feature

Retrospective clinical analysis for drug rescue: for new indications or stratified patient groups

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The increasing realization that many existing drugs do indeed provide opportunities for additional therapeutic indications suggests we should not only be alert for this potential among marketed drugs but also within the pool of developmental drugs, of which (owing to attrition) there are many more examples in existence. We present examples of drug repurposing by retrospective clinical trial analysis and suggest that this strategy presents a promising way of rescuing failed developmental candidates. We contend that the commercial barriers to successful drug rescue are less problematic than for drug repurposing. We indicate practical means for mining data from past clinical trials, either for new indications or for specific patient groups.

Introduction

It is well known that the use of sildenafil for erectile dysfunction emanated from observed side effects in a Phase I human volunteer trial where the drug was indicated for angina. This represents an example of drug rescue (i.e. new use for a developmental drug that failed for its primary intended purpose), as compared with drug repurposing – the identification of a new use for a marketed drug. Unintended consequences can accompany any scientific endeavor, and we should be alert to their possibility. In the past, failed clinical trials rarely led to anything more than abandoned drug development programs, and are a major factor in determining overall costs of new medicinal products. So, should we routinely be making more thorough evaluations of the data from clinical trials to look for unexpected findings that could permit the further development of the test drug for either a particular patient group or for a new, different indication?

Patient stratification

Taking patient stratification first, most drugs only benefit a minority of the patients for which they are prescribed [1]. The proportion varies by therapeutic area, with some indications such as cancer recording efficacy in as little as 25% of patients, even though in other diseases such as cardiac arrhythmia and asthma the proportion of responding patients is much higher, at around 60%. Many factors are probably to have an influence on this statistic, including patient compliance, interpatient variations in drug metabolism and a difference in the nature of the underlying disease. However, regardless of the reasons, the high proportion of nonresponders represents a problem for drug development because, to demonstrate statistical difference relative to placebo, the active drug needs to 'carry' a significant proportion of ineffective results. This increases the number of patients in clinical trials and reduces the measured efficacy of the drug.

The obvious application of retrospective analysis for responding patient subgroups is to convert negative trials into positive ones; however, it can also convert trials with borderline significance into much more positive ones. This can be important where the initial evaluation is clinically positive but commercially not a sufficient basis for continuing, for example because of insufficient advantage relative to competitor products.

If it is possible to identify which patients are more probable to respond, the usefulness of the treatment can be enhanced; clinical trials can be run with smaller numbers and more robust results generated, because the standard devia-

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tion of the results as a whole will be lower. Although the market size in terms of the number of patients might be smaller than originally intended, the value for the responding patients could compensate, and the overall commercial value would remain just as high. This is because the drug might have better efficacy relative to competitor products such that a pricing margin can be justified.

In fact, we would go further and state that, in today's world, patients are demanding more from therapy and it is a drug development requirement that the nonresponding proportion is limited as much as possible.

An example where this has been applied is the retrospective analysis of tissue samples from the clinical trials performed for the novel epidermal growth factor receptor (EGFR)-targeting colorectal cancer drugs cetuximab (Erbitux®) and panitumumab (Vectibix®). These studies found that the majority of patients that carry a secondary mutant gene (KRAS and BRAF) are resistant to these drugs (in a combined total of 52% of patients trialed) [2]. Subsequent confirmatory prospective trials performed led to the establishment of a mandatory testing regime for all colon cancer patients for their mutant KRAS status before Erbitux® and Vectibix® can be prescribed.

Outside the oncology area, in the developmental history of the 5-HT3 antagonist alosetron hydrochloride (Lotronex®) for diarrheal irritable bowel syndrome, it was established that the drug was effective in women and not in men. The reasons for the sex difference have not been explained but, given the fact that three out of every four sufferers are female, it was perhaps fortunate that the relative efficacy was in this direction rather than the reverse.

It is also interesting that patient stratification can lead not only to qualifications in regulatory approval but also to specific patent claims for use of the drug in particular patient groups.

New therapeutic uses

A second use for retrospective analysis is the opportunity this represents for new indications. Clinical information of this kind can be of the highest value as a method of target validation for the use of a drug in a disease.

There have been a few examples from the area of drug repurposing in which retrospective analysis of existing drugs has become the basis for further research into secondary uses. These examples provide support for the hypothesis that similar new uses could be found for rescuing developmental drugs that have failed in their original intended indication. The result could be a new opportunity for either the drug itself or for close analogs thereof, for example when the new indication suggests alternative features (such as selectivity) need to be improved.

