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A revolution in stroke therapy: reperfusion therapy effective even if late

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Arterial recanalization procedures after ischaemic stroke, are now well-established treatments, within 5 h for systemic thrombolysis, and 6 h for the endovascular treatment. Ischaemic stroke with uncertain time of symptoms onset, account for 14–27% of the cases, the vast majority of which occur just after waking up, thus it is impossible to derive an exact timeline. Accordingly, these patients are frequently not eligible for acute treatment. The results of three recent trials, DAWN, DEFUSE 3, and WAKE-UP, provided the basis for a revolution in the selection of patients eligible for late revascularization, and revealed an increase in the rate of functional independence for these patients at 90 days (mRS 0–2). Advanced neuroimaging techniques have been shown to be of utmost importance in the definition of the cerebral tissue window. A wider application of these imaging techniques and standardization of the parameters of images acquisition would provide for a significant advancement in the management of ischaemic stroke in the emergency setting.

Introduction

Arterial recanalization operations by venous and/or endovascular route are now consolidated treatments in acute ischaemic stroke (AIS). The use of the tissue plasminogen activator produced by recombinant technique (rt-PA) is currently approved in patients with AIS and symptom onset up to 4.5 h, based on data obtained from the ECASS III trial, and confirmed by the analysis of data from 664 patients with AIS of the safe implementation of treatment in stroke (SITS) treated between 3 and 4.5 h after the onset of symptoms.[2]

In 2015, five randomized trials (MR CLEAN,[3] ESCAPE,[4] REVASCAT,[5] EXTEND-IA,[6] and SWIFT PRIME[7]) validated the efficacy of primary endovascular reperfusion therapy in patients with AIS (patients not eligible for i.v. thrombolysis) or after thrombolytic therapy (to which they had responded inadequately) up to 12 h after the onset of the event.

The meta-analysis of the aforementioned trials, carried out by the Highly Effective Reperfusion Evaluated in Multiple Endovascular Stroke Trials (HERMES) collaboration group, highlighted the benefit of endovascular treatment compared to medical therapy alone, in terms of a greater percentage of functional independence at 90 days, expressed as a score (0–2) in the modified Rankin Scale (mRS). However, this benefit was strictly dependent on reperfusion time, reducing, up to not being significant, for intervention times beyond 7.3 h from the onset of symptoms.[8]

These indications have been implemented by the current Italian guidelines (ISO SPREAD).[9]

Time from the onset of symptoms is therefore a central element in AIS management.

Ischaemic strokes with unknown onset of symptoms, according to literature data, amount to 14–27% of cases: it is mainly a stroke upon awakening (WAKE-UP STROKE) in which, although it is assumed an onset in the hours immediately preceding the awakening,[10] the exact time determination is impossible. This results in clinical practice difficulties in the decision as to the best therapeutic option

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to be implemented and often the exclusion of such patients from the aforementioned treatments.

However, in the last year, the results of three trials, DAWN,[11] DEFUSE,[12] and WAKE-UP,[10] laid the foundations for a further revolution in the selection of patients eligible for late revascularization therapy, demonstrating the importance of a new and fundamental criterion in addition to time in the treatment of AIS, that is the extent of ischaemic brain damage.

In these trials, the correct selection of patients was made possible thanks to new advanced neuroimaging methods that allowed to investigate the timing of the pathophysiology of AIS, by calculating the volume of the ischaemic core (central area of tissue irreversibly damaged in which the blood flow is almost abolished) and of ischaemic penumbra (peripheral zone to the core with potentially reversible ischaemic insult). In this context, a transition takes place from the concept of 'temporal therapeutic window' to that of 'cerebral tissue window', in part related to individual neuro-anatomical-physiological parameters that determine a different response to the ischaemic insult. Patients without good collateral circulation, for example, although subjected to reperfusion treatment within 6 h, have a rapid evolution of ischaemic penumbra in necrosis (fast progressor), while patients treated after 6 h, but with good collaterals are able to preserve the reversibility of the ischaemic penumbra longer (slow progressor).[13]

The neuroimaging methods used for this purpose are the perfusion computed tomography (TCp), the triphasic angioscopy, the magnetic resonance (MR) with diffusion-weighted imaging sequences (DWI), perfusion-weighted imaging (PWI), fluid-attenuated inversion recovery (FLAIR), sometimes supported by the use of automatic software for calculating volumes (RAPID). The best method for the correct selection of such patients is still a matter of debate.

