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Research

Postmarket safety of drugs approved by Health Canada on the basis of clinical and surrogate outcomes: a cohort study

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Abstract

Background: Health Canada approves drugs on the basis of evidence from clinical trials using clinical or surrogate outcomes. This study compares the postmarket safety of these 2 groups of drugs.

Methods: Information about whether clinical or surrogate outcomes were used and the date of market approval were obtained from Health Canada's Summary Basis of Decision documents issued from Jan. 1, 2005, to Dec. 31, 2014. Safety warnings and the dates they were issued were identified through advisories on the MedEffect Canada website. Kaplan–Meier survival curves were calculated to determine the likelihood that drugs in the clinical and surrogate outcome groups would receive a serious safety warning. The time from market authorization to first serious safety warning was compared for the 2 groups of drugs.

Results: A total of 124 drugs were approved by Health Canada using clinical outcomes and 114 using surrogate outcomes. Kaplan–Meier curves did not differ between the 2 groups ($p < 0.9$). The median time from market authorization to first serious safety warning was 722 days in the clinical outcome group and 818 days in the surrogate outcome group (difference 96 days, 95% confidence interval –295 to 425).

Interpretation: We found no statistically significant difference in postmarket safety between drugs approved using clinical outcomes and those approved using surrogate outcomes. Because drugs in the surrogate outcome group are approved before their benefit:harm ratio is fully established, these drugs should be used with caution until their clinical benefits are better understood.

Health Canada approves drugs on the basis of clinical trials that use clinical outcomes, surrogate outcomes or a combination of both. The use of surrogate outcomes is attractive to many groups involved with pharmaceutical products, including the pharmaceutical industry, regulators, health care practitioners and patients. Their use allows trials to be done less expensively with fewer patients in a relatively short period, with the result that promising new drugs can reach patients faster. However, surrogate outcomes can fail to predict clinical effects accurately, and the effects of the intervention could be offset substantially by unintended, unanticipated or unrecognized mechanisms.[1] Some drugs approved on the basis of surrogate outcomes have had serious safety problems and have had to be withdrawn from the market or have their indications substantially restricted.[2–5]

If drugs approved on the basis of surrogate outcomes are less safe than those approved on the basis of clinical outcomes, and possibly not as beneficial, their overall benefit:harm ratio will be less favourable and these drugs should be used with caution until their benefits are fully established. We conducted this study to compare the postmarket safety of drugs approved on the basis of clinical and surrogate outcomes. We determined the likelihood of a serious safety warning being issued by Health Canada and the time taken to recognize a serious safety issue for drugs in each group. In addition, we examined the time spent in the review process and the type of review (standard review, priority approval or Notice of Compliance with conditions) that the 2 groups of drugs underwent. We expected drugs approved in a shorter time to be more likely to receive a serious safety warning than those receiving a standard review.[6,7] If drugs in the surrogate outcome group spend less time in the review process, that could account for more postmarket safety problems.

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Methods

Since Jan. 1, 2005, Health Canada has issued a Summary Basis of Decision document for each new drug it approves (www.hc-sc.gc.ca/dhp-mps/prodpharma/sbd-smd/drug-med/index-eng.php). The document outlines the clinical grounds used to grant market authorization. We obtained copies of all Summary Basis of Decision documents issued until Dec. 31, 2014, and read them independently to determine whether the clinical trials of the product used surrogate or clinical outcomes. Disagreements were resolved by discussion until consensus was reached. Clinical outcomes were defined as "a characteristic or variable that reflects how a patient [or consumer] feels, functions, or survives."[8] Surrogate outcomes were defined as "a biomarker that is intended to substitute for a clinical endpoint. A surrogate endpoint is expected to predict clinical benefit (or harm or lack of benefit or harm) based on epidemiologic, therapeutic, pathophysiologic, or other scientific evidence."[8] Only the outcomes defined as primary objectives in pivotal trials were used. Health Canada defines pivotal trials as "trials of high scientific quality, which provide the basic evidence to determine the efficacy, properties, and conditions of use of the drug."[9] If a drug was approved for one or more indications using both clinical and surrogate outcomes, we considered the approval to be based on clinical outcomes.

In addition to the type of outcomes used, we extracted the following additional information from the Summary Basis of Decision documents: the drug's generic and brand names, the company marketing the product, the therapeutic indication, the date of new drug submission (application to market the drug) and the date of Notice of Compliance (date of marketing authorization).

