Seeing within: Magnetic Resonance Imaging in drug development

Magnetic Resonance Imaging (MRI) can be used to provide quantitative measurements in the form of imaging biomarkers. These measurements have a number of attractive characteristics: They are non-invasive, can provide organ and lesion localisation of morphology, physiology and metabolism and can be repeated over time. These characteristics enable monitoring of the biological impact of drugs and can be helpful in patient selection. With appropriate deployment they can assist in go/no-go decision making and in some cases can provide endpoints for late stage trials. This article describes the deployment and potential benefit of MRI biomarkers via a number of examples of their use in drug development in different disease areas.

Non-invasive imaging equipment is commonplace in clinical environments, where it is used to assist the diagnosis of traumatic injury and disease. Arguably the most versatile and powerful of the available modalities is Magnetic Resonance Imaging (MRI), which, since its arrival in clinical practice in the 1980s, has developed into a mainstay of modern clinical investigation. MRI scanners can be found in virtually every hospital worldwide alongside other diagnostic imaging tools, such as x-ray, Computed Tomography (CT), nuclear medicine methods and ultrasound. In common with these other modalities, MRI has the powerful property of being able to reveal the structure and workings of internal organs. Unlike the alternatives, MRI combines this non-invasive capability with an ability to deliver high-resolution morphological information and a wide range of physiological and metabolic readouts with very low risk to the patient. These properties, plus the strong pre-clinical to clinical translatability of MRI, make it a valuable tool for monitoring the

signatures of disease processes and their response to therapeutic intervention, with the potential to influence the drug development process.

The role of imaging biomarkers in drug development

Non-invasive imaging is traditionally used in a radiological context to provide high-resolution images of organs and lesions, relying on the skills of radiologists to interpret what they see to provide a diagnosis. These diagnostic procedures contribute to a large number of clinical trials as part of patient selection and in the monitoring disease progression and response to intervention. Although less commonly deployed in the everyday radiological environment, the same imaging modalities can also provide a rich array of quantitative readouts, allowing radiological imaging devices to be used as objective measurement tools, in addition to sophisticated picture-generating machines. This quantitative capability allows the generation of imaging biomarkers – a capability that can be deployed on

By Dr Geoff J.M. Parker

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preclinical and clinical imaging equipment to enable drug development decision-making in animal models and patient groups.

Imaging has a role at many stages of the drug development process. In the pre-clinical phase, imaging can be used to monitor the response to intervention at multiple time points in a longitudinal study within the same animal, thereby potentially reducing the number of animals required to understand drug effects. Molecular imaging can be used to confirm targeting of new pharmaceuticals that have labelled to provide sensitivity for the imaging method being used. Dose-finding information can be provided by determining the doses of a new pharmaceutical that perturb metabolism, physiology or morphology.

Imaging in early phase human studies can provide evidence of biological activity of pharmaceuticals as well as helping to define optimum doses. Perhaps the most useful information that can be provided at this stage is that which can be used to assist in go/no-go decisions for progression of the drug development process to later phases. Certain imaging readouts can be used to support the outcomes of Phase III studies and subsequently to provide rich post-marketing information. Other readouts can be of use in assessing aspects of the safety profile of a drug – by, for example, providing cardiac or hepatic function measurements. Selection of patients for a study can be enhanced by the detailed diagnostic and phenotyping information provided by imaging.

The utility of imaging at each step in the drug development process means that it (alongside numerous other assessment methods) can significantly affect the progress of a drug from the first *in vivo* measurements to regulatory approval. The non-invasive, localised and repeatable nature of imaging means that imaging biomarkers can often provide useful information with relatively small numbers of participants, providing tools for early identification of drug effects. Deployed wisely, imaging can therefore be a cost-effective and powerful component of drug development strategies.

The place for MRI

MRI is used extensively in clinical trials of interventions in many disease areas. The following examples do not represent a comprehensive list of applications but provide an indication of the diversity of settings within which MRI biomarkers can be deployed. Each measurement is in active use today within trials sponsored by the pharmaceutical industry and most can be deployed in preclinical and clinical settings.

Example 1: Multiple Sclerosis lesion burden measurement

MRI is an important contributor to the diagnosis and monitoring of multiple sclerosis (MS)[1]. The soft tissue contrast provided by MRI allows high sensitivity detection of MS lesions, which are poorly visualised by other non-invasive imaging methods. The lesions typically observed on MRI reflect the localised inflammation often associated with MS lesions and the associated destruction of tissue components. MRI lesion burden measurements (measurements of lesion number and overall lesion load) have proved useful in monitoring the disease modifying effects of new pharmaceuticals. Such imaging biomarkers can serve in proof of concept studies and dose-finding studies[2-4]. Other MRI-derived markers, such as brain atrophy measurements (*vide infra*) may also have a role to play in some circumstances for trials in MS[2,5].

