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Quantitative Imaging in Clinical Trials

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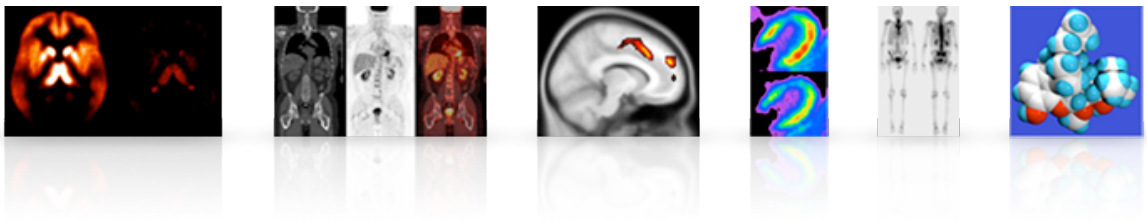

Introduction

The pharmaceutical industry spends approximately $65 billion annually for R&D, with approximately $50 billion spent by the large pharmaceutical companies. Nonetheless, only 24 new drugs were approved in 2009, with just 10 developed by the large pharmaceutical companies (Mathieu). Only 8% of new molecular entities (NMEs) make it to launch from the preclinical candidate selection stage, costing an average of $1.8 billion per NME (Paul et al., 2010). Since approximately 63% of the cost for each NME is spent in the clinical development phases I-III, improving the clinical success rate and reducing costs is a major goal.

Development of new drugs for mechanistically novel targets is critical for the pharmaceutical industry, but the risks are significant. While experimental animal models are essential for the drug development process, direct extension to human patients is not always straightforward, especially for psychiatric and neurological indications where mechanistic understanding is incomplete.

Quantitative modeling of the drug development process suggests a fine balance between the number of NMEs coming into clinical development and the clinical success likelihood of each NME (Paul et al., 2010). Quantitative de-risking of each NME pre-clinically and through the clinical development process is essential to manage a company's pipeline and to help ineffective drug candidates fail quickly.

Successful quantitative modeling and management of the drug development process requires reliable and measurable input parameters in order to decide, at each development stage, whether to exercise the option to abandon the drug candidate and channel resources into programs with higher expected likelihoods of success. Fortunately, molecular and biomarker imaging technologies have become highly quantitative and permit increasingly accurate measurement of the high-value parameters that help predict the success of new drugs. Yet, the spatially and temporally dense data sets of today's anatomic and molecular imaging technologies present significant analytic challenges. A decade ago a radiologist's visual interpretation of an image or scan was adequate to gauge the effectiveness of some drugs, but this is rarely the case today. In fact, the value of most new imaging technologies is inextricably linked to the model or analytic technique used to extract information from the image. Nonetheless, visual image interpretation by expert readers continues to play a major role in imaging for clinical trials.

The choice of an analytic method for a specific modality, technique and clinical trial endpoint is oftentimes a difficult process that requires balancing analytic rigor with practicality and cost. More time consuming and costly methods must demonstrate added value before being adopted. They must also be validated and have regulatory acceptance. This article addresses image quantitation from early stage evaluation to later efficacy measurements.

Early-stage imaging

Development of new drugs for novel targets is one of the most challenging approaches. This is demonstrated by the fact that of the 24 new drugs approved in 2009 only about 17% can be viewed as first-in-class acting at mechanistically novel targets (Paul et al., 2010). Fortunately, molecular imaging offers several strategies for successively retiring risk around new candidate drugs as they move toward and through the clinical development process. First is to demonstrate that the drug has organ bioavailability and reaches the intended target. Positron emission tomography (PET) is extremely useful at this stage since NMEs can be labeled with ^{11}C or ^{18}F or the unlabelled NME can be evaluated by competitive binding against existing ^{11}C or ^{18}F PET ligands for the target of interest. If no targeting is observed a candidate will be abandoned, saving the company the costs of further development

Even more important that the presence or absence of targeting is the quantification of target occupancy as a function of drug dose. This information can then be used to plan clinical trials to ensure that the dose is not too low to be efficacious or higher than necessary leading to unwanted side effects. Quantification at this stage, whether using the NME in the radiolabeled or unlabeled form, usually requires rigorous tracer kinetic models with radio metabolite-corrected arterial blood kinetics or reference-region kinetic approaches. Application of these and other techniques can result in reliable estimates of the occupancy of the target by the drug as a function of dose and time after administration. In many cases a rigorous compartmental model can be simplified and made more practical for follow-on studies, but only after a careful analysis of drug pharmacokinetics in the organ of interest and blood is completed. Pharmacokinetic models can be applied on a pixel-by-pixel basis, thus creating a drug occupancy image that permits examination of occupancy as function of target concentration.

Imaging for efficacy

The paramount use of imaging in drug development is as an efficacy biomarker. Both anatomic and molecular imaging have important roles. In anticancer drug development CT and MRI are used extensively for quantifying the growth of tumors during drug trials. The quantitative methodology follows RECIST 1.0 or 1.1 where the 2-dimensional size of tumors and metastases is measured using expert-reader defined regions-of-interest. The RECIST paradigm is, however limited by the fact that irregular tumor growth or contraction is not well quantified by simple line length measurements, resulting in decreased sensitivity for change measurement.

