CHIEF SCIENTIST OFFICE

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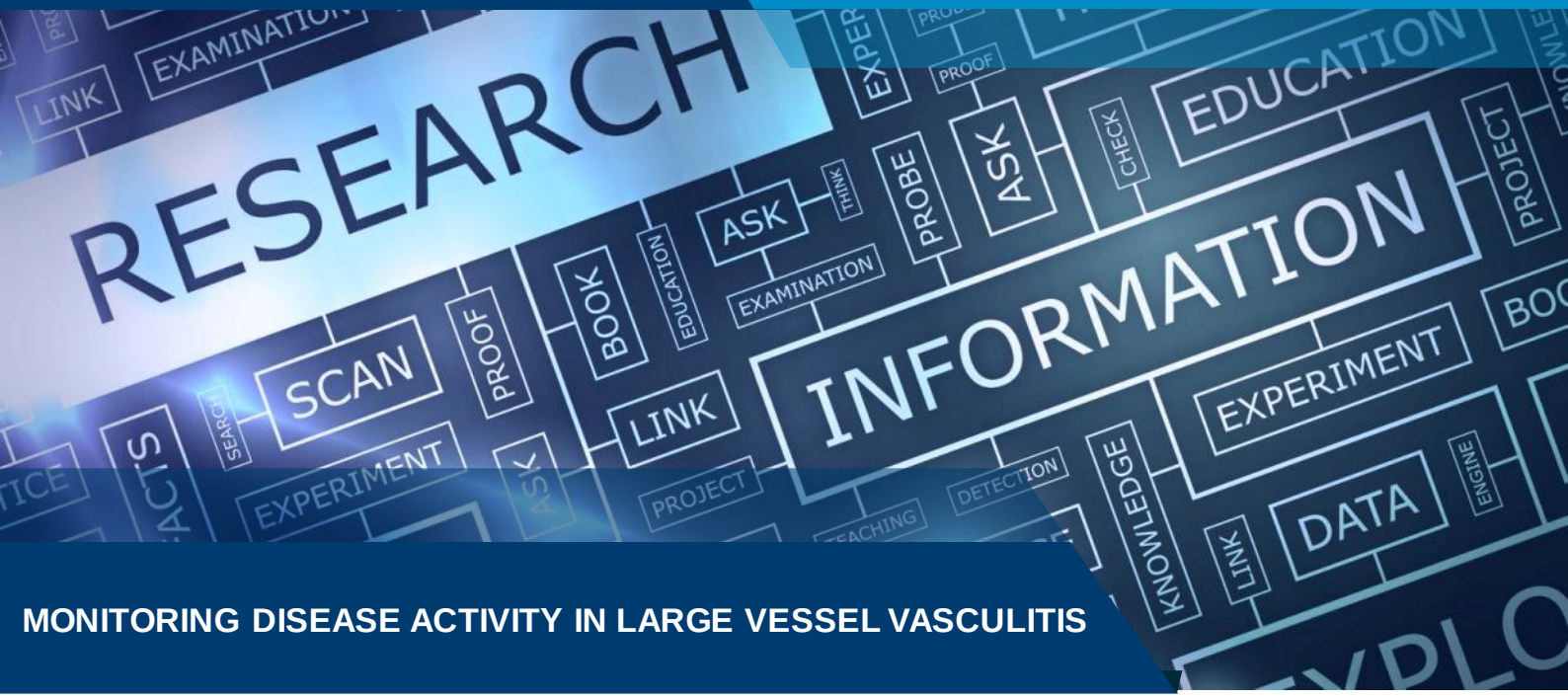
RESEARCH PROJECT BRIEFING



MONITORING DISEASE ACTIVITY IN LARGE VESSEL VASCULITIS

AIMS

Large vessel vasculitis (LVV) is a condition which causes blood vessel inflammation leading to pain, fatigue, and catastrophic complications such as heart failure and stroke. Though treatments are effective, current methods of determining disease activity are limited. This often leads to over- or under-treatment of disease, with resultant complications and reduced quality of life for those affected. The aim of this Fellowship was to develop new methods of assessing disease activity in order to better guide treatment for patients with LVV.