Example 2: Assessment of atrophy in Alzheimer's disease

Atrophy of the brain, at a whole-brain and regional level, is strongly associated with a range of neurological conditions. In Alzheimer's disease, a progressive loss of grey matter is linked to neuronal loss. Typical unchecked rates of overall brain volume loss in patients are of the order of 1-2% annually[6], a level of change that is within the sensitivity range of morphological measurements of the brain using MRI[7]. Drugs aiming to reduce the rate of decline associated with Alzheimer's disease are typically assessed with the aid of cognitive and other scoring systems[8], which suffer from high variability and subjectivity, necessitating large patient cohorts in order to provide adequate statistical power for the assessment of change over a reasonably short timescale. Objective measurement of whole brain size (or of ventricular size, or of brain regions, such as the hippocampus) has the benefit of good precision, allowing smaller patient group sizes and/or shorter study timescales than are achievable when imaging is not included in the study design[7]. However, despite the strong interest in atrophy measurements for clinical trials for Alzheimer's over the last few decades there is not yet agreement on their use as outcome measures. This is in part due to the lack of detection of a disease modifying effect in many clinical trials to date[7].

Example 3: Assessment of tumour vasculature

The most commonly-used method for assessing response to treatment in solid tumours is the assessment of tumour size using imaging methods including MRI via the RECIST criteria, which provide
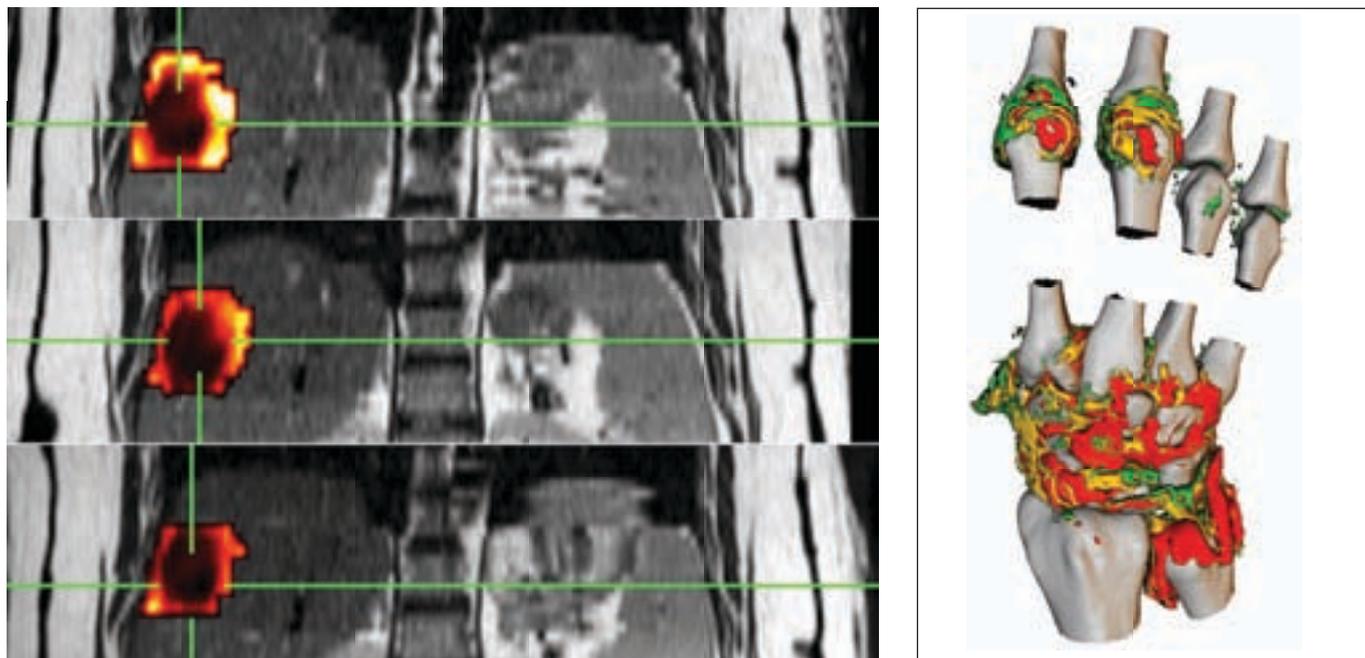
widely accepted imaging-based endpoints for clinical trials[9]. However, the use of MRI in cancer is not limited to assessment of tumour size alone, as a range of physiological and metabolic assessments are also achievable, and used in numerous preclinical and clinical trials[10]. One of the most extensively applied sets of biomarkers of this type are those derived from dynamic contrast-enhanced MRI (DCE-MRI), which has been used in particular to provide markers of tumour vascular response to antivascular and antiagiogenic interventions[11]. DCE-MRI makes use of intravenous contrast agents (essentially MRI-visible dyes), which accumulate in regions with high blood vessel density and/or elevated capillary permeability and extracellular space before being excreted via the kidneys or liver. Due to the angiogenic process, most tumours demonstrate increases in all of these features, making DCE-MRI a useful method for monitoring the physiological impact of drugs designed to target tumour vasculature[11,12]. **Figure 1a** shows an example of the DCE-MRI parameter Ktrans (a marker of perfusion and capillary permeability[13]), mapped within a colorectal cancer liver metastasis undergoing treatment with bevacizumab[14].