Information about the type of review process (standard review, priority approval or Notice of Compliance with conditions) came from annual reports that we obtained directly by contacting the Therapeutic Products Directorate and the Biologics and Genetic Therapies Directorate (at publications@hc-sc.gc.ca). For drugs approved after Apr. 1, 2013, we obtained additional information on the Notice of Compliance website (http://webprod5.hc-sc.gc.ca/noc-ac/index-eng.jsp).

We identified safety warnings and withdrawals of drugs for the period Jan. 1, 2005, to Dec. 31, 2014, by reviewing advisories for health professionals in the Recalls and Safety Alerts Database on the MedEffect Canada website (www.hc-sc.gc.ca/dhp-mps/medeff/advisories-avis/prof/index-eng.php). According to Health Canada, this database is a comprehensive list of recalls, advisories and safety alerts. We recorded the date for each safety advisory or notice of withdrawal of a product. We included all serious safety advisories (defined as those using bold black print or boxed warnings, or both). We excluded advisories concerning the withdrawal of a specific batch or lot number because of manufacturing problems and those issued because of misuse of a drug (e.g., an unapproved use) or medication errors (e.g., a warning about remembering to remove a transdermal patch before applying a second one). If a drug received more than one serious safety warning, we used the date of the first warning. When necessary, notices on the MedEffect website were supplemented by information we obtained by searching the product name in the Drug Product Database (http://webprod5.hc-sc.gc.ca/dpd-bdpp/index-eng.jsp). This database contains product-specific information on drugs approved for use in Canada as well as all products discontinued since 1996.

Statistical analysis

We calculated Kaplan–Meier survival curves for the period from receipt of market authorization to first serious safety warning or product withdrawal for drugs in each of the clinical and surrogate outcome groups. We compared the curves using a log-rank (Mantel–Cox) test. A Kaplan–Meier analysis accounts for the fact that some drugs had received a safety warning and some had not by the end of the study period (Dec. 31, 2014).

The time from application for market authorization to receipt of approval and the time from receipt of approval to a safety warning or withdrawal from the market were calculated in days. We report means for the first period and compared them using a t test. We report medians for the second period, because these values are not normally distributed (Shapiro–Wilk test), and compared them using the Mann–Whitney test. We compared the proportion of drugs in the 2 groups that were approved under the 3 different approval processes using the χ^2 test. Counts were made of the number of clinical- and surrogate-outcome drugs approved for different therapeutic uses. A p value of less than 0.05 was considered significant. We used Excel 2011 for Macintosh (Microsoft) and Prism 6.0 (GraphPad Software) for all calculations.

Results

We identified 251 drugs that had Summary Basis of Decision documents. We excluded 13 drugs: 5 were diagnostic agents, 5 were either bioequivalents or subsequent entry biosimilars and there were no outcomes documented, 2 were vaccines approved on an emergency basis and 1 was a disinfectant not used for treatment in humans. Of the remaining 238 drugs, 124 (52.1%) were approved by Health Canada using clinical outcomes and 114 (47.9%) using surrogate outcomes. The 238 drugs and their indications, the outcome used for approval and the classification of the outcome are listed in Appendix 1 (available at www.cmajopen.ca/content/3/3/E286/suppl/DC1).

We found no difference in Kaplan–Meier curves between the 2 groups of drugs (Figure 1, $p < 0.9$), which meant that the likelihood of drugs in each group acquiring a serious safety warning after they were marketed was the same. The median time to first serious warning was 722 days (interquartile range [IQR] 482 to 1257) for drugs in the clinical outcome group and 818 days (IQR 559 to 1556) for drugs in the surrogate outcome group, for a difference of 96 days (95% confidence interval [CI] –295 to 425).

