

selection in multicenter clinical trials, and hopefully play a part in the establishment of AIS treatment guidelines in the future.

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#### CONFLICT OF INTERESTS

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#### TO THE EDITOR

##### Repeated Systemic Thrombolysis After Early Recurrent Stroke: Always Hazardous?

The management of early recurrent ischemic stroke (ERIS) represents a challenging clinical problem. Neurological deterioration following improvement (NDFI) may occur after systemic thrombolysis (ST).<sup>1</sup>

Clinical guidelines don't clearly specify how to proceed and in this situation a second ST is considered off-label; in fact, basing on current protocols,<sup>2</sup> any previous stroke within the last three months is listed as a contraindication for ST for the presumed higher risk of intracranial haemorrhage.

We describe the case of a patient with a marked NDFI who underwent a second ST within 40 hours from the first ST. Basing on the available literature, the case we presented is the second<sup>3</sup> report on a patient who received a repeated ST within a few days.

A 73-year-old man was admitted to our Stroke Unit because of sudden onset of mild aphasia and mild right hemiparesis. National Institute of Health Stroke Scale (NIHSS) score was 4. He denied any relevant previous disease, and he was not taking any drug. Non contrast-enhanced brain computed tomography (CT) scan resulted negative for recent vascular lesions.

After informed consent, ST with 69 mg rt-PA was started four hours after stroke onset according to the SITS-MOST protocol. After an initial worsening, the NIHSS score at 24 hours was 0.

Post-procedure CT scan showed no haemorrhagic complications. A treatment with acetylsalicylic acid (ASA) (300 mg/die) and statin was then introduced. Laboratory analysis performed during hospitalization revealed the presence of hyperglycemia and hyperlipidemia. Trans-thoracic echo-

cardiography resulted normal and duplex ultrasound imaging showed no relevant stenosis of internal carotid arteries.

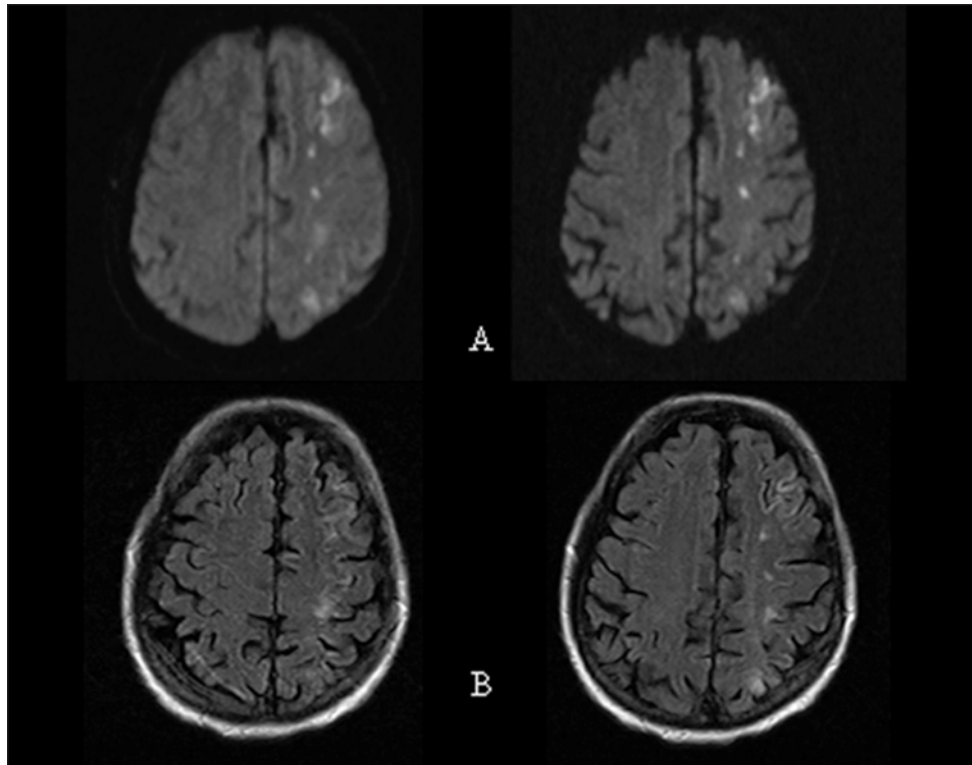
Forty hours after ST, there was a sudden neurological deterioration with appearance of severe aphasia and right-sided hemiplegia, without any significant change in blood pressure. NIHSS score was 12. Non contrast-enhanced CT, compared with the first CT scan, showed neither haemorrhagic complications nor direct or indirect signs of recent ischemic lesions. Magnetic resonance imaging (MRI) showed multiple small foci of diffusion restriction in left fronto-parieto-occipital regions (Figure). The MRI perfusion imaging showed perfusion deficit in the same regions of diffusion restriction. FLAIR and T2-weighted images showed multiple small area of hyperintensity in approximately the same regions of diffusion restriction (Figure). magnetic resonance angiography (MRA) showed neither occlusion nor significant stenosis of internal carotid arteries and middle cerebral arteries.