Example 4: Assessment of tumour cellularity
Most of the MRI signal in medical images comes from the water in the body's tissues. MRI can be sensitised to the passive diffusion of this water within and between cells in tissues, and the microscopic structure of those tissues then influences the observed image signal. Changes in the diffusion MRI signal can be quantified to provide an apparent diffusion coefficient (ADC), which can be interpreted to indicate alterations in cell packing within a tissue, such as a tumour. This may indicate early tissue changes in response to therapeutic intervention such as cell swelling, cell shrinkage or cell death that often precede changes in tumour volume[15]. Measurement of water diffusion in this way therefore provides a potential sensitive indicator of early biological action of drugs on individual tumours.

Example 5: Assessment of joint structure and inflammation in rheumatoid arthritis
The rheumatoid arthritis MRI score (RAMRIS) scoring system has shown utility in quantifying the extent of disease in clinical trials by quantifying the observable features of disease on MRI in the hands and wrist[16]. One of the hallmarks of joint inflammation seen in rheumatoid arthritis and related conditions is an altered blood supply, with a greater number of microvessels and generally high levels of vessel endothelial permeability. These vascular features are not dissimilar to those seen in the example of DCE-MRI applied in tumours (*vide supra*), which explains why this technique also finds a role in assessing the response of joint inflammation to therapeutic intervention[17,18]. The categorical and physiological readouts provided by approaches such as RAMRIS and DCE-MRI allow an objective approach to quantifying the extent

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and intensity of joint disease and its response to intervention. **Figure 1b** shows an example of the joint inflammation information provided by the DCE-MRI parameter Ktrans in the hand and wrist of a rheumatoid arthritis patient.

MRI practicalities and cost

MRI's flexibility means that it is used at all stages of drug development across a wide range of therapeutic areas. Many large pharmaceutical companies maintain a preclinical MRI capability, although a number of third party commercial providers also provide off-site imaging services. The use of MRI in patient groups for clinical trials is generally within the routine or research clinical environment. Typically MRI in the clinical phases of drug development will be deployed alongside other measurements within the trial protocol, providing primary, secondary or exploratory readouts, depending on the MRI method, trial phase and intervention under consideration. Often the MRI readouts are provided by specialist imaging contract research organisations (CROs) or by dedicated groups within larger CROs. These providers enable standardisation of imaging methods, scanner operator training, image data transfer, quality control and centralised image analysis for final imaging biomarker delivery.

The processing of MRI data to provide imaging biomarkers can range from expert reader-based categorical scoring of image features to complex quantitative image processing and image-derived pharmacokinetic modelling. When deployed in clinical trials, the processes of MRI image acquisition and data processing require effective training of personnel and, in the case of multi-centre studies, standardisation of image acquisition and analysis, with the image analysis phase typically the responsibility of a central analysis provider, often under blinded conditions.

Routine MRI scanning procedures are widely available in radiological centres but, as discussed above, more advanced MRI methods may require the input of a central body of expertise, often from a CRO. The pricing of an MRI scan varies substantially from country to country and from centre to centre and will also vary with the complexity of the required imaging. The provision of imaging services to enable standardisation and MRI biomarker quantification adds an additional cost. The justification for these costs is the ability of MRI to deliver unique non-invasive, localised, safe and repeatable measurements that have the potential to add valuable information to a trial, typically from relatively small patient groups. This is particularly valuable when ethical concerns exist regarding long-term placebo-controlled clinical trials, and when the size and cost of trials comparing new therapies with existing interventions is high.

Conclusion

MRI is a flexible and widely-available tool for detection of the effects of drugs and plays a role in many disease areas, both clinically and pre-clinically. With appropriate implementation it is therefore well placed to enhance information content in drug trials, often requiring smaller patient groups than alternative measurements. This offers the possibility of reducing the overall cost and/or duration of the drug development process by assisting go/no-go decision making, patient selection and enhancing sensitivity to drug effects.   DDW

Dr Geoff Parker is Chief Executive Officer of Bioxydyn, a company that provides imaging biomarkers to the pharmaceutical industry and quantitative imaging software to healthcare. He is also Professor of Biomedical Imaging at the University of Manchester, where he has worked since 2001. Prior to this he was a research fellow at the Institute of Neurology, Queen Square, UCL, London, after completing his PhD on cancer MRI at the Institute of Cancer Research, London. His core scientific expertise is MRI physics and medical image analysis.