Positron emission tomography to image cerebral neuroinflammation in ischaemic stroke: a pilot study

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Scientific summary

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Scientific summary

Background

Activated microglia play a complex role in neuroinflammation associated with acute ischaemic stroke. As a potential target for anti-inflammatory therapy, it is crucial to understand the correlation between its intensity, extent and the clinical outcome of the stroke.

The 18-kDa translocator protein is a marker of cerebral microglial activation and of macrophage infiltration after damage to the brain, and it can be imaged by positron emission tomography. The 'gold standard' for imaging 18-kDa translocator protein is the radiopharmaceutical [^{11}C]-(*R*)-PK11195. However, the very short half-life of ^{11}C is unsuitable for widespread clinical use, whereas ^{18}F-labelled compounds could be potentially applied as diagnostic tools in routine clinical settings.

We therefore studied microglia activation in the human brain using the recently developed radiopharmaceutical [^{18}F]-GE180 with positron emission tomography in patients after mild to moderate stroke.

Objectives

Objectives for phase 1 were to:

1. evaluate the tolerability of positron emission tomography scanning using a questionnaire given to the participants
2. assess the technical feasibility of imaging the 18-kDa translocator protein (TSPO) using [^{18}F]-GE180 as a radiopharmaceutical
3. correlate imaging measures obtained with [^{18}F]-GE180 in focal abnormalities with [^{11}C]-(*R*)-PK11195 as a reference.

Objectives for phase 2 were examining the relation of positron emission tomography imaging with a clinical outcome, magnetic resonance imaging and systemic inflammation. However, the study was ended after phase 1 because of the results obtained in that phase and did not enter phase 2.

Methods

Ten participants (aged 24–89 years, median 68 years) (eight male and two female) who suffered ischaemic stroke of mild to moderate severity (modified Rankin scale score of 2–3) in the middle cerebral artery territory were enrolled to the study 4–28 days (median 12 days) after the clinical event. Patients were recruited, consented and assessed clinically at multiple sites in the Greater Manchester Stroke Operational Delivery Network. Five more participants were consented but subsequently withdrawn before receiving the scans.

Inclusion criteria

- Aged $\geq$ 18 years.
- $\leq$ 4-week history of ischaemic stroke in middle cerebral artery territory at the time of screening for study inclusion, confirmed clinically or by computed tomography or magnetic resonance imaging scans.
- Mild to moderate severity (modified Rankin scale score of 1–3).

Participants had to have been able to give informed consent either written or verbally, or in the presence of at least one witness if they were unable to sign or mark the consent form because of mobility issues. The witness(es) signed the consent form as evidence that the information was accurately explained to, and understood by, the participant and that consent was freely given.

Exclusion criteria

- Neurological diagnosis of neurodegenerative disease.
- Inability to understand study information and/or express willingness to consent to the study because of communication difficulties.
- History of brain surgery, brain tumour, neuroinflammatory or neurodegenerative disease.
- Severe uncontrolled systemic illness.
- Patients in whom carotid endarterectomy/carotid stenting is due to be carried out within 3 months of recruitment to the study.
- Treatment with other drugs known to influence microglial activation (e.g. minocycline, corticosteroids or benzodiazepines) (2 weeks prior to date of the scan).
- Pregnancy/breastfeeding women.
- Contraindications to MRI scanning.
- Patients receiving treatment with disulfiram (Antabuse®, Actavis).

Clinical data were recorded at the recruitment sites by the clinical fellow and transmitted to the Christie (now University of Manchester) clinical trials unit. At the clinical trials unit, the data were controlled for quality, curated and presented to the chief investigator for scientific evaluation.

Patients were scanned at the Wolfson Molecular Imaging Centre, Manchester, 18 to 63 days (median 34.5 days) after the stroke by magnetic resonance imaging (Philips 1.5 T; Philips, Amsterdam, the Netherlands), [^{18}F]-GE180 (200 MBq, 30-minute dynamic scan) and [^{11}C]-(*R*)-PK11195 (740 MBq, 60-minute dynamic scan) positron emission tomography (Siemens HRRT; Siemens, Munich, Germany). At the Wolfson Molecular Imaging Centre, venous blood samples were also taken to look for systemic inflammation markers (C-reactive protein, interleukin 6).

The two positron emission tomography scans were performed on 2 separate days (median 3.4 days apart). Five patients were randomised to receive the [^{18}F]-GE180 scan at the first session and five patients were randomised to receive it at the second session. Participants were genotyped for the rs6971 18-kDa translocator protein polymorphism, which is known to affect binding of [^{18}F]-GE180 but not of [^{11}C]-(*R*)-PK11195.

All positron emission tomography and magnetic resonance data sets were co-registered with T1-weighted magnetic resonance image scans. Binding of [^{18}F]-GE180 was compared with [^{11}C]-(*R*)-PK11195 for the infarct and contralateral reference regions. Spearman's rank-order correlation coefficient was used to compare tracers and *t*-tests were used to compare patient subgroups.

Image data acquisition and analysis was performed at the Wolfson Molecular Imaging Centre by the study chief investigator with co-investigators and staff under the Wolfson Molecular Imaging Centre quality assurance system, which has undergone regular successful reviews by the Medicines and Healthcare products Regulatory Agency.

Results

The mean score from the 10 participants' tolerability questionnaire was 4.36 (range 4 to 5), which is well above the threshold (neutral = 3) that we set to accept.

We did not observe any serious adverse events. Non-serious adverse events occurred but had no obvious link to the tracer.

A close correlation between [^{18}F]-GE180 and [^{11}C]-(*R*)-PK11195 (correlation coefficient range 0.79–0.84) was observed. Genotyping showed that eight patients were high- or mixed-affinity binders for [^{18}F]-GE180. [^{18}F]-GE180 does not provide a specific 18-kDa translocator protein signal in low-affinity binders (two patients). Ischaemic lesions with contrast enhancement on magnetic resonance showed significantly higher uptake of [^{18}F]-GE180 than lesions without enhancement and, even in low-affinity binders, [^{18}F]-GE180 binding in normal cortex was very low with significant dependency on genetic polymorphism. Three patients had elevated levels of interleukin 6 and high-sensitivity C-reactive protein and they also showed significantly higher lesion-to-reference ratios with [^{11}C]-(*R*)-PK11195 ($p = 0.005$, *t*-test) and [^{18}F]-GE180 relative to the rest of the participants with normal inflammatory marker levels.

The pilot phase of this study had not been powered to demonstrate associations with clinical outcome. As expected, none of the imaging data or plasma markers showed significant correlations with clinical outcome in this small pilot sample.

Conclusions

[^{18}F]-GE180 positron emission tomography scanning was safe and well tolerated. However, a strong dependency of uptake on blood–brain barrier damage and a genetic 18-kDa translocator protein polymorphism, as well as a high contribution of vascular signal and non-specific binding to the uptake in ischaemic lesions with blood–brain barrier damage, limits the clinical applicability of [^{18}F]-GE180 in acute stroke.

Because of these limitations, the present study could not be progressed beyond the pilot phase. Further research is needed to investigate the relation between microglial activation in ischaemic stroke and outcome, and to establish an imaging technique of microglial activation that could be applied in clinical stroke trials and services.

Trial registration

Registered as a clinical trial with EudraCT 2014-000591-26.

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