Surrogate outcome markers in research and clinical practice

Scott Twaddell, *Clinical Pharmacologist and Clinical Toxicologist, and Advanced Trainee in Respiratory and Sleep Medicine, John Hunter Hospital, Newcastle, NSW*

Summary

A surrogate measure or marker aims to predict a clinical outcome or prognosis. Surrogates are often used in drug or therapeutic intervention trials as they reduce the size, duration and cost of the study. Surrogates are commonly used as trial end points and often become the standard by which new drugs gain regulatory approval for marketing. The surrogate marker should be able to reliably predict an effect of the drug or intervention on the long-term clinical outcome. Surrogate markers should be validated in longer term trials to confirm their association with the clinical outcome. They should not be adopted as true markers of disease in the absence of evidence of their validity. Clinicians should manage the whole patient and not just their surrogate markers.

Key words: clinical trials, drug regulation.

(Aust Prescr 2009;32:47–50)

Introduction

A surrogate end point, or marker, is a laboratory measurement or physical sign that is used in therapeutic trials as a substitute for a clinically meaningful end point that is a direct measure of how a patient feels, functions, or survives and that is expected to predict the effect of the therapy.

US Food and Drug Administration[1]

The essential feature of this definition is the strong association between the marker and the clinical end point or outcome. The effect of a treatment on a surrogate marker must reflect its effect on the clinical outcome.[2] For example, a drug which reduces intraocular pressure will reduce loss of vision in patients with glaucoma.

The cost and time constraints of large clinical trials make surrogate markers an attractive proposition in research. Many new drugs gain approval by showing positive effects on surrogate measures that have been previously accepted as markers of a particular disease, for example, the concentration of low density lipoprotein (LDL) cholesterol as a marker of cardiovascular disease. While some surrogates achieve acceptance in clinical practice as markers of disease, based on the results of phase III trials[3], others are adopted even though they have little correlation with the progression of disease (Table 1).

Table 1

Surrogate markers often used in clinical practice

Generally accepted as valid		Doubt still exists about validity	
Surrogate marker	**Predicts**	**Surrogate marker**	**Predicts**
HbA1c	Diabetic microvascular complications	HbA1c	Diabetic macrovascular complications
FEV$_1$	Mortality in chronic obstructive pulmonary disease	Bone mineral density	Fracture risk
Blood pressure	Primary and secondary cardiovascular events	Prostate specific antigen	Prognosis of prostate cancer
Viral load	Survival in HIV infection	Suppression of arrhythmia	Long-term survival
Cholesterol concentration	Primary and secondary cardiovascular events	Carotid intima-media thickness	Coronary artery disease
Intraocular pressure	Visual loss in glaucoma	Albuminuria	Cardiovascular events

HbA1c   glycated haemoglobin
FEV$_1$ forced expiratory volume in one second

Reliable surrogates in clinical practice

Reducing a patient's blood pressure is a well accepted risk reduction strategy for the primary and secondary prevention of cardiovascular events. The relationship between blood pressure (the surrogate marker) and the risk of cardiovascular events is continuous and independent. Drugs that reduce blood pressure significantly more than other drugs consistently show better results in clinical outcome trials. The relationship is considered so strong that we presume a drug will reduce future cardiovascular events if it effectively controls blood pressure.

One of the most reliable of all surrogate measures is the intraocular pressure in glaucoma. There is a strong correlation between increasing intraocular pressure and the clinical end point of visual loss. Any drug which lowers intraocular pressure will reduce the risk of visual loss.[4]

Forced expiratory volume in one second (FEV_1) as a percentage of the predicted volume is used for prognosis in chronic obstructive pulmonary disease (COPD). Interventions that slow the rate of deterioration of FEV_1 are considered the most clinically useful treatments for patients with COPD. There is good long-term evidence to support the utility of this measure.[5,6]

Surrogate markers in clinical trials

In phase II trials[3], surrogate markers provide interim measures of interventions and thereby predict whether longer term, more extensive and costly phase III trials are worthwhile. There is great interest in markers that allow researchers to make predictions of drug effects or disease progression by extrapolating short-term results to long-term clinical end points. Studies frequently make use of these markers rather than clinical outcomes. Surrogate markers can be used to monitor disease control, for example glycated haemoglobin (HbA1c) as a marker of diabetes control. They can also be used to determine disease prognosis, for example increased viral load and decreased CD4 cell count as a predictor of progression to AIDS in patients infected with HIV. Other markers are used to determine the risk of developing a separate outcome, for example, blood pressure and the risk of adverse cardiovascular events.