Newer approaches have proposed volumetric change measurements that would overcome existing sensitivity limitations and identify treatment responses earlier (Mozley et al., 2010; Buckler et al., 2010). These efforts are being led by the Quantitative Imaging Biomarker Alliance (QIBA). This group and allied investigators have demonstrated the technical feasibility of volumetric measurements and importantly, that they have the increased sensitivity for change detection. For example, a study of lung cancer patients undergoing treatment and CT scanning demonstrated that 11 of 15 subjects had

volumetric changes ≥20%, whereas only one subject had a change ≥20% in the longest dimension line length (RECIST 1.0) and 4 showed a ≥20% change in the bidirectional line lengths (RECIST 1.1) (Zhao et al., 2009). Another lung cancer study in 35 patients showed that 86% of subjects treated with pazopanib had a significant decrease in tumor volume, while only 3 subjects met RECIST criteria for partial response (Altorki et al, 2008). While the number of studies and subjects is still small, the available data support the hypothesis that volumetric quantification of tumor size will permit smaller trial sample size, earlier detection of change, and reduced costs.

Quantification of volumetric changes in the brain using MRI is important for degenerative disorders associated with selective regional volume loss. For example, in Alzheimer disease the hippocampus undergoes atrophy as cognitive decline progresses. A number of computer algorithms using methods including tissue segmentation, global boundary shift integrals, voxel-based morphometry, and tensor-based mophometry, have been developed to measure changes in the volume of the hippocampus and other brain structures (Ciumas et al., 2008). Quantitative volumetric brain measurements are increasingly used not only as a measure of disease progression and therapeutic response, but also as an approach to explore the relationship between brain loss and amyloid burden in Alzheimer's disease (Storandt et al. 2009; Scheinin et al. 2009; Halperin et al. 2009) and in clinically healthy individuals (Bourgeat et al. 2010). Other imaging techniques that are difficult or impossible to interpret without quantification methods include MR DTI and DWI, perfusion MRI, BOLD fMRI and MR-spectroscopy (Mueller et al. 2006).

Quantification also plays a role in molecular imaging assays of disease burden. A current example is the imaging of beta-amyloid using Pittsburgh compound B (PIB). Rigorous tracer kinetic modeling analysis of 11C-PIB binding to brain amyloid were subsequently simplified to permit more practical application to clinical trials (Price et al., 2005). For PET tracers with equilibrium binding properties, a reference region devoid of the binding site and unaffected in the disease process a "reference region" approach may be employed. A recent study employed the ratio of regional brain radioactivity to that in the cerebellum at 60-90 min. after injection in Alzheimer disease subjects treated with bapineuzumab, a humanized anti-amyloid antibody (Rinne et al., 2010). The results showed a 25% in reduction in the region-to-cerebellum ratio in the treatment group compared to placebo over 78 weeks. The validation that decrease in the ratio corresponds to a 25% reduction in beta amyloid is based on previous detailed examinations of PIB binding kinetics prior to adoption for a clinical trial.

Molecular imaging analytic methods begin in the early phase studies with new molecular agents and then, as the data supporting the viability of the candidates accrue, are applied with increasing confidence as efficacy biomarkers. Short cuts in this process can result in invalid study results and high hurdles to regulatory approval.

Reader versus software

While computer algorithm-based image analysis is an increasingly essential component of outcome evaluation in clinical trials, the importance of expert readers has not

diminished. In the early phase studies of drug bioavailability and quantitative targeting the current role of expert readers is much less than in later stage trials, where the identification and quantification of individual tumors and brain structures is performed by expert readers with increasing software support. The barriers to broad regulatory acceptance of quantitative computer algorithms and the absence of transparent pathways to approval will continue to maintain a central role for the expert reader. Oncology trials currently using RECIST criteria commonly include confirmatory evaluation of the of the overall response pattern to verify that the quantitative RECIST outcome is in accord with the radiologists global evaluation. In brain imaging there is a complimentary role for software algorithms and the expert reader (Ertl-Wagner et al., 2009; White et al 2008). The reader's role and molecular imaging experience and expertise will, however, need to evolve with the complexity of the mechanisms targeted by novel first-in-class drugs. Concomitantly, software applications will continue to be developed, compared and validated (for example see: Morey et al., 2009a; Morey et al., 2009b), leading over time to broad regulatory approval.

Summary

Quantitative imaging in clinical trials is growing in acceptance for more sensitive and efficient detection of change response following drug treatment. The primary applications are currently in oncology and CNS, but new developments are applicable to a wide range of other indications. Early stage evaluations of drug bioavailability and targeting are highly dependent on model-based measurement of target occupancy and kinetics, whereas later stage efficacy assessments still requires dual evaluation by expert readers and computer-based analysis algorithms. Both approaches have pitfalls, but together offer compelling opportunities for drug candidate de-risking and eventual approval.

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