Of fundamental importance was the definition of the criteria for identifying and calculating the volume of the ischaemic core, the penumbra and their reciprocal relationships.

With a combined study of magnetic resonance imaging (MRI) with DWI and PWI sequences, it is possible to evaluate the possible presence of diffusion/perfusion mismatch that is that portion of brain tissue that does not show hyperintensity in DWI, but presents a reduction in flow in PWI which roughly corresponds to the ischaemic penumbra area. This method was used in the DEFUSE 3 trial, which enrolled 182 patients with ischaemic stroke and occlusion of the internal carotid artery or proximal middle cerebral artery (MCA), between 6 and 16 h from the last time that the patient was seen to be in good health. In this trial, a diffusion/perfusion ratio to neuroimaging $\geq$1.8 was considered an inclusion criterion, associated with an initial ischaemic core volume $<$70 mL. Patients were randomized to endovascular revascularization treatment (92 patients) and control group (90 patients). Patients who underwent thrombectomy presented functional independence at 90 days (mRS = 0–2) in 45% of cases compared to 17% in the control group, with a lower mortality (respectively 14% against 26%).[12]

Instead, the DAWN trial made use of MR DWI or TCp sequences for measuring the ischaemic volume. Two hundred and six patients with ischaemic stroke and occlusion of the intracranial internal carotid artery or proximal cerebral middle artery (MCA) were enrolled 6–24 h after the patient was last seen in good health, and with presence of mismatch between the clinical deficit [assessed in terms of the National Institutes of Health Stroke Scale (NIHSS)] and the volume of cerebral ischaemia, with identification of three groups of patients in relation to age (greater or less than 80 years), NIHSS score and ischaemic core volume. Patients undergoing endovascular treatment showed a favourable clinical outcome with a lower degree of disability at 90 days compared to the control group (utility-weighted-mRS 5.5 in treated patients and 3.4 in the control group; mRS 0–2 49% in treated patients and 13% in the control group).[11] In both trials, the incidence of symptomatic haemorrhagic transformation was comparable between the two groups. In addition, both trials used automatic volume calculation software (RAPID).

Moreover, the literature shows that the use of CPT is able to predict the possible benefit from reperfusion treatment, evaluating the mismatch between the volume of the ischaemic core and that of the penumbra. Specifically, the parameters that define the ischaemic core are an increase in mean transit time, associated with a marked reduction in cerebral blood volume (CBV $<$2 L/min) and relative cerebral blood flow (rCBF) $<$30% compared to healthy brain tissue. The parameters that define the ischaemic penumbra are instead an increase of MMT, associated with a reduced cerebral blood flow and normal or slightly increased CBV ($\geq$2 L/min, for the self-regulation mechanisms in the initial phase of ischaemia). It was also shown that a 'time to maximum of the tissue residue function' (Tmax)$>$ of 6 s is able to identify more accurately the penumbra that can be saved.

Although most of the patients enrolled in the trials were selected with TCp rather than MRI, correspondence between the core volume calculated in MRI DWI and in TCp in terms of rCBF reduction, and between the ischaemic penumbra values calculated by the Tmax$>$ of 6 s in the CT and MRI perfusion sequences.

The SWIFT-PRIME trial highlighted, on a population of patients treated with endovascular therapy, that following complete reperfusion [determined with thrombolysis score in cerebral infarction (TICI) 2b-3 or reperfusion $>$ 90%] the initial volume of the ischaemic core, determined as a reduction of rCBF $<$30%, correlates with the ischaemic volume at 27 h, while in patients with poor reperfusion rate (TICI score 0–1 or reperfusion $<$10%) the volume of the ischaemic penumbra evaluated in a T perfusion sequence max $>$6 s correlates with the volume of the ischaemic core at 27 h, the latter, however, based on a too small number of patients (only 12 patients out of 151 had obtained poor reperfusion after treatment).[14]

In fact, we have seen that for every 1% of re-canalized penumbra volume there is a 7.4% increase in the probability of reaching a 90-day mRS of 0–1, the figure is more significant when the clinical outcome data are corrected for ischaemic core volume at the onset.