While surrogate markers are useful for reducing the duration of studies, the translation of results from trials involving one drug to trials of another drug is likely to be invalid unless the marker has been shown to be valid in multiple different trials.[7] However, surrogate markers are frequently used in drug comparison studies. Improvements in surrogate markers may be accepted by drug regulatory authorities as evidence that one drug is more efficacious than another.

Validating surrogate markers

The only way to properly validate potential surrogate markers is through stringent examination in phase III clinical trials. The primary end point then needs to be a relevant clinical event. Final evidence of a strong association is shown through consistent performance of the marker in meta-analyses of multiple phase III trials.

There are criteria which define the validity of surrogate markers.[8] Although these are controversial[7], they provide a useful framework on which to base a model for surrogate markers. The ideal situation is one in which the surrogate lies directly in the causal pathway to the clinical end point and the drug or intervention has a predictable and direct effect on both the surrogate and the clinical end point.

Perhaps more useful is an explanation of how surrogates fail to predict clinical end points. There are four possibilities (see Fig. 1).[2]

1. The surrogate may not be in the causal pathway of the disease, therefore any effect of the drug or intervention on the surrogate has no effect on the clinical end point. For example, the mechanisms leading to the development of macrovascular complications in type 2 diabetes may not involve HbA1c.

2. There may be several causal pathways, of which the surrogate is one, and the drug or intervention may affect only the surrogate without affecting the true clinical end point. For example, improvement in bone mineral density with bisphosphonates may not be a reliable predictor of fracture risk because reduced bone mineral density is not the only reason for the increase in risk.

3. The surrogate may be involved in the causal pathway of the disease but be unaffected by the drug or intervention. In patients with HIV, the incidence of opportunistic infections may not be reduced by a specific antiretroviral drug even though the drug improves prognosis.

4. The drug or intervention has effects independent of the disease and may or may not affect the surrogate or clinical end point. For example, prostatectomy may influence survival in prostate cancer via a pathway for which prostate specific antigen is a marker, but also via mechanisms independent of that effect. This makes the measurement of prostate specific antigen unreliable as a sole prognostic marker.

An example of a surrogate marker which may not be causally related to clinical outcome is the thickness of the walls of the carotid artery. A proven reduction of intima-media thickness seen on ultrasound has been suggested as a surrogate marker for the success of drugs in reducing overall cardiovascular risk. However, concerns have been raised about the reliance on changes in one area of the carotid and the inference that this reflects changes in other vascular areas. Measuring changes in the media may be a poor substitute for a disease process that occurs primarily in the intima. The changes in intima-media thickness induced by 'statins' cannot necessarily be extrapolated to effects produced by other drugs.

Fig. 1

Examples of failure of surrogate end points to reliably predict true clinical outcomes [2]

- pathways involving surrogate markers
- causal disease pathways
- other potential mechanisms of action
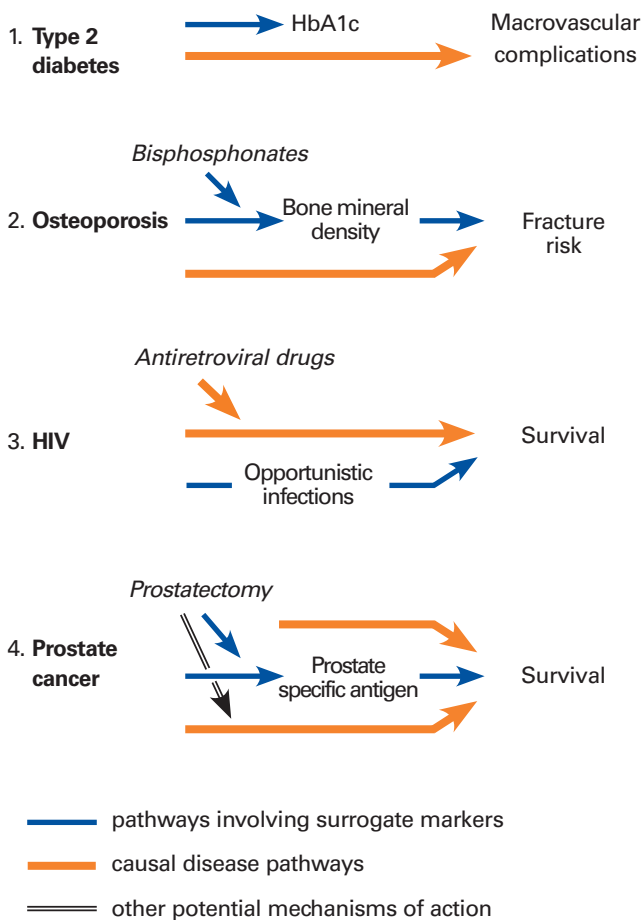
1. Glycated haemoglobin (HbA1c) may not be in the causal pathway of macrovascular disease.
2. Bisphosphonates affect only the bone mineral density but there may be other causal pathways.
3. Antiretroviral drugs alter survival by effects independent of the number of opportunistic infections.
4. Prostatectomy for prostate cancer has mechanisms of action including but also in addition to the pathway affecting prostate specific antigen.

