Review Article

Medical imaging in new drug clinical development

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ABSTRACT Medical imaging can help answer key questions that arise during the drug development process. The role of medical imaging in new drug clinical trials includes identification of likely responders; detection and diagnosis of lesions and evaluation of their severity; and therapy monitoring and follow-up. Nuclear imaging techniques such as PET can be used to monitor drug pharmacokinetics and distribution and study specific molecular endpoints. In assessing drug efficacy, imaging biomarkers and imaging surrogate endpoints can be more objective and faster to measure than clinical outcomes, and allow small group sizes, quick results and good statistical power. Imaging also has important role in drug safety monitoring, particularly when there is no other suitable biomarkers available. Despite the long history of radiological sciences, its application to the drug development process is relatively recent. This review highlights the processes, opportunities, and challenges of medical imaging in new drug development.

Key Words: new drug; medical imaging; diagnostic radiology; clinical trials; clinical development; pharmaceutical industry

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Introduction

It takes approximately 15 years to take a drug from laboratory discovery to FDA approval. Out of every 5-10 000 compounds evaluated pre-clinically, only five enter clinical trials, and of these only one gains regulatory approval. More information on the efficacy, safety and mechanism of action should be sought from early-stage clinical trials to minimize late-stage attrition. Medical imaging has an enlarging role in new drug development. This progress is driven by several factors, including the growing technical capabilities of imaging methods and the increasing focus by drug developers on chronic diseases. The application of medical imaging in pharmaceutical clinical trials involves its use to determine disease predisposition; to identify likely responder patients; to diagnose lesions and evaluate their severity; and to monitor therapy effects and follow-up. Considerable emphasis has also been placed on linking pre-clinical imaging and clinical data in order to increase the success rate of clinical trials (1). Pre-clinical imaging in appropriate disease animal models can contribute to the identification of new imaging biomarkers, whereby histological correlation can be obtained. It is anticipated that greater use of imaging during pre-clinical stages will facilitate better translation from animal models to human subjects.

In this article some basic principles of new drug development are explained and unique aspects of study design for clinical trials with an imaging component are discussed. The main emphasis is on the application of medical imaging in therapeutic drugs trials; however, many principles may be equally applicable to the development of novel imaging contrast agents and radiopharmaceuticals.

New drug clinical development process

A new drug can be a small inorganic molecule or a complex organic molecule such as an antibody. Drug discovery involves the identification of a target (eg, an enzyme or a receptor), and the design and optimization of a drug to interact with it. Preclinical studies conducted in animals are typically used to demonstrate the safety and effectiveness of a new drug. If promising, the new product then proceeds to clinical trials in human subjects, a process that usually involves multiple stages commonly known as phases (2,3). Thus drug discovery and development can be broken down into pre-clinical drug discovery (approx. 6.5 years), Phase I testing (approx. 1.5 years), Phase II testing (approx. 2 years), Phase

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III testing (approx. 3.5 years), and FDA approval (approx. 1.5 years). The aim of phase I trials is principally to study pharmacokinetics and initial tolerability in humans. Where possible, the duration and dose dependency of the drug effect is explored. To avoid the confounding influence of other diseases, medications and age, phase I studies usually start with young, healthy volunteers. With some types of drug, such as some cancer drugs which carry a significant risk of adverse effects, patients for whom there may be a therapeutic benefit are recruited. To assess tolerability, a dose-ranging schedule may be applied in which successive volunteers are exposed to increasing drug doses. Phase I studies typically involve 50 to 150 subjects.

Phase II trials study the safety and effectiveness of the drug in cases with the indication in question, and seek to identify the optimum dosage schedule. Phase II studies, which typically involve 100 to 200 subjects, can also investigate the pharmacological differences between patients and healthy volunteers.

The phase III study is the most extensive phase of development. Its purpose is to confirm the effect, tolerability and safety of the new drug compared with standard therapy (or placebo), and to prove the correct dose in cases with the indication in question. Phase III studies usually involve 500 to 5000 patients, and patient demographics should as far as possible be representative of the population in which the new drug will ultimately be used. Phase IIIb studies are not needed for registration, but typically answer specific questions in order to support the new drug's use in particular populations or territories.

