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Understanding the pharmacology of stroke and multiple sclerosis through imaging

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Stroke and multiple sclerosis (MS) illustrate how clinical imaging can facilitate early phase drug development and most effective medicine use in the clinic. Imaging has enhanced understanding of the dynamics of evolution of disease pathophysiology, better defining treatment targets. Imaging measures can enable stratification of patients for clinical trials and for most cost-effective use in the clinic. In MS, imaging has allowed smaller Phase II clinical trials and contributed to medicine differentiation. It also has led to consideration of suppression of inflammation and neurodegeneration as meaningfully distinct pharmacodynamic concepts. Similar imaging measures can be used in preclinical and clinical studies. Testing translational pharmacological hypotheses using clinical imaging more explicitly could improve the success of the next generation of stroke therapeutics.

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Introduction

Imaging is a powerful tool for translational neuropharmacology. Molecular imaging biodistribution studies can be used to assess blood brain barrier penetration for small molecules and to estimate best dose–response ranges [1,2]. Widely available methods such as computerized X-ray tomography (CT), magnetic resonance imaging (MRI), positron emission tomography (PET) and optical coherence tomography (OCT) enable testing of pharmacodynamic hypotheses for proof of concept or medicines differentiation. As similar imaging methods are in routine use in the clinic, approaches can be translated from late phase clinical trials to aid in optimization of clinical effectiveness [3]. Here we will review recent developments in imaging for the support of clinical trials of treatments for multiple sclerosis (MS) and stroke, focusing on opportunities that enable early diagnosis, patient stratification and pharmacodynamic studies (Figure 1).

