Outlook

New drugs and indications in 2014
Some advances this year, but many drugs are poorly evaluated, too expensive, or more dangerous than useful

Abstract

- Three drugs analysed by Prescrire in 2014 provided a significant therapeutic advance for some patients.
- In 2014, too many drugs are still best avoided, have undergone minimal evaluation, or are excessively expensive.
- Drug regulatory agencies should continue their efforts to improve pharmacovigilance and transparency.

In 2014, Prescrire published 249 independent, systematic drug reviews in its French edition, including 43 new products (excluding generics), 26 new indications for existing products, 9 line extensions, 13 new generic drugs and 18 labelling changes.

Some tangible progress in 2014

Since the early 2000s, very few new drugs or indications have provided a tangible advance for patients (see the overview of past Prescrire Drug Awards p. 109).

In 2014, Prescrire singled out three new drugs that constitute a significant or major therapeutic advance for some patients.

Three significant advances. Cholic acid (Orphacol°), which received a “Bravo” rating in our analysis, was authorised at the European Union level in late 2013 for certain hereditary defects of bile acid synthesis. The only known curative treatment for these rare disorders, which are usually fatal during childhood, is liver transplantation (Prescrire Int n° 157). In these patients, when initiated early, cholic acid greatly increases life expectancy and eliminates most of their symptoms. Cholic acid was previously available in France as a hospital product and subsequently through a temporary compassionate authorisation (ATU) programme.

Two drugs were rated as “a real advance” in 2014. Intravenous artesunate (Malacef°) is now the standard treatment for severe malaria and is more effective in reducing mortality than injectable quinine. Although few patients require this drug in Europe, it provides a benefit to many patients in regions of the world where malaria is common. In France, artesunate has been available since mid-2011 through an ATU protocol, involving collection of data on the treated patients. As of 3 December 2014, no drug companies had applied for marketing authorisation (MA) for artesunate, which would facilitate access to this drug in the European Union (Prescrire Int n° 154).

The cytotoxic tyrosine kinase inhibitor imatinib (Glivec°) constitutes an advance for some children with Philadelphia chromosome-positive acute lymphoblastic leukaemia, because it prolongs survival considerably (Prescrire Int n° 157).
New drugs and indications in 2014

Hypoglycaemic drugs to avoid. In 2013, the harm-benefit balance of several new hypoglycaemic drugs or indications was considered unfavourable. This was also the case in 2014. Four of the 19 new drugs or indications rated as “not acceptable” are hypoglycaemic drugs. Insulin degludec, alone or in combination with insulin aspart, has no proven advantages over other long-acting insulins and appears to expose patients to a greater risk of cardiovascular adverse effects (Prescrire Int n° 150). Glitins such as saxagliptin and vildagliptin have no demonstrated efficacy, yet their serious adverse effects are well established (Prescrire Int n° 152). Canagliflozin, a “me-too” of dapagliflozin, has disproportionate adverse effects, given that its efficacy in preventing the clinical complications of type 2 diabetes has not been demonstrated (Prescrire Int n° 157).

Monoclonal antibodies to avoid. Among the 14 analyses of monoclonal antibodies published in our French edition in 2014, mainly used in rheumatology, oncology or multiple sclerosis, three were rated “not acceptable” due to their unfavourable harm-benefit balance. The adverse effects of monoclonal antibodies are generally serious, because these drugs have effects well beyond their intended target, including immunosuppression, infections, possibly cancers, etc. These adverse effects are unacceptable when the benefit that patients can expect to derive is poorly demonstrated or appears marginal, as is the case with canakinumab in gout attacks (Prescrire Int n° 151), or natalizumab and alemtuzumab in relapsing-remitting multiple sclerosis, for example (Prescrire Int n° 158).

Dangerous routes of administration

A drug’s harm-benefit balance is sometimes unfavourable because its route of administration exposes patients to serious risks. This is the case for the cytotoxic monoclonal antibody trastuzumab, which provokes more frequent serious adverse effects (infections and cardiac disorders) when administered subcutaneously for certain types of breast cancer than when it is administered intravenously (Rev Prescrire n° 374). The same is true for loquai-ne for oral inhalation, a neurotropic used in acute agitation, which exposes patients to a high risk of bronchospasm when administered by this route; in addition, it requires the cooperation of agitated patients (see in a coming issue).

Minimal evaluation is still too common

In 2014, Prescrire gave a “judgement reserved” rating to 7 newly authorised drugs or indications, as well as one drug authorised several years ago which we re-assessed with more follow-up. In most of these cases, the established adverse effects were disturbing, and while the clinical evaluation included some positive elements, there were insufficient data to determine the harm-benefit balance. This was the case for: the cancer drugs bosutinib, vismodegib and trastuzumab emtansine (Prescrire Int n° 151, 156 and 154); bedaquiline in multidrug-resistant tuberculosis (Prescrire Int n° 153); and the ophthalmology drugs aflibercept in central retinal vein occlusion and ociplastrin in vitreomacular traction (Prescrire Int n° 157).