The mean length of time in the review process was 465 days (95% CI 420 to 510) for drugs in the clinical outcome group and 461 days (95% CI 409 to 512) for drugs in the sur-

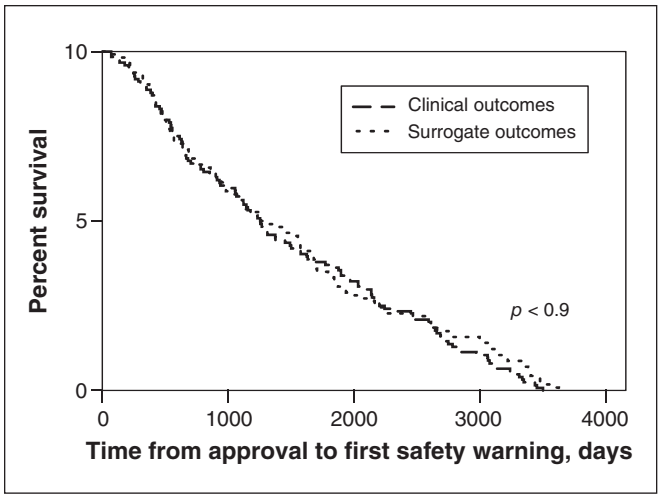

Figure 1: Kaplan–Meier curves showing time from approval to first serious safety warning or removal from market for drugs approved by Health Canada on the basis of clinical and surrogate outcomes.

rogate outcome group ($p < 0.9$). In the clinical outcome group, 101 drugs underwent a standard approval, 22 a priority approval, and 1 a Notice of Compliance with conditions. Respective figures for the surrogate outcome group were 67, 29 and 18 (Table 1, $p < 0.001$).

Table 1 shows the distribution of therapeutic indications for the drugs in the clinical and surrogate outcome groups. Table 2 gives examples of outcomes for each group. Drugs for allergy, dermatology, genitourinary, gastrointestinal, "other" infectious diseases, neurology, psychiatry and rheumatology were more likely to be approved on the basis of clinical outcomes, whereas drugs for cancer, diabetes, hepatitis, HIV, inborn errors of metabolism and "other" metabolic diseases were more likely to be approved on the basis of surrogate outcomes. Twelve (33%) of the 36 cancer drugs in the surrogate outcome group were approved under the Notice of Compliance with conditions process, whereas none of the 16 cancer drugs in the clinical outcome group used this approval process.

Interpretation

Based on the 2 measures of safety considered in this study — the likelihood that Health Canada will issue a serious safety warning and the time from market approval to first serious safety warning — we found no statistically significant difference between drugs approved on the basis of surrogate outcomes and drugs approved on the basis of clinical outcomes. This is reassuring news in view of the anecdotal evidence about safety issues with some of the drugs in the surrogate outcome group. The comparable postmarket safety profiles may also reflect the equal time that the 2 groups of drugs spent in the review process. The speed of the review process has been associated with postmarket safety warnings.[6,7,10,11]

We need to recognize that the use of serious safety warnings is only an indirect measure of safety. The warnings do not measure the number of people potentially affected by safety problems nor the seriousness of the harms that the drugs cause. In addition, the information about safety from this study does not tell us whether the benefit:harm ratio is equivalent for the 2 groups of drugs. A recent meta-analysis found that clinical trials using surrogate outcomes were more likely to report larger treatment effects than trials reporting final clinical outcomes, a conclusion that could not be explained by differences in the risk of bias or characteristics of the 2 groups of trials.[12] The Common Drug Review, through which the Canadian Agency for Drugs and Technologies in Health makes recommendations to federal, provincial and territorial drug plans about whether to fund a drug, felt that 28% of surrogate outcomes used in the trials that it assessed were not valid.[13] These findings suggest that the benefit:harm ratio may be more robust for drugs with clinical outcomes than for some drugs with surrogate outcomes.

The different balance in the review processes between the clinical and surrogate outcome groups reflects the fact that trials of drugs for some high-priority indications are much more likely to have used surrogate outcomes. Of the 52 cancer drugs, 36 (69%) were in the surrogate outcome group, and 12 of the 36 were approved with a Notice of Compliance with conditions. Similarly, all 9 drugs for HIV infection were in the surrogate outcome group, and 3 of these drugs were approved with a Notice of Compliance with conditions.