Phase IV studies are needed after registration. Many questions may remain unanswered after the phase III study, such as effectiveness and safety in children or the elderly. Large post-marketing surveillance studies are now often conducted on new drugs to identify rare adverse events.

Clinical trials have historically used clinical endpoints (outcomes) to establish whether the therapy is safe and effective. A clinical endpoint is defined as a characteristic or variable that measures how a patient feels, functions or survives. The classic endpoint of mortality determines whether the new therapy decreases the rate of death in comparison with that of a control group. Another endpoint is morbidity, in which investigators examine whether patients undergoing the therapy are in some way more functional or enjoy a higher quality of life than those who do not receive the therapy. Trials with these clinical outcomes often have a long duration and require a large number of subjects, and are therefore extremely costly.

A surrogate endpoint is a laboratory measurement or physical sign used as a substitute for a clinical endpoint (4,5). Regulatory approval for a drug may be secured when the regulatory authority decides that the product has an effect on a surrogate endpoint that is reasonably likely to predict clinical benefit (6). It has been shown that small improvements in clinical trial outcomes and decision-making translate into great cost-savings and a faster time-to-market (7). Examples of surrogate endpoints include: (i) blood pressure as a risk for myocardial infarction or stroke; (ii) cholesterol measurements for risk of myocardial infarction or death; (iii) CD4 cell count for risk of progression to AIDS; and (iv) CT or MRI measures of tumour size. In a survey of oncology drug approvals by the FDA, of the 57 oncology drugs approved for marketing during the period of 1990-2002, only 18 relied upon traditional survival data. Of the additional 14 drugs that gained accelerated approvals, none relied upon traditional survival data. The clinical trials of 53 out of 71 oncology drugs used surrogate endpoints, the most common one being the change in tumor size as a result of the drug therapy (3). On many occasions, the use of a surrogate endpoint shortens substantially the total time required for confirmation of clinical benefits.

True surrogate endpoints will require a comprehensive validation, i.e. strong evidence of positive predictive clinical outcome. Approval under this section may be subject to the requirement that the sponsor study the drug further, to verify its clinical benefit. However, in some instances surrogate endpoints used to assess the efficacy of new drugs were found not to predict the clinical outcomes of mortality or morbidity, leading to the withdrawal of those drugs. Among various explanations for such a failure is that the disease process could affect the clinical outcome through several causal pathways that are not mediated through the surrogate. The drug might also affect the clinical outcome by unintended and unrecognized mechanisms of action that operate independently of the disease process and are not recognized by the surrogate endpoint (8). One notable example is the reliance on suppressing ventricular dysrhythmia determined from electrocardiograms for the development and approval of anti-arrhythmia drugs, the result of which is the marketing of drugs that were later found to cause mortality at two to two and a half times higher than that of the placebo group (9,10).

A biomarker is a characteristic that is objectively measured as an indicator of biological processes or pharmacological responses to a therapeutic intervention (4,5). In phase I/II studies, biomarkers can provide an indication of efficacy and safety or confirm a pharmacological mechanism. Highly responsive biomarkers, which change quickly in response to therapy, are very useful for identifying patients who are failing therapy and may require dose adjustments or change to a different treatment. Although a limited number of biomarkers are likely to attain surrogate status, other biomarkers can still contribute to the early stages of drug development. In phase III studies, biomarkers can be used to support clinical outcome claims. A list of imaging biomarkers and imaging surrogate endpoints has been discussed elsewhere (4,11).

Imaging in pharmacokinetics studies

Imaging has great potential to address key mechanistic and efficacy questions at the first stage of clinical development. Nuclear imaging techniques such as positron emission tomography (PET) offer the sensitivity required to monitor drug distribution and pharmacokinetics (PK) and to image specific molecular endpoints (11,12). At relatively small additional cost, the information can guide the clinical program by optimizing subsequent studies.