Surrogates and safety

Surrogate markers may have implications for safety because they may be unaffected by the adverse effects of an intervention. The ILLUMINATE trial in cardiovascular disease was stopped because there was higher mortality with the study drug (torcetrapib) even though it was effective at reducing LDL cholesterol.[9]

The use of a surrogate marker in a short-term study using relatively small numbers of patients may not reveal rare adverse effects, whereas a longer, larger phase III trial would be more likely to detect these events. This risk may be further increased if these surrogates move from research to clinical practice. Unless there is a strong correlation between the surrogate and the clinical outcome, clinicians should focus on treating the disease, not just the surrogate marker.

The risk of translating surrogate markers to clinical practice

Even if an intervention has an effect on a surrogate marker and that marker is clearly in the causal pathway of the clinical end point, the effect may not persist long enough for the drug to alter the long-term clinical outcome. The drug may seem to be efficacious because of its short-term effect on the surrogate marker, but have no effect on the clinical outcome.

There is evidence that LDL and total serum cholesterol are valid markers or 'risk factors' for cardiovascular outcomes, based on a number of well validated long-term studies. However, there is doubt about whether a reduction in LDL or total cholesterol over a short period of time will predict the long-term effect and therefore outcome. An example of this would be when a new drug is shown to be more effective than another at lowering LDL cholesterol over 16 weeks and the result is extrapolated to imply a greater reduction in the long-term risk of cardiovascular events.

A recent example is the ENHANCE trial.[10] Although the combination of ezetimibe and simvastatin lowered LDL cholesterol over a two-year period, there was an increase in the carotid intima-media thickness. The trial relied on the combination of one well accepted (LDL cholesterol) and one controversial (intima-media thickness) surrogate marker to show the drug's effect. One of the many questions raised by this study is whether a reduction in intima-media thickness will translate into a reduction in cardiovascular events. This question will remain until the results of larger phase III trials are available.

Questions remain as to the utility of bone mineral density in predicting fracture risk. The major problem seems to be establishing a threshold level for acceptable risk in a condition which has multiple contributing risk factors such as age, sex, smoking history and alcohol intake. The introduction of bisphosphonates and how much benefit can be gained, based solely on changes in bone mineral density, is difficult to determine for an individual.[11,12] The restriction of bisphosphonate use, at least in Australia, to those who have sustained a fracture may seem overly cautious but might be the most reasonable way to attribute individual risk because of the poor individual correlation between bone mineral density and risk of fracture.

Conclusion

Surrogate markers are born of phase II trials and are not necessarily ideal for use in clinical decision making. Phase III trials should be the true testing ground for the validity of

surrogate markers. There are some valid surrogate markers of disease progression which can be reliably used to monitor chronic conditions, and as treatment goals. However, the clinical utility of many surrogates is open to question and their validity is largely untested. Practitioners need to keep in mind that some widely used surrogate markers of disease have not been adequately validated for use in clinical situations. A disease may be associated with a surrogate marker, but this does not mean that treating the marker will improve the outcome of that disease.