The finding that surrogate outcomes were used in the decision to approve 48% of new drugs is consistent with results from the US Food and Drug Administration and the European Medicines Agency. In the United States, pivotal trials using surrogate outcomes as their primary outcome formed the exclusive basis of approval for 91 (45%) of 206 indications for 188 drugs.[14] The European Medicines Agency evaluated 81 pivotal trials for 39 new products. No study measured a patient-relevant primary outcome for 21 (54%) of the approvals (45 [56%] of the trials).[15]

Whether surrogate outcomes should continue to be widely used for drugs for some therapeutic indications is open to question. Cancer drugs are frequently approved on this basis in multiple jurisdictions.[16,17] Garattini and Bertele[18] looked at 12 oncology drugs approved by the European Medicines Agency from 1995 to 2000. The outcomes for the clinical trials of these drugs tended to be subjective (e.g., "time to progression"), and there was seldom an evaluation of survival or quality of life. A second study examined 14 cancer drugs approved by the European Medicines Agency for 27 indications from January 1995 to December 2004. Only 2 of the 27 were supported by changes in overall survival, as compared with 13 for response rate, 11 for time to progression or progression-free survival, and 1 for "other."[16] Tumour size does not correlate with overall survival,[19] and the use of progression-free survival as a valid biomarker seems to depend on the type of cancer being treated.[19–21] The continued use of surrogate outcomes as the basis for approval of drugs to treat non–insulin-dependent diabetes seems difficult to justify given the lack of correlation between a reduction in concentration of glycated hemoglobin and cardiovascular events.[22] However, all 9 drugs approved for this indication were in the surrogate outcome group.

Limitations

There are 3 major limitations to our study. First, we based the definition of a serious safety warning on the way that Health Canada displayed the information (bolded black print or boxed text, or both). However, the criteria Health Canada uses to develop its safety warnings and the emphasis it places on any particular safety issue are vague. One Health Canada document states "Regulatory actions … are taken according to the regulatory framework in place. This implies an evaluation of the signal and the appropriate benefit–risk review of the information available."[23]

Second, we could not evaluate whether differences in the detection of safety problems was a reflection of the number of people exposed to the drug in premarket trials, because the Summary Basis of Decision documents do not reliably report population sizes in pivotal trials.[24]

The final limitation is that all of the surrogate outcomes were treated equally and not assessed for their validity. This would be difficult to accomplish in many cases, as the example of disease-free progression in cancer illustrates, where it seems to be valid for some cancers and not for others. Using an increase in CD4 cell count in HIV as a surrogate for improved survival can present difficulties in interpretation. A 1993 review looked at 16 trials of drug therapy for HIV that used the CD4 cell count as a surrogate outcome.[25] An increase in cell count was significantly favourable in 7 of the 8 trials in which treatment improved the clinical outcome of progression to AIDS or death. But at the same time, there was also an increase in CD4 cell count in 6 of the 8 trials in which treatment did not retard progression to AIDS or death.[1] Although the 6-minute walk test was initially considered a valid surrogate marker in pulmonary hypertension, there are now calls for clinical trials to use primary outcomes that reflect long-term disease progression and morbidity.[26]

In some cases, the use of surrogate outcomes is reasonable, because clinical outcomes would present a major barrier to conducting trials. Such cases include amyotrophic lateral sclerosis

Table 1: Therapeutic indications for drugs approved by Health Canada from January 2005 to December 2014, by outcome and approval type

	Outcome and approval process; no. of drugs approved					
	Clinical outcome			Surrogate outcome		
Therapeutic indication	Standard	Priority	NOC/c	Standard	Priority	NOC/c
Allergy	3	0	0	0	0	0
Cancer	7	9	0	15	9	12
Cardiovascular	2	2	0	5	0	1
Dermatology	6	0	0	0	0	0
Genitourinary	6	0	0	0	0	0
Gastrointestinal	6	1	0	0	0	0
Gynecology	2	0	0	1	0	0
Hematology	5	0	0	4	2	1
Inborn error of metabolism	0	1	0	3	2	0
Infectious disease, hepatitis	0	0	0	0	6	0
Infectious disease, HIV	0	0	0	4	2	3
Infectious disease, other	12	2	1	0	0	0
Infectious disease, vaccine	3	1	0	6	2	0
Metabolic disease, diabetes	0	0	0	9	0	0
Metabolic disease, other	0	0	0	10	3	0
Miscellaneous	6	1	0	0	0	1
Musculoskeletal	3	0	0	0	0	0
Neurology	16	1	0	1	0	0
Ophthalmology	2	2	0	2	1	0
Psychiatry	13	0	0	0	0	0
Pulmonary hypertension	1	1	0	2	1	0
Respirology	2	0	0	5	1	0
Rheumatology	6	1	0	0	0	0
Total	**101**	**22**	**1**	**67**	**29**	**18**

Note: NOC/c = Notice of Compliance with conditions.

