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The impact of the DWI-FLAIR-mismatch in the ECASS-4 trial – A post hoc analysis

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Abstract

Introduction: To investigate the impact of a mismatch between diffusion-weighted imaging (DWI) and fluid attenuated inversion recovery (FLAIR) on functional outcome in patients with acute stroke in a prolonged time window or unknown time of symptom onset randomized to intravenous thrombolysis or placebo.

Patients and Methods: We performed a post-hoc analysis of the European Cooperative Acute Stroke Study-4 (ECASS-4) trial. ECASS-4 was an investigator driven, phase 3, multi-center, double-blind, placebo-controlled study which randomized ischemic stroke patients presenting within 4.5 and 9h of stroke onset or unknown time-window to either rt-PA or placebo after MR-imaging. Two subgroups "no mismatch" (nMM) and "any mismatch" (aMM) were created by applying a DWI-FLAIR-mismatch criterion. We calculated frequency of nMM and aMM and performed a univariate analysis (Fisher's Test) for excellent clinical outcome (mRS 0-1) and mortality (mRS=6).

Results: MR-Imaging of n=111/119 (93.2%) patients was suitable for this analysis. DWI-FLAIR mismatch was found in 49 patients (44.1%). Proportions of mismatch nMM and aMM were comparable in treatment-groups (aMM: Placebo 46.3%, Alteplase 42.1%; p=0.70). Patients with nMM showed no benefit of rt-PA-treatment (OR (95%CI) mRS 0-1: 0.95 (0.29-3.17)). Patients with aMM showed a point estimate of the odds ratio in favour of a treatment benefit of rt-PA (mRS 0-1: OR (95%CI) 2.62 (0.68-11.1)). Mortality within 90 days was not different in patients treated with rt-PA if nMM (15.2%) or aMM (12.5%) was present.

Discussion: In this analysis no significant evidence, but subtle indication towards patients treated with rt-PA in a prolonged time window reaching an excellent clinical outcome if a DWI-FLAIR-mismatch is present on initial stroke MR-imaging.

Conclusion: A DWI-FLAIR mismatch in the region of ischemia as imaging based surrogate parameter for patient selection for i.v. rt-PA should be strongly pursued.

Keywords

Thrombolysis, acute ischemic stroke, diffusion-weighted imaging, fluid-attenuated inversion recovery, magnetic resonance imaging, DWI-FLAIR-mismatch, European Cooperative Acute Stroke Study-4

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Introduction

Recombinant tissue plasminogen activator (rt-PA) is the only approved thrombolytic therapy for patients with acute ischemic stroke presenting within a defined time window of 4.5 h with the exception of USA, Canada, Croatia and Moldova (up to 3 h). Until the publication of the Extending the Time for Thrombolysis in Emergency Neurological Deficits (EXTEND) trial, it was deemed that the risk of administration of i.v. rt-PA beyond a 4.5-h time window outweighs potential benefits.[1] Especially in patients with unknown symptom onset, treatment benefit of i.v. rt-PA was questionable. This changed when a multicentre, randomised, double-blind, placebo-controlled trial to test the efficacy and safety of magnetic resonance imaging-based thrombolysis in wake-up stroke patients (WAKE-UP) was published.[2] The WAKE-UP trial showed that selected patients presenting as a wake-up stroke and treated with i.v. rt-PA had significantly better functional outcome than patients who received placebo.[2] Among other in- and exclusion criteria in the WAKE-UP trial, a major criterion for patient inclusion was a diffusion-weighted imaging–fluid-attenuated inversion recovery (DWI-FLAIR) mismatch on initial magnetic resonance imaging (MRI). The reason behind this selection criterion is that MRI findings change during the time course of acute cerebral ischemia reflecting the natural changes in tissue water.[3] A negative FLAIR imaging, respectively a DWI-FLAIR-mismatch reliably identifies acute ischemic stroke patients at 4.5 h or less.[4] This criterion appears to classify patients to be eligible for i.v. rt-PA treatment even if they present within an unknown time window. A DWI-FLAIR-mismatch, however, could still be seen in patients presenting up to 6 h after symptom onset and in a substantially smaller proportion in patients even beyond 6 h of symptom onset.[4]

We sought to investigate whether the presence of a DWI-FLAIR-mismatch would identify patients with acute ischemic stroke presenting within 4.5 h and 9 h of stroke onset or unknown time-window to benefit from i.v. rt-PA treatment.