KEY FINDINGS

- A new type of scan called positron emission tomography with magnetic resonance imaging (PET/MR) can be used to determine disease activity in patients with LVV.
- Accuracy of PET/MR-based disease activity assessment can be improved by applying a novel scoring system.
- A panel of new blood tests also provides a useful assessment of disease activity in LVV.
- Changes in the retina, imaged using a type of simple eye scan called optical coherence tomography (OCT), may reflect the small blood vessel changes involved in LVV.
- The methods of disease activity assessment described here may allow clinicians to more accurately match treatment intensity with LVV disease activity in the future.

WHAT DID THE STUDY INVOLVE?

Patients with active LVV were recruited from all over Scotland and invited to attend the University of Edinburgh for two visits, a baseline visit (at time of initial disease activity) and a follow-up visit (after 6-18 months). At each visit, participants underwent a clinical assessment of LVV disease activity followed by two types of scan – an eye scan (retinal OCT) and a whole-body PET/MR scan. The OCT scan takes around 5 minutes to complete and is similar to the type of scan you might expect at the opticians. The PET/MR scan involves injection of a radioactive substance which binds to areas of LVV activity within the body. The PET/MR scanner is then able to detect these areas of activity, in addition to providing a detailed 3D picture of the blood vessels. Participants also provided a blood sample at each visit.

Images from both the OCT and PET/MR scans as well as the results of a panel of novel blood tests (designed to identify LVV-specific inflammation in the blood) were then compared with clinical assessment of disease activity (i.e., how active the treating clinician thought disease was based on standard tests).

In addition to patients with LVV, a group of healthy volunteers were also recruited and underwent OCT scanning and provided blood samples. Results of both OCT scans and blood tests could then also be compared between the group with LVV and the healthy group.

The study was designed in collaboration with PMR-GCA Scotland (a patient group for those affected by LVV), and the Scottish Systemic Vasculitis Network (a collaboration between healthcare providers across Scotland with an interest in vasculitis). The study design was approved by a local ethics committee to ensure that it answered the questions posed in the least intrusive manner possible.

WHAT WERE THE RESULTS AND WHAT DO THEY MEAN?

27 patients with LVV were recruited and underwent a total of 44 study visits. 16 patients had a subtype of LVV known as giant cell arteritis (GCA), 6 had Takayasu arteritis (TAK) and 5 had LVV which was otherwise unspecified. The average age of patients was 61 years and ranged from 18 to 82 years.

Part 1: PET/MR

Using previously described methods of quantifying LVV disease activity, PET/MR was able to distinguish patients with active disease from patients with inactive LVV in our cohort. Compared with previously reported data, PET/MR was able to do this with at least as much accuracy as the next best alternative (PET/CT), but with less radiation. Additionally, PET/MR was able to monitor changes in disease activity over time within individual patients. Creation of a new method of scoring disease activity on PET/MR scans (the **V**asculitis **A**ctivity using **M**R **P**ET (**VAMP**) score) further improved the accuracy of disease activity assessment. Considering that PET/MR utilises ~20% of the radiation dose associated with PET/CT, these results suggest that PET/MR could be a valuable tool for long-term disease monitoring in LVV.