PET has been applied to a wide number of drugs to demonstrate activity in vivo, from standard chemotherapy such as 5-fluorouracil to molecular agents such as those involved in tumour angiogenesis and antivascular therapy (13). The use of PET imaging techniques to establish dosing regimens has been pursued (14,15). PET can be applied before traditional Phase 1 studies to test compounds in humans at tracer (non-pharmacologically active) concentrations. Such an approach uses as little as one-thousandth of the starting dose (i.e. micro-dosing) of a typical Phase 1 study. In broad terms, imaging of PK properties falls into two categories. The first category involves the radiolabeling of compounds that interact with, or neutralize, agents from the environment, such as toxins, bacteria and viruses. In this case, generally only tissue concentrations of drugs are necessary. In the second category, if the drug is expected to alter or modulate some aspects of the pathophysiologic process, then imaging studies are generally used to characterize the number of receptors, binding efficiency and receptor occupancy (11). As an example of the first category, the development of 18F-labeled antifungal agent fluconazole (Diflucan, Pfizer) was monitored by PET to establish the concentration of the drug in different organs, particularly at the site of infection. The imaging study found that the observed concentrations compared favorably to the concentrations required to inhibit in vitro pathogen growth (11, 16). PET imaging of aprepitant (Emend, Merck) belongs to PK imaging of the second category. Aprepitant is a neurokinin-1 (NK-1) receptor antagonist that crosses the blood-brain barrier and was developed as, among other things, a treatment for emetogenic chemotherapy-induced nausea and vomiting. By using a 18F-labeled ligand with known high affinity and specificity for the NK-1 receptor, PET was used to image the displacement of this radioligand by aprepitant. During the clinical trial, because NK-1 receptors have been found to be most abundant in the caudate and putamen, and least abundant in the cerebellum, this information was used to establish a reference and to compute the displacement of the PET tracer (11,17).

Imaging modalities other than PET have been used to evaluate dosing regimens, for example, MRI was used to evaluate drug regimens for interferon-β (IFN-β) treatments of multiple sclerosis (MS) (18), infliximab (Remicade, Centocor) for psoriatic arthritis (19), and PTK787 for colorectal cancer (20).

The lack of proper bioactivity or pharmacodynamic -pharmacokinetic profiles can also help to terminate unpromising drug development efforts (11,21).

Imaging in pharmacodynamics and drug efficacy studies

On many occasions, the use of imaging biomarkers and surrogate endpoints can facilitate small group sizes, quick results and good statistical power. In assessing new drug efficacy, mortality often takes years of follow-up to establish. The determination of morbidity is often subjective. On the other hand, imaging biomarkers and surrogate endpoints can be more objective and faster to measure. Imaging can reveal small, subtle changes indicative of incremental progression or regression that might be missed with traditional approaches. Furthermore, findings evaluated by individuals with no direct subject contact can be very useful in limiting bias related to lack of effective investigator blinding. Measurement of tumour shrinkage is used as a surrogate for other measures of clinical benefit, including time to event (death or disease progression) and symptom control, allowing quicker and more objective assessment of the effects of the anticancer agents. In one trial of the VEGF-specific monoclonal antibody bevacizumab (Avastin, Genentech) on rectal cancer patients, CT measurements of tumor blood flow and blood volume decreased significantly twelve days after a single infusion of the drug (22). This observed decrease in tumor perfusion demonstrated a positive correlation with other tumor indicators, including microvessel density (22). Imatinib mesylate (Gleevec, Novartis) is a tyrosine kinase inhibitor that has gained FDA approval for chronic myelogenous leukemia and gastrointestinal stromal tumors (GIST). Using FDG-PET it was found that reduction in glucose metabolism preceded CT response by a median of seven weeks, and all GIST patients with a complete or major metabolic response subsequently reached partial or durable stable disease on CT (23). Other examples of early imaging assessment of tumor angiogenesis are available in literature (3,11,24,25,26,27).

Etanercept (Enbrel, Immunex, now Amgen) is a tumor necrosis factor inhibitor for the treatment of rheumatoid arthritis. When examining the potential for etanercept as a first-line treatment, early trials used two sets of criteria: (i) American College of Rheumatology (ACR) scores, which use a combination of subjective pain and function assessments, in addition to serum C-reactive protein levels; and (ii) conventional radiography images of joint-space narrowing and erosion. Whereas clinical scoring showed no significant difference between etanercept and methotrexate (the standard therapy at the time), the imaging-based erosion score showed statistically significant differences (28). On the basis of these data, the FDA granted Immunex marketing approval with the condition that

additional supporting data be collected. A subsequent study showed etanercept achieved sustained improvements over methotrexate in terms of both clinical and imaging scores (29).