Perhaps the most famous example of this kind of analysis is the identification of two new uses for aspirin: first for the prevention of myocardial infarction and stroke; and second for the prevention of cancer.

The story of aspirin's first 'new life' started with a hypothesis in 1950 that the drug might prevent coronary thrombosis because it prolonged prothrombin time and sometimes caused hemorrhagic complications after tonsillectomy or tooth extraction [3]. It took a long while for this new use to be embedded in medical practice, with prospective trials taking place many decades later, after the discovery that prostaglandins and cyclooxygenase were involved in the mechanism of action.

Aspirin's second new life, as a preventative agent for cancer, was proved in 2010 by retrospective analysis of clinical trials with mean duration of treatment of four years or longer (although the possibility of this association had been around for some time before the publication of this study) [4]. It is presumed that it will take a while to conduct the prospective trials required to confirm this finding.

One of the reasons for the long lag time before prospective trials can be carried out is because aspirin is generic. Commercial barriers to gaining market approval for secondary indications normally supersede clinical ones.

Multiple secondary therapeutic areas

A variety of examples of findings emanating from retrospective trial analysis revealing secondary uses are shown in Tables 1–3. These examples concern existing drugs, but support the central theme of this paper: that a similar analysis might be fruitful for developmental drugs too. According to Chris Lipinski (Melior Discovery), 30% of clinical phase drugs have a new use (https://www.collaborativedrug.com/buzz/2011/07/20/); a similar view has been expressed by Pfizer. In March 2008, the company declared that approximately half of its assets that would advance from Phase II to Phase III clinical trials were for new indications (http://www.pfizer.com/files/investors/presentations/analyst_webcast_march030508.pdf). A central difference between the two cases, and an advantage of developmental drugs relative to marketed drugs (in addition to the previous comment about there being more of the former), is the lack of generic off-label competition. Thus, although the majority of the examples listed below have not resulted in product labels for their potential secondary use, there is usually little commercial incentive on the part of the innovator company to conduct the large scale trials to support the registration for such new uses, unless it can be completed within the patent lifetime of the original product. The same disincentive does not apply for drugs rescued from incomplete primary developmental campaigns.

The examples in Table 1 come from a range of new therapeutic areas: oncology, cardiovascular, fibrotic and central nervous system (CNS) indications. This broad range shows that the opportunities for this approach are not limited to any one area. Because of the commercial barriers to full development of these new uses, it is not possible to analyze their therapeutic validity properly.

However, these observations involve humans rather than *in vitro* or *in vivo* experimentation, and this feature makes them of huge relevance. They can dramatically improve our understanding of the importance of pathways in disease and as translational tools. A recent review highlighted the opportunity for electronic health records to identify new indications for existing drugs [5].

Cancer

Although there are opportunities across multiple therapeutic indications, cancer is a rich area for this type of analysis. The measurements or

TABLE 1

Broad Opportunities Across Multiple Therapeutic Areas and Drug Classes for New Uses Arising from Retrospective Analysis

Drug	Class of drug	New use	Basis for new use
Aspirin	Cox inhibitor	Colorectal cancer	[4]
Tamoxifen	Estrogen receptor modulator	Acute coronary syndrome (ACS)	[14]
Angiotensin II blockade	Angiotensin II antagonists	Hepatic fibrosis	[15]
Statins	HMG-CoA reductase inhibition	Epilepsy	[16]

TABLE 2

New Uses Arising from Retrospective Analysis in Cancer

Drug	Class of drug	New use	Basis for new use
Raloxifene	SERM	Breast cancer	[17]
Metformin	Insulin sensitizer	Breast cancer	[18]
Chlorimipramine (and others)	Tricyclic antidepressant	Cancer (glioma and colorectal cancer)	[19]

TABLE 3

New Uses Arising from Retrospective Analysis for Beta-Blockers

Drug	Class of drug	New use	Basis for new use
Propranolol	Beta-blocker	Osteoporosis	[20]
Propranolol	Beta-blocker	Melanoma	[21]
Propranolol/etodolac	Beta-blocker/NSAID[a]	Cachexia	[22]
MT102[b]	Catabolic/anabolic transforming agent		

[a] Combination being developed by Vicus Therapeutics.
[b] Being developed by PsiOxus, referred to as a 'beta-blocker and catabolic/anabolic transforming agent' in [23].