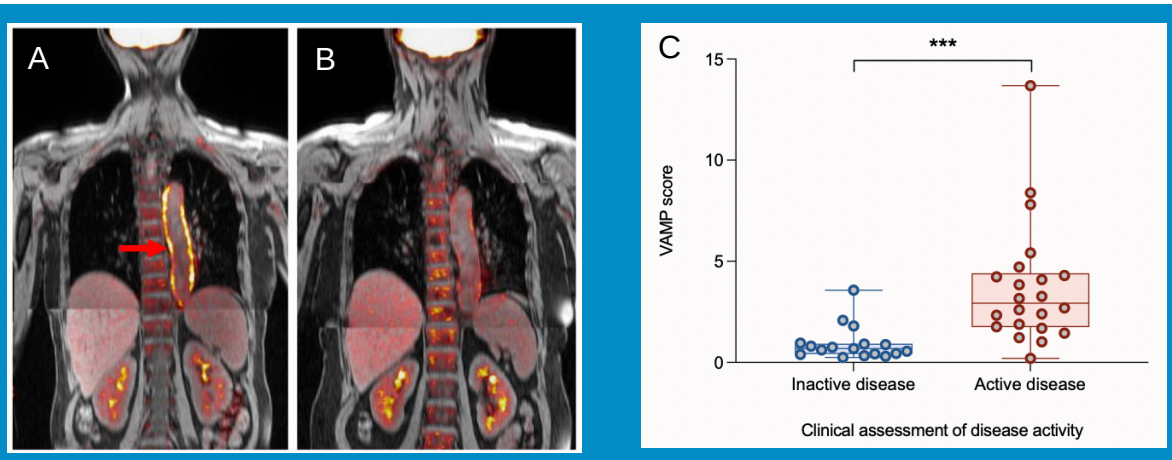


Figure 1. Images A and B demonstrate PET/MR images from a patient with active LVV (A) affecting the aorta (red arrow), and a patient with inactive LVV (B). Image C demonstrates the ability of a novel scoring system, the VAMP score, to distinguish active from inactive disease.

Part 2: Blood tests

This part of the study demonstrated that a series of five novel blood tests - LRG1, Ang-2, sFlt-1, osteopontin, and calprotectin – were all elevated in LVV compared with healthy people of the same age and sex. Additionally, LRG1, Ang-2 and osteopontin were able to distinguish active LVV from inactive LVV. Importantly, all of the blood tests were able to distinguish active from inactive disease with more accuracy than the blood tests currently in use. While some of these blood tests have been studied in LVV before, none have been assessed longitudinally (*i.e., over time*) in a 'real-world' group of patients with LVV, including those with both the GCA and TAK subtypes. These results suggest that new blood tests might be able to assist with the assessment of disease activity in LVV.

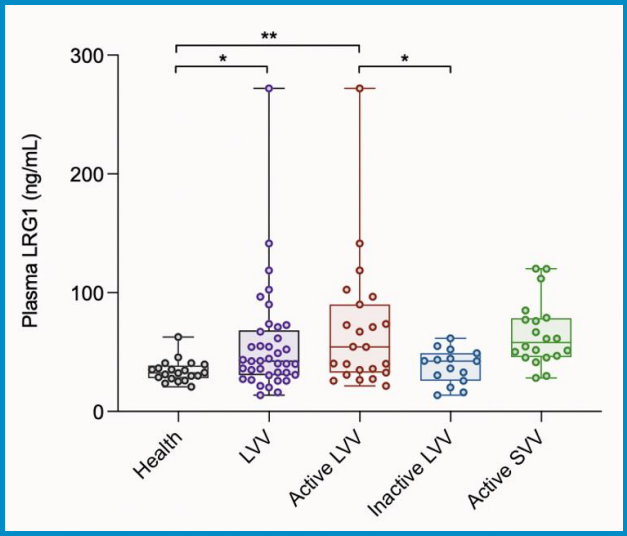


Figure 2. This figure demonstrates levels of LRG1, one of the five novel blood tests examined, in patients with LVV, small vessel vasculitis (SVV) and health. Each dot represents an individual participant. Levels are higher in LVV than health, and active versus inactive LVV.

Part 3: OCT

The final part of the study demonstrated that several important retinal structures undergo thinning in patients with active LVV when compared with people without LVV. Furthermore, these changes are partially reversible with treatment. These results suggest that, although LVV is primary considered a condition involving the large blood vessels, small blood vessel changes are apparent and are likely to contribute to the progression of disease. This finding suggests that using treatments which target small blood vessel health may be effective for those with LVV, though further study is required. Additionally, the retinal changes demonstrated here could also be utilised for disease monitoring.