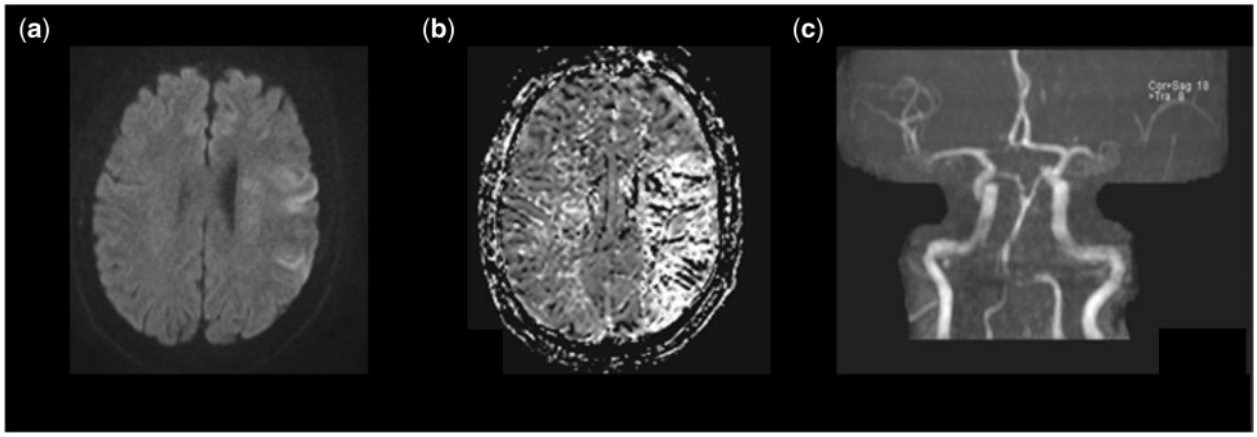

Figure 1 Patient with left hemispheric cerebral ischemia. National Institutes of Health Stroke Scale.[10] (*A*) Diffusion-weighted imaging shows acute ischaemic injury in the left fronto-parietal region. (*B*) Perfusion-weighted imaging shows a wider hypoperfusion region, indicative of ischaemic penumbra. (*C*) TOF sequences show occlusion of proximal left middle cerebral artery.

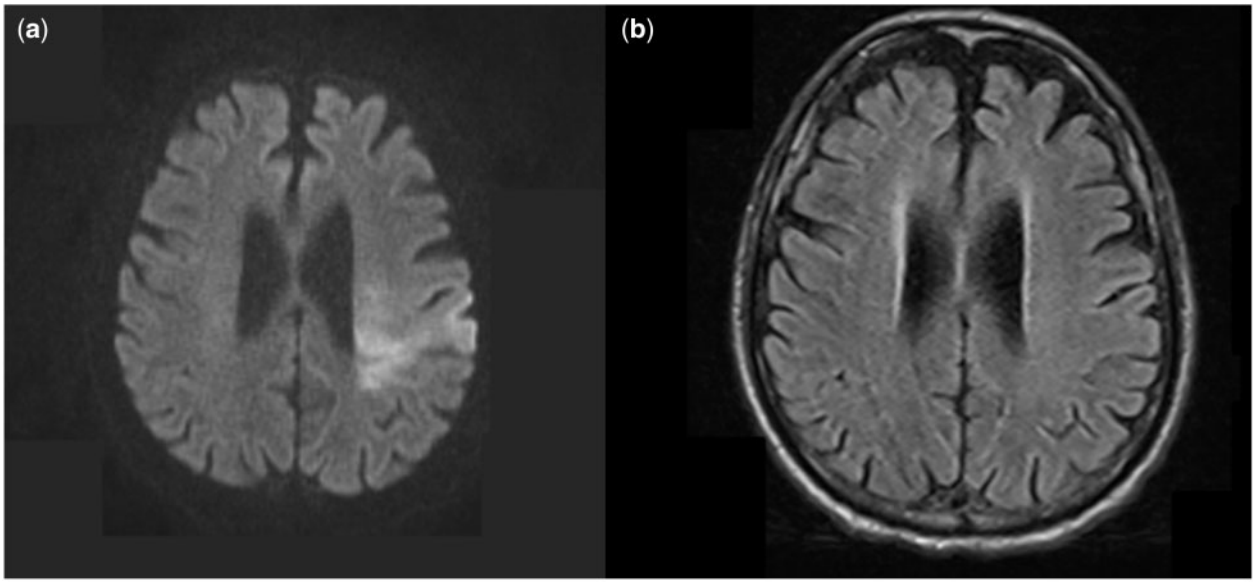

Figure 2 Mismatch diffusion-weighted imaging/fluid-attenuated inversion recovery: patient with left cerebral ischemia (*A*) diffusion-weighted imaging shows acute ischaemic lesion in the fronto-parietal region; (*B*) the fluid-attenuated inversion recovery sequences show no pathological hyper-intensities.