The current gold standard for assessing outcomes of Alzheimer's disease comprises behavioural or cognitive measures, but these suffer from poor reliability. MRI measurement of whole brain or hippocampal atrophy rate can be used to support clinical outcome measures in therapeutic trials for Alzheimer's disease, and functional brain activity can be objectively quantified by measuring regional glucose metabolism with PET (30,31,32). With clinical trials for MS, there has been great reliance on imaging data, especially using T2-MRI lesion burdens, and the number of contrast-enhancing lesions. These imaging biomarkers can serve as primary outcome measure in Phase I and Phase II trials, and also can serve as secondary outcome in Phase III trials (33,34,35). Other examples of early bioactivity assessment include MRI and CT for examining ischemic stroke (36,37) and imaging assessment of cardiovascular disease (38).

Imaging can also help to detect early disease and define stratified study groups. Imaging can be used to separate - as early as possible - responders from non-responders in patients undergoing therapeutic intervention. Many diseases have a "therapeutic window" in their course, during which medical intervention may have a more significant impact (39). In clinical trials, excluding patients who are not likely to progress can substantially increase the statistical power of a study and thereby reduce the number of patients and study duration needed to prove therapeutic efficacy. In one study examining advanced non-small-cell lung cancer, 55 patients were imaged with FDG-PET after a single course of chemotherapy. The results showed a statistically significant difference both in time to progression and overall survival between responders (i.e. those with observed decrease in tumor metabolism as seen on PET) and non-responders (40). Similarly, in a study involving 40 gastroesophageal cancer patients, FDG-PET segregated responders from non-responders with a sensitivity of 93% and specificity of 95% (41).

When choosing whether to use imaging surrogate endpoints, it is important to bear in mind that imaging surrogates are most helpful when clinical outcome is difficult to assess; and that changes detected by imaging may not always reflect true clinical outcome (42).

Imaging in drug safety assessment

There is huge potential for imaging in drug safety evaluation during clinical trials. In preclinical studies, although in many cases drug safety information is better obtained through imaging, the information may also be obtained by histopathological means. In clinical trials, imaging can sometimes be the only practical mean to obtain drug safety information (43). After organ toxicity occurred, serum and urine assays can be normal due to the function reserve of the affected organs, on the other hand, imaging offers the possibility to provide region-specific information about tissue abnormality. In addition, some structural and functional information is better acquired through imaging techniques. For example, the quantification of tissue lipid content is easier with MRI or MR Spectroscopy than histology techniques. The hepatotoxicity can display manifestations such as hepatic steatosis, glycogen deposition, hepatocyte necrosis and cholestasis. Imaging provides a valuable tool in safety studies when other biomarkers for toxicity, such as routine serum chemistry measures are not suitable. Hepatic steatosis, a common finding in drug safety studies, does not always correlate with elevations of hepatic serum enzymes. In some cases, drug-induced hepatic steatosis patients can present with a rapid evolution of severe hepatic failure, lactic acidosis and ultimately death (44).

The heart has limited capacity to repair itself. Toxic findings in the heart can be serious. While electrical activities of the heart can be monitored in clinical trials by ECG, due to delayed release of serum markers of cardiac damage, structural histopathology, such as cardiomyocyte inflammation, degeneration and necrosis lack conventional early biomarkers. Echocardiography has been widely used in preclinicaland clinical drug safety evaluation for new drug cardiotoxicity (45,46). Echocardiography can be used to measure the cardiac wall thickness, lumen volume and cardiac output. It has further advantages that it provides low cost, real-time images. MRI has also been used to determine myocardial volume, wall thickness, left and right ventricular end-diastolic and end-systolic lumen volumes, stroke volume and ejection fraction.