After an accurate evaluation of both pros and cons, we decided to administer a second full dose of rt-PA. Treatment started 60 minutes after the sudden neurological deterioration. NIHSS was 9 at one hour after the end of the second ST, 3 at two hours and 0 at discharge.

A control MRI performed one day after the second ST showed no substantial variations with respect to the first MRI scan.

When discussing the pros and cons of performing a second ST, we considered mainly the clinical severity of the ERIS and the risk of bleeding after a second ST.

The patient, who had fully recovered after the first ST, presented a sudden severe neurological deterioration before our eyes despite the "best medical therapy" administered (platelet inhibitor and statin).



**Figure:** MRI of the patient. A) DWI: multiple small foci of diffusion restriction in left fronto-parieto-occipital regions. B) FLAIR: multiple small area of hyperintensity in approximately the same regions of diffusion restriction.

We were well aware that, according to the European license, a second ST would be considered off-label because of concomitant diabetes. Basing on current protocols<sup>2</sup> a second ST shortly after a first ST is contraindicated. However, it's known that rt-PA is cleared rapidly from the circulating blood by the liver, although its pharmacodynamic effects may be prolonged up to 24 hours. In our patient, neurological deterioration occurred 40 hours after first ST. Therefore, considering only pharmacological aspects, another ST could be viewed as a procedure with low risk of bleeding.

Similarly, any prior stroke in the previous three months is considered an exclusion criterion for ST<sup>2</sup>, even if this recommendation is derived from trials of thrombolytic therapy in patients with acute myocardial infarction. Therefore, direct information on the presumed higher risk of bleeding in the presence of a prior stroke in patients undergoing ST for cerebral ischemia is largely lacking.

Although it's reasonable that the risk of intracranial hemorrhagic complications could be higher after a second ST, especially in previously infarcted areas, in our patient the CT performed immediately before the second ST was still negative, the areas of DWI hyperintensity were very small; moreover, glycaemia and blood pressure were under control at the time of the second ST. We therefore considered a second ST as a therapy with relatively low risk of bleeding complications. According to current protocols,<sup>2</sup> a concomitant therapy with ASA was not considered a contra-indication for ST.

Basing on MRI finding (Figure), it's reasonable that artery-to-artery embolism or cardio-embolism has occurred, even if we were not able to find any carotid stenosis or cardiac thrombus. Similarly, it's very difficult to establish whether the first ST may have contributed through a downstream embolisation following a lysis of such hypothetical arterial or cardiac thrombus. This hypothesis seems anyway unlikely, as ERIS occurred more than 24 hours after the first stroke.

However, others factors may have contributed to the NDFI which occurred after the first ST. In fact, the ischemic penumbra is a very unstable entity, and its fate depends on the achievement of a durable recanalization, from systemic factors (hyperglycemia, pyrexia), from the efficiency of collateral vessels, and from the status of the haemostatic balance. Systemic thrombolysis could alter this delicate equilibrium in a "paradoxical" prothrombotic way.<sup>4</sup> Considering that, after the second ST, when the patient was taking platelet inhibitor, there was a full recovery of neurological deficit, it is possible that antiaggregant activity of ASA may have protected the patient against the prothrombotic effect of ST.

We are aware that the therapeutical management of our case may be considered challenging. We think that only through discussion and humble confrontation within the medical community will it be possible to extend indications for ST, which nowadays is unfortunately too often underutilized. More data are required in order to understand which drug combination may be more useful in treatment of acute ischemic stroke.

In conclusion, although considered off-label, in case of severe ERIS determining NDFI with no evidence of vascular lesions on CT and little DWI lesion volume, a second ST might be considered.