Methods

We performed a post hoc analysis of the European Cooperative Acute Stroke Study-4: Extending the time for thrombolysis in emergency neurological deficits (ECASS-4: ExTEND) trial. In ECASS-4: ExTEND, patients with acute ischemic stroke symptoms presenting within 4.5 and 9 h of stroke onset, who fulfil clinical requirements (National Institutes of Health Stroke Score (NIHSS) 4–26 and pre-stroke modified Rankin Scale (mRS) 0–1) underwent MRI. Patients who meet additional imaging criteria (infarct core volume <100 ml, perfusion lesion: infarct core mismatch ratio >1.2 and perfusion lesion minimum volume of 20 ml as per local assessment) were randomised to either rt-PA or placebo. All imaging data were electronically transferred and read at the imaging core lab for quality assurance of the recruiting centres. The imaging core lab was blinded to clinical information and randomisation allocation and performed the analysis of the secondary radiological outcome measures. The trial protocol and results have been published previously.[5,6]

Imaging analysis

For this post hoc analysis, the DWI-FLAIR-mismatch criterion was applied to the acute stroke MR-imaging of the ECASS-4 patient cohort. Thereby, ECASS-4 patients could be allocated to a "no mismatch" subgroup or "any mismatch" subgroup. In accordance with the WAKE-UP trial protocol, patients allocated to the any mismatch subgroup showed no or discrete or rather partial FLAIR-hyperintensity in the region of suspected ischemia. Imaging analysis was performed by visual examination on a standard diagnostic workstation (Centricity PACS, Radiology RA 1000 Workstation, GE, Barrington, IL, USA; monitor: RX250 RadiForce, EIZO Corporation, Hakusan, Ishikawa, Japan) by an attending neuroradiologist with eight years of clinical experience blinded to randomisation/treatment allocation (JP).

Time window

In contrast to the WAKE-UP trial, which included only patients with unknown symptom onset (e.g. stroke symptoms recognised upon awakening) and excluded those with duration of symptoms of more than 4.5 h, the ECASS-4 trial included patients which could be randomised within a time window of 4.5–9 h after known or suspected stroke onset. By this measure, patients with wake-up stroke (i.e. patients who went to bed with no neurological symptoms, but showed stroke symptoms upon awakening) could be included in ECASS-4 as well, if randomisation to either placebo or i.v. rt-PA could be achieved within a 4.5–9-h time window.

Statistical analysis and ethical approval

Frequency of "no mismatch" and "any mismatch" was calculated. A univariate analysis (Fisher's Test) for excellent clinical outcome (mRS 0–1) and mortality (mRS = 6) was performed, and the result is shown as

odds-ratio (OR) with exact Fisher 95% confidence-interval (95%CI). Statistical analysis was performed using StatsDirect (V 3.1.14).

Ethical approval was provided by the local ethics committee (Ethikkommission der Medizinischen Fakultät der Universität Heidelberg; No AFmu-328/2013). All patients or their legal representative provided written informed consent for study inclusion. The trial was registered at the European Union Clinical Trials Register: Eudrat-CT-Number: 2012–003609-80.

Results

Patient medical history and baseline clinical data of the ECASS-4 patients were published previously.[6] MR-imaging of $n = 111/119$ (93.2%) patients of the ECASS-4 trial was suitable for this analysis. The majority of these patients were treated as 'wake-up' stroke as defined above, yet 34 patients (30.6%) were treated within a known prolonged time window (see Table 1).

DWI-FLAIR mismatch was found in 49/111 patients (44.1%). No FLAIR-hyperintensity was observed in $n = 40/111$ (36%) patients, and $n = 9/111$ (8.2%) patients had partial FLAIR-hyperintensity in the region of suspected ischemia. Proportions of patients with no mismatch and any mismatch were comparable in treatment-groups ($p = 0.70$; see Supplemental Figure 1). Patients with no mismatch showed no benefit of rt-PA-treatment (OR (95%CI) mRS 0–1: 0.95 (0.29–3.17)). Excellent clinical outcome was numerically, but not significantly observed more often in patients with any mismatch after treatment with rt-PA (mRS 0–1: OR (95%CI) 2.62 (0.68–11.1)).

Mortality within 90 days was not different in patients treated with rt-PA if no mismatch (15.2%) or any mismatch (12.5%) was present ($p > 0.99$). However, mortality was higher in both groups comparing rt-PA vs. placebo treatment (no mismatch: 15.2% vs. 10.3%; OR 1.53, 95%CI 0.27–10.89; any mismatch 12.5% vs. 4.0%, OR 3.43, 95%CI 0.25–187.3). There was one fatal intracranial haemorrhage in a patient with DWI/FLAIR match who received rt-PA.