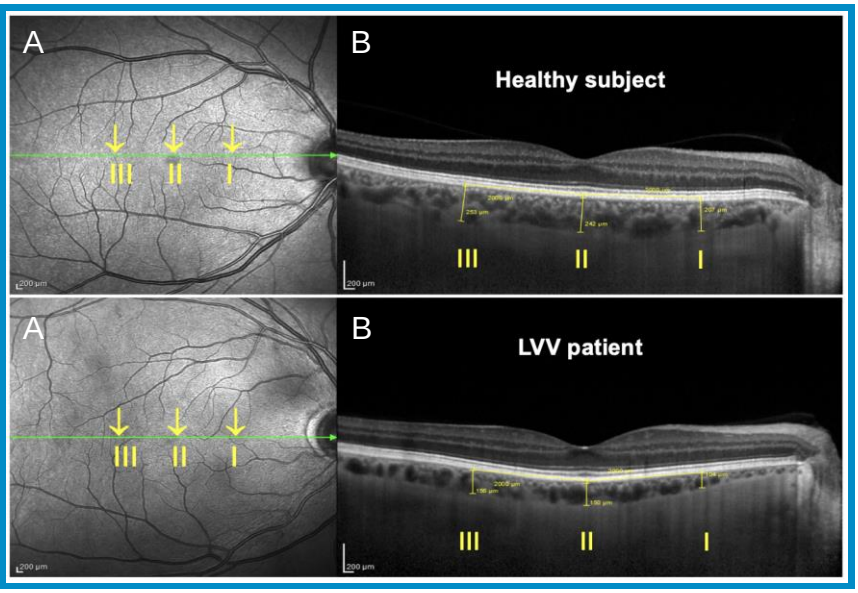


Figure 3. Retinal images obtained from a healthy volunteer (top images) and a patient with active LVV (bottom images) using OCT scanning. The images on the left (A) are taken *en face* (straight on) showing the small blood vessels spreading across the retina. The images on the right (B) show a slice through the retina, allowing the thickness of the choroid, a key retinal layer, to be measured. Areas I, II and III are where measurements of the choroid are taken. In these images, the healthy subject has a thicker choroid at all areas compared with the LVV patient.

WHAT IMPACT COULD THE FINDINGS HAVE?

The results presented here suggest that PET/MR, retinal OCT, and the panel of novel blood tests investigated may be able to improve disease monitoring for patients with LVV. Current methods of determining disease activity in LVV are not fit for purpose. As a consequence, clinicians find it difficult to determine when to start and stop treatment. This often leads to over-treatment, which causes significant side effects, or under-treatment, which leads to complications of active disease including heart failure, aneurysms, and stroke. Thus, the novel scans and blood tests described here have the potential to improve the quality of life of people living with LVV by reducing burdensome treatment whilst ensuring that disease flares are dealt with quickly. This is of particular relevance as several new treatments for LVV are either available or are approaching the market; however, clinicians are currently struggling to determine when to start and stop these treatments, limiting their effectiveness.

Additionally, clinical trials of drugs which may benefit patients with LVV have been difficult due to a lack of study endpoints. This means that, although a new drug may work, there is no test good enough to prove that it has worked, and that disease activity has reduced. PET/MR may be able to act as this endpoint in future trials. This may encourage such trials to go ahead, leading to the development of new drugs with which to treat this condition.

HOW WILL THE OUTCOMES BE DISSEMINATED?

The results of this study are currently being compiled for publication in high-impact scientific journals. We have recently published an article which outlines the current LVV landscape, including the problems associated with managing LVV, many of which this study addresses. Additionally, this work has recently been presented at the International Vasculitis and ANCA Workshop in Dublin in April 2022 where it was awarded the Best Young Investigator Award.

On a more local level, I maintain close links with PMR-GCA Scotland, a patient support group for those affected by LVV, and aim to present the results of this study to this group and other interested parties in due course.

As well as addressing several unanswered questions regarding the management of patients with LVV, this study has suggested some important areas for future study, including evaluation of new types of radiotracers which may allow binding to LVV-specific inflammation, making interpretation of scans easier.

CONCLUSION

In summary, this Fellowship has identified several ways in which assessment of disease activity in LVV might be improved. These findings have the potential to improve patient care for those affected by LVV by allowing more accurate matching of treatment intensity with disease activity.

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Additional Information

- This project was completed between August 2019 and February 2022
- The total amount of funding awarded was £144,277.96