Marketing authorisations granted too easily. Drug regulatory agencies too often grant marketing authorisations on the basis of minimal evaluation (Rev Prescrire n° 363). For example, nalbuphine has not been compared with standard drugs used to treat alcohol dependence (Prescrire Int n° 150). And the dose equivalence of tapentadol with other opioids has not been determined (Prescrire Int n° 149).

A new European regulation on clinical trials, adopted in 2014, failed to require that pharmaceutical companies demonstrate that their new drug constitutes a therapeutic advance, thereby missing the opportunity to encourage comparative evaluations of new drugs against those already available (see english.prescrire.org).

Some useful cases of regulated off-label use

Marketing authorisations give pharmaceutical companies the right to market their drugs, but there is no guarantee that the drug has undergone robust evaluation or that patients will derive any benefit from treatment. They do, however, define how and in which situations a drug should be used, based on the evaluation of the health authorities, and...
provide healthcare professionals and patients with useful information about the drug through its summary of product characteristics (SPC) and patient leaflet.

Sometimes, however, in serious or rare disorders, drugs without national or European marketing authorisations are presumed to be useful and are used off-label. In France, this use can be regulated through a temporary compassionate use programme, subsequently lowered to €41 000 when marketing authorisation is granted. The committees that grant marketing authorisations must now take into account the recommendations of the European Medicines Agency’s Pharmacovigilance Risk Assessment Committee (PRAC), and must justify any decisions to change the marketing authorisation. Transparency is required of drug regulatory agencies.

Several improvements were made to the pharmacovigilance system. The information made available through ATUs and RTUs remains temporary and is upgradable as soon as appropriate.

Exorbitant prices for certain drugs

The price of various drugs, in particular cancer drugs, has soared in recent years. In 2013, a group of over one hundred oncologists from around the world spoke out against the high cost of tyrosine kinase inhibitors, such as dasatinib, nilotinib and imatinib (Prescrire Int n° 153). In 2014, Gilead Sciences charged the exorbitant price of about €57 000 in France for 12 weeks of treatment with its product Sovaldi® (sofosbuvir), provided through an ATU compassionate use programme, subsequently lowered to €41 000 when marketing authorisation was granted. This price bears no relation whatsoever to the cost of research and development or production. It is typical of the business model adopted by some pharmaceutical companies, based on financial speculation at the expense of patients and society (Prescrire Int n° 154).

Other overpriced drugs that we reviewed in 2014 include: catakinumab, best avoided in gout attacks, and costing about €12 000 for a single injection (Prescrire Int n° 151); and ivacafarin, with an uncertain harm-benefit balance in cystic fibrosis, which costs about €19 000 per month (Prescrire Int n° 366).

The need for robust pharmacovigilance, independent of industry

Pharmacovigilance was reorganised in the European Union in 2010, and again in 2012 (Prescrire Int n° 153, 157).

Some progress, but drug companies still play a key role in pharmacovigilance. Several improvements were made to the pharmacovigilance system. For example, European patients now have the option of reporting adverse drug reactions directly to health authorities. The committees that grant marketing authorisations must now take into account the recommendations of the European Medicines Agency’s Pharmacovigilance Risk Assessment Committee (PRAC), and must justify any decisions that differ from the PRAC’s recommendations. The information made available to the public about the harms of drugs has been improved, and greater transparency is required of drug regulatory agencies.

However, this reorganisation has given pharmaceutical companies a key role in the collection and interpretation of adverse drug reaction reports, despite the obvious conflicts of interest that would lead them to downplay the adverse effects of their own products.

Prescrire’s ratings of new products and indications over the last 10 years (a)

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(a) Results for the years 1981 to 2004 can be found in Rev Prescrire n° 213 p. 59 and 258 p. 140. This table includes new products (other than generics) and new indications proposed in France, as well as re-assessments “with more follow-up”.

(b) The drug is: cholic acid in type 1 or 2 hereditary defects of primary bile acid synthesis (Prescrire Int n° 157).

(c) The drug are:– alemtuzumab in relapsing-remitting multiple sclerosis (Prescrire Int n° 159, p. 88-90).

(d) The drugs are:– coated-granule formulation of sodium phenylbutyrate in urea cycle disorders (Prescrire Int n° 157).

(e) The drugs are:– coated-granule formulation of sodium phenylbutyrate in urea cycle disorders (Prescrire Int n° 157).

(f) The drugs are:– the combination of beclomitocort + fomectrin in asthma attacks (Rev Prescrire n° 367).

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New drugs and indications in 2014

In 2014, Prescrire singled out three drugs that provided significant therapeutic advances.

Health authorities have made some efforts to improve pharmacovigilance and transparency, but they need to do more.

Pharmaceutical companies continue to play key roles in which conflicts of interest exist. They still have a central role in generating the data that underpin their marketing authorisations, and in collecting and analysing adverse effect reports. They demand increasingly exorbitant prices for new drugs, which bear no relation to the cost of production and research, thus endangering access to healthcare and the sustainability of universal healthcare systems.

If we are to put patients’ interests first, the focus of clinical research must shift towards unmet needs, and health authorities must serve the public rather than acting as service providers for the pharmaceutical industry. The mobilisation of healthcare professionals, patients and citizens, in France and in Europe, is more necessary than ever to create the political will to resist illness-based financial speculation by drug companies.