Table 2: Examples of clinical and surrogate outcomes used to approve drugs, by therapeutic indication

Therapeutic indication	Clinical outcome	Surrogate outcome
Allergy	Bulbar conjunctival injection and ocular itching (seasonal allergic conjunctivitis)	No drugs approved
Cancer	Duration of survival (metastatic colorectal cancer)	Proportion of patients who achieved complete response or partial response (Hodgkin lymphoma)
Cardiovascular	Time to first event of cardiovascular death, myocardial infarction and stroke (acute coronary syndromes)	Change from baseline in trough sitting diastolic blood pressure (hypertension)
Dermatology	Change in total inflammatory lesions in adults (rosacea)	No drugs approved
Genitourinary	Number of incontinence episodes per week (overactive bladder)	No drugs approved
Gastrointestinal	No emetic episode and no rescue medication within 24 hours (emetogenic chemotherapy)	No drugs approved
Gynecology	Percentage of women with a reduction in uterine bleeding (uterine fibroids)	At least one follicle ≥ 17 mm, pre-ovulatory estradiol serum level ≥ 109 pg/mL (400 pmol/L), and mid-luteal phase progesterone level ≥ 7.9 ng/mL (25 nmol/L) (follicular development)
Hematology	Annualized bleeding rate per patient (congenital factor IX deficiency)	Proportion of patients who experienced a hemoglobin response (anemia associated with chronic kidney disease)
Inborn error of metabolism	Proportion of patients alive and free of invasive ventilator support (Pompe disease)	Reduction in mean spleen volume (type 1 Gaucher disease)
Infectious disease, hepatitis	No drugs approved	Cell histology (hepatitis B)
Infectious disease, HIV	No drugs approved	Proportion of patients with a treatment response ≥ 1 log10 reduction in viral load (HIV)
Infectious disease, other	Improvement in respiratory symptoms (cystic fibrosis)	No drugs approved
Infectious disease, vaccine	Protecting against severe rotavirus gastroenteritis episodes (rotavirus gastroenteritis)	Ability to induce antibodies against viral hemagglutinin (influenza)
Metabolic disease, diabetes	No drugs approved	Change in glycosylated hemoglobin (type 2 diabetes)
Metabolic disease, other	No drugs approved	Percent change in serum low-density lipoprotein cholesterol concentration (Frederickson type IIa familial hyperlipidemia)
Miscellaneous	Time to onset of relief of symptoms of abdominal or facial attack (hereditary angioedema)	Complete or partial cytogenetic response (graft-versus-host disease)
Musculoskeletal	Pain intensity, patient's global assessment of disease activity, and the total score of the Western Ontario and McMaster Universities questionnaire (osteoarthritis of knee)	No drugs approved
Neurology	Median percent reduction in seizure frequency (epilepsy)	Biochemical marker 8OH2'dG (Friedreich ataxia)
Ophthalmology	Proportion of patients who maintained vision (macular degeneration)	Change from baseline in anterior chamber cell grade (anterior uveitis)
Psychiatry	Positive and Negative Syndrome Scale total score (schizophrenia)	No drugs approved
Pulmonary hypertension	Time to first occurrence of morbidity or mortality event (pulmonary arterial hypertension)	Distance covered in 6-minute walking test (pulmonary hypertension)
Respirology	Annual rate of moderate and severe exacerbations (chronic obstructive lung disease)	Forced expiratory volume in 1 second and peak expiratory flow (asthma)
Rheumatology	Proportion of patients with an ACR20 response (rheumatoid arthritis)	No drugs approved

Note: 8OH2'dG = 8-hydroxy-2′-deoxyguanosine, ACR20 = American College of Rheumatology 20% improvement response.

and some forms of cancer that are uniformly fatal and lack effective therapy, rare diseases for which validation of hard outcomes may take an unreasonable time to complete, and situations where it is ethically impossible to test candidate drugs (e.g., for treatment after exposure to biological or chemical weapons).[2]

Conclusion

Based on the metrics used in this study, we found no statistically significant difference in postmarket safety between drugs approved on the basis of clinical outcomes and those approved on the basis of surrogate outcomes. Because drugs in the surrogate outcome group are approved before their benefit:harm ratio is fully established, these drugs should be used with caution until their clinical benefits are better understood.

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