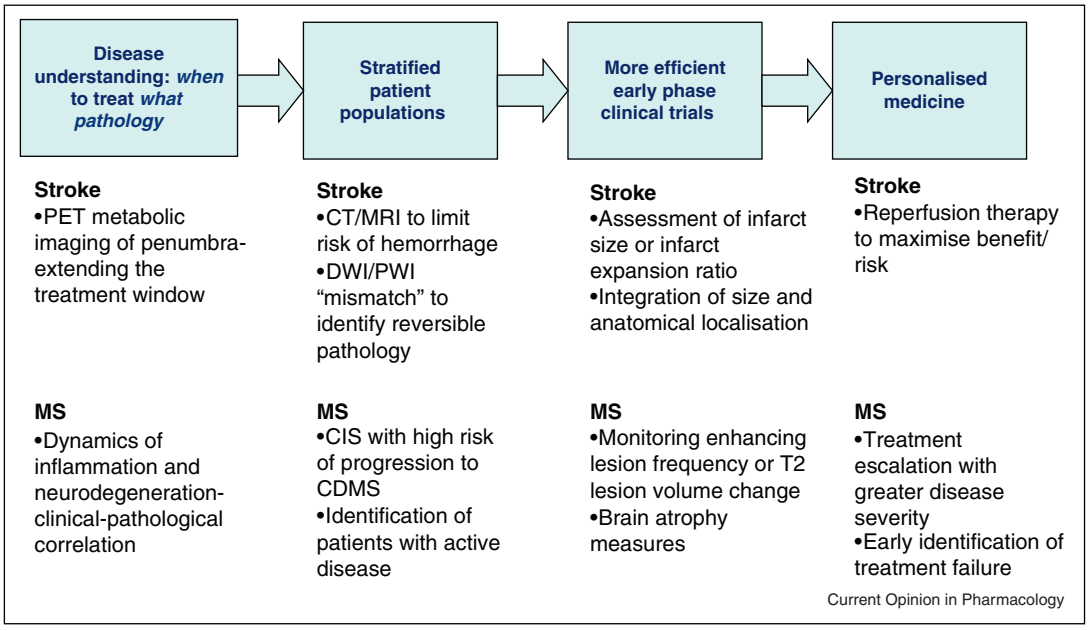
Stroke

Patient selection for trials

Efforts to develop new pharmacologic treatments for stroke have been disappointing. One factor is that the clinical presentation of patients with ischaemic stroke is non-specific. Confident early diagnosis is a major determinant of treatment outcome [4], as the extent of brain tissue damage depends on both the severity of hypoperfusion and duration of occlusion [5]. Imaging can contribute to defining specificity of the stroke phenotype in several ways. Computerized X-ray tomography (CT) accurately identifies most cases of intracranial haemorrhage and helps discriminate non-vascular causes of the stroke syndrome [6]. However, physicians' abilities for reliably and reproducibly recognizing the early CT changes of ischaemic stroke are variable [7–10]. Use of scoring systems for early CT changes may soon improve identification and consistency within a clinical trial [11], but CT is relatively insensitive for detecting acute and small cortical or subcortical infarctions, especially in the posterior fossa. MRI diffusion-weighted imaging (DWI) sensitively defines an acute ischaemic lesion within minutes of arterial occlusion and therefore has become important for early diagnosis, particularly of smaller lesions and those in the brain stem or cerebellum [12]. Although smaller lesions may show reversible changes with reperfusion, DWI contrast most commonly reflects the irreversible core of the ischaemic stroke [13].

A major issue in early stratification of patients with larger infarcts is the identification of patients at high risk of secondary haemorrhagic transformation with reperfusion, the risks of which can be assessed from the extent of signal hypodensity in the middle cerebral artery (MCA) territory [14]. Large MCA infarcts also may progress malignantly with more widespread secondary ischaemia from increased intracranial pressure with rapid evolution of oedema [15]. Imaging based predictors incorporated into quantitative risk assessment tools include proximal occlusion of MCA, carotid occlusion and involvement of superficial and deep territories [16,17••,18,19].

Figure 1



Major objectives of imaging in drug development for stroke and MS. Topics discussed in this review are highlighted in summary. *Abbreviations*: CIS, clinically isolated syndrome; CDMS, clinically definite multiple sclerosis; DWI, diffusion weighted MRI imaging; PWI, perfusion weighted MRI imaging.

Pharmacodynamic outcome measures

Monitoring of perfusion

Imaging of brain perfusion further contributes to diagnosis and can be used to stratify patients by the extent and volume of tissue with reduced blood flow or as a pharmacodynamic measure for treatments directed towards reperfusion. This may help in therapeutics development by defining better the extent of potentially salvageable tissue, either as a covariate for outcomes analysis or as an inclusion criterion. Computed tomography perfusion imaging relies on serial images rapidly acquired after intravenous injection of a bolus of contrast agent [20,21]. Perfusion-weighted MR imaging (PWI) is based either on similar principles with intravenous MRI contrast injection [22] or uses contrast properties of flowing blood non-invasively 'tagged' (arterial spin labelling) [23]. Both contrast injection methods remain more practical in the setting of acute stroke and provide similar information [21]. Volumes of the lesions on both DWI and PWI correlate well with the final volume and severity of stroke as rated by clinical scales [24–26].

In the context of multi-centre trials, CT methods have been favoured, as MRI imaging is slower, is more susceptible to movement artefacts and has operational constraints that complicate rapid delivery of thrombolysis [27–29]. A challenge for use of both CT and MRI perfusion in multicentre interventional studies lies in standardization of the perfusion measures [6,22].

Identifying brain 'at risk'

Because of heterogeneity of hypoperfusion across the ischaemic volume of brain, the period of opportunity for delivery of neuroprotective treatment extends over hours and days after onset [5]. Good collateral blood flow is associated with decreased infarct extension and improved tissue survival [30]. Direct measures of collateral flow therefore afford further precision in stratification of patients for outcome, as well as assessing the potential for delivery of a therapeutic molecule to ischaemic territories [31].

Integrated perfusion and metabolic imaging can be used to characterize more accurately the hypoperfused volume 'at risk' around the ischaemic core than can perfusion alone. This was first highlighted using positron emission tomography (PET) oxygen-15 metabolic and perfusion positron-emission tomography (PET), which together quantify regional brain perfusion and oxygen consumption, to identify an 'ischaemic penumbra' of decreased cerebral blood flow (CBF) and increased oxygen extraction fraction (OEF) with relatively well-preserved oxygen utilization [32–34]. Longitudinal multimodal MR imaging has characterized the associated selective neuronal necrosis over short periods of ischaemia in preclinical models [35].

Without reperfusion, the irreversibly damaged ischaemic core expands over time to include tissue in this penumbra [36]. While these PET methods are not practical in