endpoints that can be used in the original trial(s) will govern the opportunity space for the retrospective analysis wherein the new indications can be identified or the patient stratification performed. Thus, although there are an increasing variety of text mining techniques for predicting alternative therapeutic uses [6], the opportunity to use such tools is limited because retrospective data analysis implies working with existing data, rather than being able to rerun the trial. Cancer incidence is usually recorded during pharmacovigilance studies associated with the prescription of any drug, because it could be associated with carcinogenic properties of the drug itself. In addition to the example of aspirin, three other examples of retrospective analyses that show an association of an existing drug with reduced incidence of cancer are shown in Table 2.

The discovery of the protective effects of raloxifene in breast cancer is poignant, because the drug was previously considered as a new agent for tamoxifen-resistant breast cancer treatment. The initial clinical studies for this indication were unsuccessful, but the drug was found to produce estrogen-like effects on bone and lipid metabolism, reducing bone resorption and increasing bone density in postmenopausal women. This led to approval from the FDA in 1997 for osteoporosis. The re-repurposed use for raloxifene was confirmed among postmenopausal women with osteoporosis, in which the risk of invasive breast cancer was decreased by 76% during three years of treatment with raloxifene.

The association of metformin use with reduced cancer risk was altogether more unexpected. Although population studies had suggested that metformin use in diabetic patients decreases cancer incidence and mortality, and there had been *in vitro* studies showing the inhibition of cancer cell growth, the mechanism by which this occurs is not well understood. Metformin is associated with an increase in pathologic complete responses in patients receiving neoadjuvant chemotherapy for early-stage breast cancer.

The identification of a cancer-preventative effect associated with tricyclic antidepressant use relied on the reporting of cancer as a serious adverse event in depressed patients treated with this class of drug (indeed, at one point there was suspicion that a potential carcinogen status was caused by their putative genotoxic activity). The choice of this class for evaluation was based on the prior substantial evidence that tricyclics, including chlorimipramine (clomipramine), imipramine, citalopram, amitriptyline and desipramine, have demonstrated anticancer effects *in vitro* [7]. The database in which this information is recorded, the General Practice Research Database (GPRD), is the world's largest computerized database of anonymous longitudinal patient records from general practice that are linked with other healthcare data. It contains over 45 million patient-years of data spread across 6.5 million patients in the UK. The database was established in 1987, with its development corresponding to the increased computerization of GP practices, and its validity has been well documented.

In all the associations between cancer and certain types of drug use, it is important to recognize that the prevention, or lower incidence, of an indication is not the same as treatment.

Routes to commercialization

In cases where there is an association between an existing mechanism and a new indication an additional step might be required to identify a valid commercial strategy. This is a general consideration for all drug repurposing projects, but is most clearly exemplified in the examples shown in Table 3, which shows a range of associations between beta-blocker usage and noncardiovascular diseases.

Beta-blockers were originally considered for the treatment of supraventricular tachycardia before being approved for angina and hypertension; more recently they have been approved for the treatment of congestive heart failure.

In the case of the association between beta-blocker use and osteoporosis various studies [8] have examined the association between fracture risk and beta-blocker use in population-based pharmacoepidemiologic case control studies. These studies considered beta-blockers used alone as well as in combination with thiazide diuretics. Patents were filed and a company called Osteocorp was founded with a view to conducting further specialized research. However, despite the significant evidence base, the anticipated commercial issues associated with the eventual off-label use of generic propranolol for osteoporosis meant that Osteocorp could not raise venture finance for the development of a proprietary propranolol formulation specific for the new indication, and the patents have now been abandoned.

The second example, for the use of propranolol in melanoma, is based on preclinical evidence showing that beta-blockers inhibit tumor and metastasis progression in animal models. The retrospective analysis focused on patients

with thick malignant melanoma, either treated with propranolol or not treated, and showed a 36% reduction in risk of tumor progression for each year of beta-blocker use. A similar report has also been made regarding the reduced relapse-free survival (but not overall survival) among breast cancer patients prescribed beta-blockers [9]. These findings, only recently published, have not yet had sufficient time for commercialization to proceed; however, if they do, they will need to overcome the difficulties faced by Osteocorp. Two ways in which this could be done are exemplified in the treatment of cachexia by beta-blockers.