Many non-invasive tests of kidney function can only show renal damage after the functional reserve had been eliminated. This reserve can compensate for up to 75% of the loss, which make many serum and urine biomarkers insensitive for early kidney damages. MRI can offer advantages over methods that measure global functional changes by providing anatomically specific information of kidney injury. For example, a wide range of compounds can cause renal papillary necrosis (RPN). In the early development of RPN, there are few clinical symptoms and specific urine or blood biomarkers. The progression of renal damage is insidious and renal function may be severely compromised before the condition becomes obvious. The diagnosis of RPN tends to be made in the late stages of this disease after irreversible destructive changes have occurred. The use of imaging modalities has led to an increased positive diagnosis in human population (47). Lang et al reported that contrast-enhanced multi-phasic CT scan can identify early manifestations of RPN and medullary necrosis, and CT scan can further be used to monitor lesion progression or regression after treatment (48).

The absence of a reliable clinical safety biomarker can lead to the withdrawal of an attractive new drug from further clinical study. Vigabatrin (Sabril), an irreversible inhibitor of gamma-aminobutyric acid transaminase, is an effective treatment for refractory epilepsies. Animal toxicology showed that administration of Vigabatrin induces intra-myelinic oedema and microvacuolation in discrete brain regions in rats and in dogs which are detectable with MRI (49,50). Peyster et al reported when Vigabatrin was withdrawn, both MRI abnormality and pathological changes began to decrease, and 16 weeks after vigabatrin withdrawal, MRI and histopathology returned to normal (50). Therefore, MRI being a safety biomarker for the surveillance of Vigabatrin -induced neuropathy enabled further clinical trials of Vigabatrin. Throughout development and post-marketing phase, MRI and neuropathological studies of patients exposed to long-term Vigabatrin treatment have provided no evidence of neuropathy (51). Later, it was concluded that the neurotoxicity of vigabatrin bears a species specificity, with rats and mice being highly susceptible, dogs moderately susceptible and primates and humans not significantly affected at all.

In a recent example, MRI has been proved as a valuable tool for monitoring the liver toxicity of 6-thioguanine (6-TG), an effective treatment option for inflammatory bowel disease (IBD, 52). Despite promising clinical data, there has been a rising concern regarding potential hepatotoxic side-effects of 6-TG, which lead to the development of liver nodular regenerative hyperplasia (NRH). Seiderer et al conducted a multicentre safety study in IBD patients treated with 6-TG to investigate hepatic changes by ultrasound-guided liver biopsy and MRI (52). Forty-five patients treated with 6-TG (40-80 mg/day) for at least eight weeks were enrolled. MRI demonstrated a sensitivity of 77% and a specificity of 72% in the detection of histopathological findings consistent with and/or possibly related to NRH. Furthermore, MRI gives information on other potential NRH associated complications such as splenomegaly, portal hypertension and ascites. In their study, NRH was also found in patients who had completely normal laboratory results. This stressed that patients on 6-TG therapy should undergo safety evaluation even in the absence of laboratory changes.

Image data acquisition and quantitative image processing

For drug development, a qualitative radiological approach must be transformed into a quantitative biomarkers or surrogate endpoint useful in decision-making. For this, a parameter needs to be identified that characterizes the disease baseline and its subsequent response to treatment; examples include tumour volume (cm^3), mean tumour permeability (ml min^{-1} $100g^{-1}$), and ^{18}FDG PET SUV. The parameter needs to be comparable between patients, and the required data processing should be minimally subjective. Image acquisition protocols should be standardized (as far as practical) across centres for multicentre studies, and the specific ways in which images will be stored, processed and evaluated should be defined in the study protocol. Assessment of whether the scanner manufacturer, model and software version will potentially impact on variability need to be determined. Acquisition of pilot data prior to a clinical drug study is desirable to ensure data quality and protocol compliance across sites. In addition, specific QA procedures (eg MRI phantom measurements of geometric uniformity or scanner calibration for cross-site ^{18}FDG-PET SUV measurements) may be required during the initiation and throughout the course of the study. Consensus papers on how to conduct DCEMRI and analyse the data across multiple studies have been published (53,54). Simliar activities have been undertaken for ^{18}FDG-PET (55,56,57,58). For image evaluations intended to demonstrate the efficacy of a new drug, the nature and type of information available to the readers should be discussed with the regulatory authority before the trials are initiated.

