy is so clear that one trial is sufficient to show that it radically transforms the prognosis of the disease in question. This is the case for the recipient of the Pilule d'Or (Golden Pill) in the 2024 Prescrire Drug Awards, *fexinidazole* in sleeping sickness due to infection with *Trypanosoma brucei rhodesiense* (see p. 136 of this issue and *Prescrire Int* April 2025).

In a comparative trial, even if the difference observed between two groups is statistically significant according to the protocol, it is still possible that the results obtained were due to chance alone, that recruitment bias was not recognised, that an error occurred during data collection, that the data were manipulated, etc. The uncertainty surrounding the results of a single comparative clinical trial is greatly reduced when similar results, obtained in another trial, conducted independently by a different team, are available.

Yet, in 2024, drug regulatory agencies very often endorsed marketing authorisations based only on a single comparative trial, and have been doing so for many years. This is highly regrettable, because it can result in the use of drugs whose harm-benefit balance is uncertain.

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