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## TO THE EDITOR

### Intracranial Non-Occlusive Thrombus and Multiple Strokes in Giant Cell Arteritis

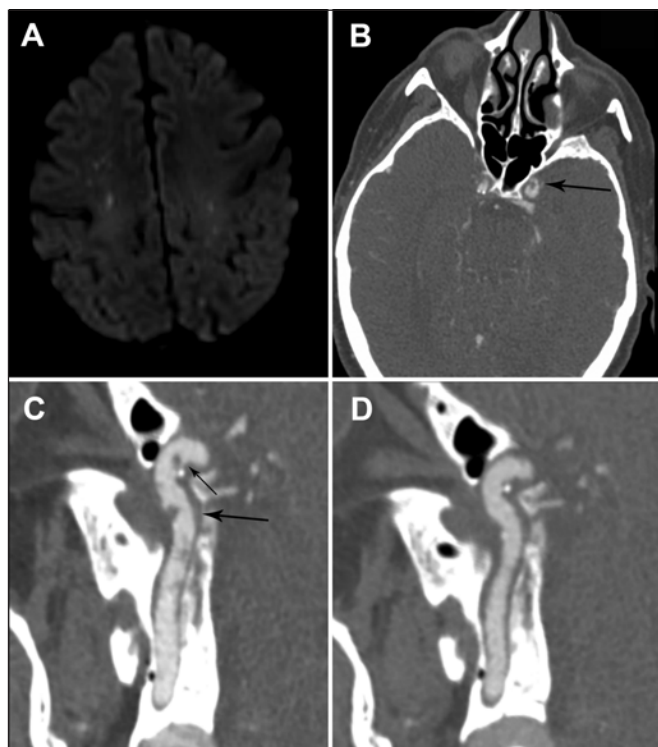
A 78-year-old woman presented with facial pain, scalp tenderness, jaw claudication and visual loss in her left eye. Her visual acuity was 20/25 in the right eye and 20/40 in the left eye. She had a left relative afferent pupillary defect (RAPD) and a constricted visual field in the left eye. Fundoscopy was consistent with anterior ischemic optic neuropathy. She had an elevated ESR at 50mm/hour, elevated CRP at 101mg/L and elevated platelet count at 621/mm<sup>3</sup>. She received methylprednisolone 1 gram IV and had temporal artery biopsies, which were consistent with giant cell arteritis (GCA). She was treated with prednisone 60 mg po daily.

Five days later, she developed aphasia followed by right arm weakness four days later, with right extensor plantar response on examination. Magnetic resonance imaging (MRI) of the brain showed multiple small strokes of varying ages in the left cerebellar, left parieto-occipital, bilateral centrum semiovale and right superior frontal regions (Figure A). Computed tomography (CT) angiogram of the head and neck showed luminal irregularity of both extracranial vertebral and internal carotid (ICA) arteries, and an intraluminal filling defect of the petrous segment of the left ICA consistent with an intracranial non-occlusive thrombus (iNOT) (Figure B, C). These occurred despite prednisone treatment; therefore, she was treated with methylprednisolone 1 gram IV daily, aspirin and heparin IV for five days. Repeat CT angiogram three days later showed resolution of the left petrous ICA iNOT (Figure D). After completion of her intravenous therapy, she was switched to prednisone 80 mg daily, aspirin and clopidogrel. Echocardiogram and Holter monitor did not reveal any cardiac source of embolus. On discharge from hospital, she had stable deficits in her vision and improvement of her language and motor functioning.

## DISCUSSION

Giant cell arteritis is a systemic vasculitis that affects medium and large-sized arteries. The pathology shows granulomatous

inflammation of the inner media, multinucleated giant cells and fragmentation of the internal elastic lamina. This leads to segmental necrosis, luminal disruption and thrombotic occlusion of the affected vessels. Giant cell arteritis has a predilection for the vertebral arteries, but can also affect the anterior circulation.<sup>1</sup>



**Figure:** Radiologic findings. Axial diffusion weighted image (1A) shows multiple small acute infarcts in bilateral centrum semiovale. Initial CT angiogram source image shows an intraluminal filling defect (arrows) in the left cavernous ICA (1B). Curved planar reformat from the CTA (1C) shows multiple intraluminal filling defects (arrows). Follow-up CT angiogram (1D) performed three days later shows complete resolution of these filling defects suggesting intraluminal thrombi.