The cachexia examples shown in Table 3 rely on the near-uniform collection of patient weight data during clinical trials, combined with an analysis by reference to the definition of cachexia as the loss of a certain amount of weight, normally 5% [10]. Two commercial developments are under way based on this finding. Although the retrospective analysis showed an association of cachexia with bisoprolol use in congestive heart failure, the beta-blocker used in the first development is propranolol combined with the NSAID etodolac, and the indication is lung-cancer-associated cachexia. By using a combination approach, the developing company Vicus Therapeutics has aimed to create a product specifically for the treatment of cachexia. Initial positive Phase II data have been reported by the development company Vicus Therapeutics, however the results do not show a clear dose-related effect and the impact of the NSAID component has not been shown to have a clear beneficial impact [11].

The second approach is currently in Phase II trials with PsiOxus; this company has taken the approach of identifying a beta-blocker with 'additional anabolic and anticatabolic properties' and results are expected in 2012. It is important to recognize that, since the original categorization of 'beta-blockers' as a class, various subtypes of the beta adrenergic receptor have been identified; in reality, the so-called 'beta-blocker' class is heterogeneous.

The development of a combination product specific for the new therapeutic indication is an approach that has also been taken for the commercialization of the tamoxifen example from Table 1. In this case, the ischemic risk of tamoxifen administration was covered off by the co-administration of a platelet aggregation inhibitor and this formed the basis for an intellectual property filing [12]. In so doing, the proposed product was differentiated for the cardiovascular use relative to the original product for cancer use, and fundraising for this project is currently underway (http://www.e-picbiotech.com/presenter/lookup?id=92).

The commercial problems generally do not apply where the drug is not marketed as, by definition, is the case in drug rescue. So, what exactly needs to be done to make this strategy a useful means of resurrecting unsuccessful development campaigns?

Practical approach

Although mining data from past clinical trials makes great sense, companies rarely take another look at such data. Typically, pharma companies working on an FDA submission do a set of trials as part of new drug application and integrate a summarization of the drug's efficacy and safety into that submission. After that, all other information from clinical trials is simply saved but not examined again unless additional analyses are requested by regulatory agencies or warranted by internal marketing requirements.

The situation is very different before submission. An innovator's decision to progress from exploratory Phase II to confirmatory Phase III development is almost always supported by extensive data assessment using a variety of analytic tools.

The vast majority of these tools used in the exploration stage employ a targeted modeling approach. This involves two major stages: setting a scientific question and thereafter testing the hypothesis using a biostatistical model. Although the targeted modeling approach will continue to govern data analyses of pivotal clinical trials, the analysis stage can be done more effectively by broadening the arsenal of analytic tools at hand.

One means of doing this is to use an inverted inferential approach, in which a given data subset is analyzed according to certain hypotheses, generated without clinical guidance; this creates a certain set of relationships and data patterns that can be tested against the remainder of the data and their significance established (Box 1). A parallel approach can be used to simulate treatment potential in related clinical indications and identify subsets of treatment responders, opening new project opportunities.

Traditionally, biostatistical clinical trial analysis attempts to estimate the overall average magnitude of a benefit in a relatively wide population range. As a result, the benefit of a potential product is erroneously underestimated simply because it dilutes the responder effect with the results of nonresponders. However, by differentiating these populations (e.g. owing to genetic markers, prognostic factors, medical condition) internal hidden data patterns can be

BOX 1

Hypothesis generation and validation: a data-led approach

There are two steps for the retrospective analysis of past clinical trials: first, a hypothesis is created; and, second, the hypothesis is tested against the data.

This example started with a double-blind placebo-controlled clinical trial designed to test for the antiobesity effect of a candidate medication. However, over the entire data set, we found that there was a trend toward an effect on weight, but one that was not statistically significant.

In the hypothesis-generating step, the data were randomly divided into two sets; the first set comprised 70% of the subjects, and was used for pattern recognition analysis (the modeling cohort).

We then looked at all the baseline characteristics of the subjects and searched for patterns. These characteristics included things like duration of disease, baseline weight, age, sex, baseline BMI and so on.

One of the patterns that was found to be interesting was based on a subset of female patients aged 18–39. This group had significant weight loss compared with the placebo group.

We then validated this hypothesis by looking at the remaining 30% of the subjects (the validation cohort). These patients were excluded from the modeling cohort. This cohort was analyzed for a change in weight, and confirmed a significant effect within this subset, in other words this group of subjects had a similar weight reduction as seen in the modeling group.