The main aim of image processing in clinical trials is to quantitatively extract parameters objectively by segmentation of tissue structures and derivation of parameters from the selected region of interest. The need for robust objective image analysis is demonstrated in the study of tumour size by Erasmus et al (59). Intra- and inter-reader performance was assessed using CT images from a study of non-small-cell lung cancer. The inter-observer variability in maximum tumour diameter was < 7.1% for a well-marginated mass vs < 140% for a poorly marginated mass. Therefore tumour response could be misinterpreted owing to the inconsistent definition of lesion size, particularly for inter-reader variability. If such variability occurred within a clinical trial, then it may not be possible to infer whether the drug worked or not (3).

Blinded image evaluation is usually the favored approach. Sometimes unblinded image evaluation is used to show consistency with the results of fully blinded image evaluation. Two blinded readers (or preferably three or more) should evaluate images. To prevent bias, it is preferable to involve a number of readers from differing centres, and readers may need to be excluded from reading cases from their own institutions. Ideally, each reader should view all of the images. In large studies, where it may be impractical to have every image read by each reader, a chosen subset of images may be selected for the assessment of interobserver agreement. Consistency among readers should be measured quantitatively (eg with the kappa statistic). Reader disagreement and inter- or intraobserver variation can often be minimized by a training period. The image readers' performance should be monitored and documented. In evaluating images, objective, quantifiable endpoints should be used whenever possible. This can result in a higher inter- and intraobserver correlation than qualitative evaluation (60). Items

on the image evaluation case report forms should be carefully constructed to gather information without introducing a bias that indicates the answer that is being sought.

In clinical trials with imaging components, a subject is typically scanned at different time points. Image alignment using registration algorithms simplifies the interpretation and correlation of findings between such studies by removing the effect due to difference in patient placement. During image assessment, images acquired at different times should be displayed using a standard format. It has been shown that the sequence in which the images from different time points in the study are viewed may have an impact on the sensitivity and reliability of the evaluation (61). Offsite image evaluations are performed at sites that have not otherwise been involved in the conduct of the study, and by readers who have not had contact with patients or other individuals involved in the study (62). Centralized offsite reading can support more complex scoring methods and quantitative analyses than are feasible in clinical practice. Trials intended to demonstrate or support efficacy generally should use offsite image evaluations at a limited number of sites (or preferably at a centralized site).

Computer-aided detection (CAD) can improve readers' performance in detection of abnormalities, as well as in characterization of detected abnormalities. Manual delineation of a structure, particularly on a 3D image series, is slow and expensive. Thus a variety of computer-assisted methods is used to identify structures of interest, and to extract information such as lesion number, area, volume, density and intensity. These computer systems need to find an appropriate balance between the amount of user interaction and automation, which improves consistency, reduces the time to completion and enables clinical experts to bring their expertise into the analysis procedure (63). Potential time saving and reduction in measurement variability achieved by automated algorithms should not be allowed to compromise the accuracy of the analysis (64).

Security is required to protect patient records and maintain the integrity of the data. When handling the imaging data, the information should be capable of transmission without unblinding. Image analysis software must employ audit trails and electronic security (64). Although the images must not be altered, analysis of the images and, in particular, the measurements and segmentations, are typically generated and modified or deleted by one or more users. Secure, computer-generated audit trails record times and types of action without obscuring previously recorded data (2).

Conclusion

Modern nuclear imaging techniques can noninvasively provide early in vivo assessment of bioactivity and help establish pharmacokinetic and pharmacodynamic profiles of new drugs. In phase I and phase II studies, imaging biomarkers may complement non-imaging endpoints to promote confidence of therapeutic efficacy or be used to study a drug's mechanism of action. In phase III studies, imaging can secure or support regulatory approval for the new drug. Imaging has important role in drug safety monitoring, particularly when there is no other suitable biomarkers. With improvements in imaging hardware, software and tracer development, the breadth of applications of imaging in new drug development is likely to increase.

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