References

1. Department of Health and Human Services. Food and Drug Administration. New drug, antibiotic, and biological drug product regulations: accelerated approval. Federal Register Vol 57 No 73. 1992. p. 13234-42.
2. Fleming TR, DeMets DL. Surrogate end points in clinical trials: are we being misled? Ann Intern Med 1996;125:605-13.
3. Barnes D. How prescription drugs are developed. Aust Prescr 2006;29:159-61.
4. Vogel R, Crick RP, Newson RB, Shipley M, Blackmore H, Bulpitt CJ. Association between intraocular pressure and loss of visual field in chronic simple glaucoma. Br J Ophthalmol 1990;74:3-6.
5. Traver GA, Cline MG, Burrows B. Predictors of mortality in chronic obstructive pulmonary disease. Am Rev Respir Dis 1979;119:895-902.
6. Dolan S, Varkey B. Prognostic factors in chronic obstructive pulmonary disease. Curr Opin Pulm Med 2005;11:149-52.
7. Berger VW. Does the Prentice criterion validate surrogate endpoints? Stat Med 2004;23:1571-8.
8. Prentice RL. Surrogate endpoints in clinical trials: definition and operational criteria. Stat Med 1989;8:431-40.
9. Krumholz HM, Lee TH. Redefining quality – implications of recent clinical trials. N Eng J Med 2008;358:2537-9.
10. Kastelein JJ, Akdim F, Stroes ES, Zwinderman AH, Bots ML, Stalenhoef AF, et al. Simvastatin with or without ezetimibe in familial hypercholesterolemia. N Eng J Med 2008;358:1431-43.
11. Kanis JA, Borgstrom F, De Laet C, Johansson H, Johnell O, Jonsson B, et al. Assessment of fracture risk. Osteoporos Int 2005;16:581-9.
12. Marshall D, Johnell O, Wedel H. Meta-analysis of how well measures of bone mineral density predict occurrence of osteoporotic fractures. BMJ 1996;312:1254-9.

Further reading

Rolan P. The contribution of clinical pharmacology surrogates and models to drug development – a critical appraisal. Br J Clin Pharmacol 1997;44:219-25.

Temple R. Are surrogate markers adequate to assess cardiovascular disease drugs? JAMA 1999;282:790-5.

Conflict of interest: none declared

Treatments for severe psoriasis: update

In March 2009 it was announced that efalizumab would be withdrawn from the Australian market. This follows a review of the drug in Europe which found the benefits no longer outweigh the risk of harm. There are reports of progressive multifocal leucoencephalopathy arising in patients who have been treated with efalizumab for more than three years.[1] The drug has also been under review in the USA.[2]

References

1. European Medicines Agency. Questions and answers on the recommendation to suspend the marketing authorisation for Raptiva. 2009 Feb 19. www.emea.europa.eu/humandocs/PDFs/EPAR/raptiva/ RaptivaQ&A_1552509en.pdf [cited 2009 Mar 13]
2. US Food and Drug Administration Center for Drug Evaluation and Research. FDA Public Health Advisory. Updated safety information about Raptiva (efalizumab). 2009 Feb 19. www.fda.gov/cder/drug/advisory/efalizumab.htm [cited 2009 Mar 13]

Comment from Dr JR Sullivan and Dr V Preda, the authors of an article about treating severe psoriasis recently published in Australian Prescriber (Aust Prescr 2009;32:14–18):

For rare side effects it takes a number of years of post-marketing surveillance for a signal to appear. This can take longer for therapies with only a single therapeutic indication such as efalizumab. This drug has only been used in 46 000 patients worldwide.

The tumour necrosis factor-alfa antagonists, infliximab and etanercept, for psoriasis have been used for a number of clinical indications over a much longer period. We have 15 years of patient safety data and over 1.4 million patient years and 630 000 patients with etanercept, and 15 years of patient safety data and 4.3 million patient years and 340 000 patients with infliximab. For these two drugs much more is known about their longer-term safety profiles.

The use of biologicals for the treatment of severe psoriasis needs to be considered in light of the safety profile of each drug and also in the context of the individual patient. Biologicals are not only used in severe psoriasis but also for a number of other disorders. Thus with regard to safety data we can benefit from the experience with these medications used in other specialties such as rheumatology and gastroenterology. From rheumatology we know to screen for tuberculosis before starting therapy to help prevent potentially serious infections. Although adverse effects are often grouped together as a class effect, it is important to consider each biological drug individually as they have their own unique pharmacological profiles.