One could conclude that hormonal influences played a part in the clinical efficacy of the candidate medication. According to this proposal, such influences would have to be concentrated in the subset of premenopausal female patients. Other workers have remarked on the tendency for females to develop different obesity phenotypes throughout their lifespan, and there have been studies on the genetic basis for these different phenotypes [24]. Further work is underway to define exactly which mechanisms are probably to be involved.

revealed and the project's value significantly upgraded.

In other cases, it might be possible to retrieve banked tissue and blood samples and reanalyze for biomarkers of disease, or patient genotypes. This is a far more sophisticated approach, which might require forward planning in clinical trial protocol development. The choice of biomarkers can be informed by prior analysis of possible additional uses for the candidate drug. The range of such biomarkers should not be too wide, reflecting only those additional uses that are well-validated by known literature. It is not necessary, nor indeed particularly desirable, to cast a wide net to find 'unexpected' new uses; unlike drug repurposing of existing molecules, the expectation is that drug rescue development can proceed with the existing composition-of-matter patent cover, and new method-of-use claims are not essential, even though they could extend a product's commercial life. However, the decision to adopt this course of action involves a significant amount of additional work, including biochemical analysis, relative to the simpler approach of reanalyzing data.

Problems

The retrospective analysis strategy is not without issues. First, as is clear from the aspirin example, retrospective analysis is not the same as prospective analysis, which took over 20 years to complete after the initial clinical reports on aspirin's antithrombotic effects. Whatever is revealed, the path to regulatory approval will require further clinical trials where the new indication or patient group needs to be studied in a prospective fashion. There is always a random chance of an association between treatment and effect, and the more signals that are studied the more the chance that the association is a false-positive result that cannot be replicated. Nevertheless, clinical trial information is of huge relevance to the real human situation and, in the many diseases where animal models are poor representations or nonexistent, such information can be invaluable.

Second, the data analysis itself is not necessarily a quick process. The revelation of the association between tricyclic antidepressant use and reduced incidence of cancer formed the basis of a three-year PhD project. It was based on the analysis of over 30,000 cases of cancer and over 60,000 age- and gender-matched controls. The analysis is significantly more complex if the plan is to reanalyze blood or tissue samples for specific biomarkers.

Third, the endpoint from the trial analysis is often not exactly the same as a new indication; in the tamoxifen case, the reduction in incidence of myocardial infarction was translated into a prospective use in acute coronary syndrome, this indication being chosen because it covered a high-risk population where the numbers requiring treatment in order to generate a statistically meaningful result made this a practical therapeutic option.

Fourth, drug development carried out after an initial Phase II failure can, and usually does, operate in a diminished patent window. The original composition of patent matter for the investigational drug will often be fairly advanced by the time the secondary development is ready for regulatory approval. By the time a drug has first failed in Phase II the patent life left for commercialization might not allow a good return on R&D investment. This can represent an important loss of the most valuable form of protection associated with composition of matter. However, new patent life can arise when associated with use in the new indication or new patient subgroup. Generating an effective means of protecting the new development is an important issue. Together with data protection or market exclusivity, if the new development is for an orphan use commercial exclusivity could be adequate. Alternatively, the commercial and scientific analysis might suggest other avenues such as new analog development; but, although this effectively represents a new discovery project, it can of course be conducted with the advantage of lower risk given the clinical efficacy information resulting from the retroanalysis.

Concluding remarks

Retrospective analysis has been used on multiple previous occasions to identify new therapeutic opportunities for existing agents. Typically, these arise from population-based studies of marketed drugs using general practice records. Sometimes, it has been possible to interrogate the more controlled investigational studies of the original development package. There are undoubtedly further examples that have not yet been discovered through an exhaustive retrospective analysis of the data. To a certain extent the opportunities are delimited by the measurements that are available; however, it is clear that there is a wide range of additional therapeutic uses across multiple treatment classes.

This approach has not yet been used in a systematic prospective sense, although the proposals for the NIH National Center for Advancing Translational Sciences (NCATS) include retrospective analyses of trial data to develop prospective risk assessors [13]. However, a more extensive use of prospective biostatistical analysis for new indications and patient subgroups can also reduce drug attrition and improve opportunities in the future.

Conflicts of interest

The authors provide consultancy services in the areas of drug repurposing (DC) and biostatistics (CS).

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