The 2018 guidelines on the treatment of AIS of the American Heart Association (AHA) recommend mechanical thrombectomy, with class of recommendation I and level of evidence A, between 6 and 16 h from the last time that patients were seen in good health, selecting them with DWI/PWI MRI according to the criteria of the DEFUSE 3 trial, and with recommendation class IIa and BR level of evidence, between 6 and 24 h from the last time the patients they were seen in good health, selecting them with TCp or perfusional MRI, according to the DAWN15 criteria.

A different neuroimaging approach in the selection of patients eligible for intravenous reperfusion therapy is instead the use of the so-called DWI-FLAIR mismatch in which the presence of areas of altered diffusion restriction in DWI sequences, associated with non-visibility or tenuous hyperintensity of the ischaemic area in FLAIR sequences is indicative of an onset of symptoms within 4.5 h, therapeutic window approved for systemic thrombolysis. This method was used in the recent WAKE-UP trial, which evaluated the intravenous thrombolytic treatment with Alteplase in 503 patients with an unknown ischaemic symptom onset, selected with an MRI study, demonstrating a clinical outcome favourable at 90 days (defined as a score on the mRS scale of 0–1) in 53.3% of treated patients compared to 41.8% in the control group (OR 1.61).[10] The incidence of symptomatic haemorrhagic transformation (defined as a clinical worsening expressed by an increase of at least four points in the NIHSS scale) in the rtPA-treated group was similar to

Table 1 •••

DEFUSE 3	DAWN	WAKE UP
Eligible 6–16 h since last time in good health	Eligible 6–24 h since last time in good health	Eligible >4.5 h since last time in good health
Occlusion intracranial or extracranial ICA, proximal ACM	Occlusion intracranial or extracranial ICA, proximal ACM	NIHSS < 25
Ischemic volume < 70 mL	Group A: >80 anni; NIHSS ≥ 10; ischaemic volume <21 mLGroup B: <80 anni; NIHSS ≥ 10; ischaemic volume <31 mLGroup C: <80 anni; NIHSS≥20; ischaemic volume 31 <51 mL	No indication for reperfusion
Diffusion/perfusion ratio ≥1.8		Mismatch DWI/FLAIR
TC o RM images	TC o RM images	RM
RAPID software for images analysis	RAPID software for images analysis	
	Recanalization with TREVO device	

DWI, diffusion-weighted imaging; FLAIR, fluid-attenuated inversion recovery; ICA, internal carotid artery; MCA, middle cerebral artery; NIHSS, National Institutes of Health Stroke Scale.

that of the patients treated within 4.5 h of symptom onset1 (*Figure 2*).

CONCLUSIONS

The new scientific evidence derived from the aforementioned trials (*Table 1*) laid the foundations for a therapeutic revolution in the patient with an ischaemic acute stroke and unknown onset of symptoms, with an increase in the percentage of patients who can benefit from late reperfusion treatments and consensual increase in functional independence rates at 90 days (mRS 0-2). The AHA 2018 guidelines for the treatment of AIS have been implemented with recommendations concerning the use of advanced neuroimaging methods for the selection of patients eligible for endovascular reperfusion and symptom onset from 6 to 24 h since the last time the patient had been seen in good health. The data obtained from the recent WAKE UP trial have not yet been acknowledged by the current guidelines, but lay the foundations for an extension of the temporal therapeutic window also for systemic thrombolysis.

The limits to date are multiple and mainly related to the limited availability of advanced neuroimaging methods, which make it necessary to transfer the patient from the Primary Stroke Center (PSC) to the Comprehensive Stroke Center (CSC) with further lengthening of the recanalization times. Another limitation is related to the lack of standardization of image acquisition parameters and dedicated software for their reproducible and reliable analysis. The resolution of these limits would allow a progress in patient management in the emergency network scenario.

Conflict of interest: none declared.

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