Shall the pharmaceutical companies decide which trials to perform?

Only drugs that are shown to be better than placebo in randomised, controlled trials are approved by the medicines agencies. The pharmaceutical companies appear to let profit determine which drugs to study. This blocks rapid development and approval of the most effective drugs.

The pharmaceutical companies make the protocols for virtually all the costly randomised, controlled trials and pay public hospital departments and private organisations to conduct them on their behalf (1, 2). The companies can prioritise the drugs that generate the highest revenues during the patent protection period of 15–20 years and give less priority to vital drugs (1, 3).

The US Food and Drug Administration, the European Medicines Agency and the Norwegian Medicines Agency essentially approve only those drugs that have shown effect in randomised, controlled trials, despite a clear commercial bias (1). In practice, this serves as the approval authorities' most important guideline for drug therapy.

Disease-modifying drugs for relapsing-remitting multiple sclerosis are a relevant example. Pharmaceutical companies have generated high revenues for disease-modifying drugs since these were first approved internationally in 1993. Since 2001, treatment trials have indicated that hematopoietic stem cell transplantation can halt the disease multiple sclerosis (4), but there is an absence of randomised, controlled trials because hematopoietic stem cell transplantation is of no commercial interest to the industry – the patents on the chemotherapy drugs have expired. A publicly funded Norwegian randomised, controlled trial is currently planned, but it lacks funding.

Off-label prescribing

An approved drug may be prescribed for an unapproved indication when this is medically justified. Treatment trials of rituximab (MabThera) by Swedish neurologists indicate that it has good efficacy for multiple sclerosis, and they have therefore prescribed the drug off-label (5, 6).

Rituximab showed good efficacy for relapsing-remitting multiple sclerosis in phase 2 trials, but Roche did not proceed with randomised, controlled trials (phase 3 trials), presumably because their patent for rituximab expired in 2015 (6, 7). The company is now putting pressure on the Swedish health authorities to stop off-label prescribing of rituximab, probably because their patented disease-modifying drug ocrelizumab will soon be approved (7).

Ocrelizumab is almost identical to rituximab and presumably a patent extender, an example of evergreening – patenting of a new drug that only represents a slight modification of an old drug (7, 8). In 2010, Roche discontinued randomised, controlled trials of ocrelizumab for rheumatoid arthritis and lupus erythematosus due to lethal infections. Rituximab has a better side effect profile (9).

Roche recently demonstrated in a randomised, controlled trial that ocrelizumab has good efficacy for relapsing-remitting multiple sclerosis (10). The efficacy of ocrelizumab is probably no better than that of rituximab, but the former is far more profitable. Ocrelizumab is now being approved and Roche will commence price negotiations – in Norway, with the Health Trust's Procurement Service (HINAS).

Secret price negotiations with the pharmaceutical companies

In spring 2016, following a request from the pharmaceutical companies, the director of the Health Trust's Procurement Service announced that the price negotiations with the companies, and pharmaceutical prices, legally were trade secrets (11). This policy change was criticised by the Norwegian Drug Procurement Cooperation, among others, and submitted to public hearing. All the responses from the hearing, except for three – including the response from the pharmaceutical industry – were negative and underscored the importance of transparency, in line with international recommendations (3, 12). The directors of the regional health trusts will soon reach their decision.

Pharmaceutical companies buy political and medical influence, most of all in countries at the forefront in medicine such as the USA, Germany, France, Switzerland and the UK (13). The approval authorities can be influenced – the European Medicines Agency is dependent on these firms for its income – in order for the companies, amongst others things, to achieve higher prices for their drugs (2, 3, 14). This year for the first time, Norwegian health personnel reported the fees they had received from pharmaceutical companies, but only for 2015 (15). A prominent neurologist in the field of multiple sclerosis reported receiving NOK 170 000 (USD 20 700). Participation was voluntary, one third declined to take part, and the amounts reported were not checked.

It is unacceptable that the pharmaceutical companies have virtually sole responsibility for selecting which drugs should be subject to randomised, controlled trials, and for funding and managing these trials. Patients can be given less costly and better drugs more rapidly if politicians ensure responsible regulation (14). The Nordic countries, for example, could establish a shared, publicly owned pharmaceutical company.

Sigbjørn Rogne
sigrogne@online.no

Sigbjørn Rogne (born 1965), specialist in geriatrics and digestive disorders.
The author has completed the ICMJE form and declares the following conflict of interest: He has multiple sclerosis and underwent hematopoietic stem cell transplantation at the University Hospital in Florence, Italy, in January 2015.

References

1. Stamatakis E, Weiler R, Ioannidis JPA. Undue industry influences that distort healthcare research, strategy, expenditure and practice: a review. Eur J Clin Invest 2013; 43: 469–75.
2. Abraham J, Bardelay D, Kopp C et al. Education and debate: Making regulation responsive to commercial interests: streamlining drug industry watchdogs. BMJ 2002; 325: 1164–9.
3. Ghinea N, Lipworth W, Kerridge I. Propaganda or the cost of innovation? Challenging the high price of new drugs. BMJ 2016; 352: i1284.
4. Burt RK, Balabanov R, Han X et al. Association of nonmyeloablative hematopoietic stem cell transplantation with neurological disability in patients with relapsing-remitting multiple sclerosis. JAMA 2015; 313: 275–84.
5. Alping P, Frisell T, Novakova L et al. Rituximab versus fingolimod after natalizumab in multiple sclerosis patients. Ann Neurol 2016; 79: 950–8.
6. Salzer J, Svenningsson R, Alping P et al. Rituximab in multiple sclerosis: A retrospective observational study on safety and efficacy. Neurology 2016; 87: 2074–81.
7. Svenningsson A. MS-läkare: Bolag vill diktera val av behandling. Svenska Dagbladet 2016.
8. Collier R. Drug patents: the evergreening problem. CMAJ 2013; 185: E385–6.
9. Ramos-Casals M, Sanz I, Bosch X et al. B-cell-depleting therapy in systemic lupus erythematosus. Am J Med 2012; 125: 327–36.
10. Hauser SL, Bar-Or A, Comi G et al. Ocrelizumab versus Interferon Beta-1a in Relapsing Multiple Sclerosis. N Engl J Med 2016. E-publisert 21.12.2016.
11. Bordvik M. Krav om hemmelighold vekker reaksjoner. Dagens Medisin 28.4.2016. https://www.dagensmedisin.no/artikler/2016/04/28/krav-om-hemmelige-priser-vekker-reaksjoner/ (9.1.2017).
12. Bordvik M. «Høyere priser, svekket legetillit og økt korrupsjonsfare». Dagens Medisin 5.12.2016. https://www.dagensmedisin.no/artikler/2016/12/05/hoyere-priser-svekket-tillit-til-helsepersonell-og-okt-korrupsjonsfare/ (9.1.2017).
13. Stiglitz JE. The Prize of Inequality. New York: W. W. Norton & Company, 2012.
14. Garattini S, Bertele' V. How can we regulate medicines better? BMJ 2007; 335: 803–5.
15. Bordvik M, Engen ØB. Se hvem som fikk honorarer i fjor. Dagens Medisin 11.8.2016. https://www.dagensmedisin.no/artikler/2016/08/11/sok-i-listen-over-utbetalinger/ (9.1.2017).

Received 31 December 2016, first revision submitted 6 January 2017, accepted 10 January 2017. Editor: Ketil Slagstad.