Discussion

This post hoc analysis of the ECASS-4 trial demonstrates additional subtle indication towards a higher likelihood of patients reaching an excellent clinical outcome after treatment with rt-PA in a prolonged or unknown time window for acute ischemic stroke if a DWI-FLAIR mismatch is present on initial stroke MR-imaging. A DWI-FLAIR mismatch in the region of ischemia as imaging-based surrogate parameter for patient selection for i.v. rt-PA should be strongly pursued. Our results are in line with the data from the WAKE-UP trial.[2] Our finding might be confounded by the circumstance that all patients included in the ECASS-4 trial had penumbral mismatch imaging via local assessment using a Tmax $\geq$ 6-s delay, a perfusion volume (PWI) to infarct core (DWI) ratio of $\geq$1.2, and a minimum perfusion lesion volume of 20 ml. Since patients with ischemic stroke with salvageable brain tissue identified by perfusion imaging presenting in a 4·5–9-h time window from stroke onset or wake-up stroke achieved better functional outcomes when treated with alteplase,[7] our findings could be the missing link to treat patients, who did not receive perfusion imaging.

Furthermore, this analysis indicates that patients with acute ischemic stroke without a DWI-FLAIR mismatch on stroke MR-imaging do not benefit from i.v. rt-PA. It is well established that treatment with i.v. rt-PA bears the risk of increasing the rate of intracranial haemorrhage, fatal intracranial haemorrhage, and mortality in the acute phase.[8] We observed an increased mortality in patients treated with i.v. rt-PA. Among these patients, one fatal intracranial haemorrhage within the rt-PA treatment cohort was observed (in a patient with DWI/FLAIR match); other deaths were considered non-neurological.[6]

Comparable to other studies,[4,9] in this post hoc analysis, the rate of patients with any mismatch declines with the natural course of stroke over time. This underlines the urge to treat patients as early as possible. The rate of patients with any mismatch, however, was still comparable to a previous observational study.[10] This indicates that more than 40% of patients presenting with acute ischemic stroke in a time window of 4.5 h–9 h or unknown time window are potential candidate to receive i.v. rt-PA.

This post hoc analysis has several limitations. First, the definition of wake-up stroke varies to some extend to other trials and comparisons of data, e.g. with the WAKE-UP trial should be done with caution. Second,

Table 1. Allocation of ECASS-4 patients according to time of randomisation and presence of DWI-FLAIR mismatch.

	Time Stratum	4.5 to 6 h		6 to 9 h		Wake-up stroke	
DWI-FLAIR mismatch	N	9		25		77	
	No mismatch	4	44.4%	14	56.0%	44	57.1%
	Any mismatch	5	55.6%	11	44.0%	33	42.9%

the sample size is limited which exaggerates our findings. The limited sample size furthermore carries an inability to adjust the analysis for baseline imbalances in prognostic markers in the patient population. Therefore, observed trends may not be specifically attributable to the MRI markers being explored.

Conclusion

This post hoc analysis of the ECASS-4: ExTEND trial shows subtle indication towards and therefore adds proof to the concept that patients treated with rt-PA in a prolonged or unknown time window are more likely to reach an excellent clinical outcome if a DWI-FLAIR-mismatch is present in stroke MR-imaging. Treatment of patients in extended time-windows based on MRI should be considered, and mismatch between DWI and FLAIR is one of the parameters which should be used for treatment-decision.

Declaration of conflicting interests

The author(s) declared the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article: The sponsor of the trial (ECASS-4: ExTEND) is the University Hospital Heidelberg. Monitoring was done by Trial Form Support International, Sweden.

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Ethical approval

Ethical approval was provided by the local ethics committee (Ethikkommission der Medizinischen Fakultät der Universität Heidelberg; No AFmu-328/2013).

Informed consent

Written informed consent was obtained from all patients or their legal representative.

Guarantor

PAR.

Contributorship

PAR and WH researched literature and conceived the study. PAR, HW, MB, GD, CM, DL, PS, SS, DT, and NW were involved in protocol development, gaining ethical approval or patient recruitment. JARP and PAR were involved in data analysis and wrote the first draft of the manuscript. All authors reviewed and edited the manuscript and approved the final version of the manuscript.

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Trial registration

The trial was registered at the European Union Clinical Trials Register: Eudrat-CT-Number: 2012–003609-80.

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