approach to select patients who are eligible for endovascular treatment.

We declare no competing interests.

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Authors' reply

We thank Jetan Badhiwala and colleagues for their comments about THRACE.[1] We did not select the best candidates for thrombectomy and we agree that the lack of imaging-based selection criteria probably played a part, together with the short time to randomisation, on the treatment effect in THRACE.

By design, the time from intravenous thrombolysis to randomisation was shorter than that in other trials. The short randomisation delay contributed to the high rate (42%) of functional independence at 3 months in the intravenous thrombolysis alone group, higher than in other trials. Patients were randomly assigned as soon as possible in the so-called mothership situation, but also in the so-called drip-and-ship in which patients had been transported from community hospitals to intervention centres while tissue plasminogen activator was infused intravenously. The time from randomisation to groin puncture was much higher than that in other trials with a negative effect only in the intravenous thrombolysis plus mechanical thrombectomy group. Short time to randomisation and longer time to groin puncture might account for the smaller treatment effect than in other trials.

We thank Nicola Morelli and colleagues for their comments about atrial fibrillation and the use of MRI in THRACE. Unfortunately, we did not collect information on atrial fibrillation and we are thus unable to say whether there was an imbalance of atrial fibrillation between groups. We agree that it is a potential source of bias. However, because of randomisation, we do not expect a substantial difference in prevalence of atrial fibrillation in the two groups. Analysis of clot imaging on CT and on gradient–echo T2 imaging is in progress.

Although we have not given details about the sequences of MRI in the protocol, we agree that the small core–occlusion paradigm with good quality non-enhanced CT and CT angiography might be a simple alternative and pragmatic approach to select patients who are eligible for endovascular treatment, especially in uncooperative patients. THRACE was a pragmatic trial and centres were asked to use MRI or CT in accordance with local practice. MRI is preferentially used in France (301 [74%] of 412 patients). The MRI protocol included conventional sequences: diffusion-weighted imaging (DWI), fluid attenuation inversion recovery, gradient echo T2, and 3D time of flight. Perfusion imaging on MRI or CT was not mandatory.

In our trial, about a third of patients who had poor baseline DWI Alberta Stroke Program Early CT scores (0–4) had good clinical outcomes at 3 months and we are working on the DWI volumes–clinical outcome correlations.

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Severe B-cell-mediated CNS disease secondary to alemtuzumab therapy

Alemtuzumab is a pan-lymphocyte depleting anti-CD52 antibody, and is approved as an escalation therapy for patients with multiple sclerosis with active disease defined by clinical or imaging features. In phase 3 clinical trials, the drug was more effective than interferon beta-1a in reducing relapses and brain volume loss.[1,2] However, concerns have been raised due to its numerous adverse effects.[3]

On Dec 17, 2015, a 41-year-old man was referred to our clinic with an apparent acute deterioration of his disease. He had been diagnosed with multiple sclerosis in 2004, after optic neuritis of his right eye with typically disseminated T2 lesions fulfilling diagnostic criteria, prolonged visual evoked potentials (VEPs) and motor evoked potentials, and oligoclonal

band (OCB) positivity. Despite receiving several immunomodulatory therapies during the following decade, including interferon beta-1a, mitoxantrone, glatiramer acetate, and dimethyl fumarate, he had several relapses and displayed continuing MRI activity. A first course of alemtuzumab was given between July 27, 2015, and July 31, 2015 (figure A and E). On Dec 17, 2015, the patient presented with severe dysarthria, marked cognitive symptoms, apraxia, and left-dominant tetraparesis. MRI revealed 20 new contrast-enhancing T1 lesions, most of which were ring-enhancing (figure B and F). He was treated intravenously with 7000 mg methylprednisolone. Due to lack of responsiveness to the steroid, and as the presence of ring-enhancing lesions is known to correlate with efficacy of plasma exchange,[4] we performed plasmapheresis and one cycle of immunoadsorption. This treatment led to marked improvement of clinical symptoms and lesion restitution by MRI (figure C and G). To stabilise the disease course, the B-cell-depleting antibody rituximab was given. This treatment resulted in a near absence of contrast-enhancing lesions (figure D and H) and, by Sept 27, 2016, the patient was almost free of the symptoms that prompted admission 9 months earlier.

A second patient, a 25-year-old woman, presented to our clinic with tetraparesis predominantly affecting the legs in July 6, 2015. She had been diagnosed with multiple sclerosis in 2011 on the basis of hypesthesia of the legs and left hand, two spinal cord lesions (one of which was contrast-enhancing), 15 cerebral T2 lesions fulfilling McDonald criteria, prolonged VEP, and OCB positivity. She had received several different treatments since diagnosis, including interferon beta-1a, natalizumab, and fingolimod—switching between these drugs due to manifestation of depression and a high anti-JC virus antibody index. Showing continued disease activity while on fingolimod, she received an initial course of alemtuzumab between Dec 1, 2014, and Dec 5, 2014. Upon admission to our clinic in July 6, 2015, she was treated with 3000 mg methylprednisolone, leading to symptom improvement but with residual deficits. On Sept 22, 2015, she was admitted with newly occurring left-sided hemiataxia and hemihypesthesia, and was treated with methylprednisolone and plasma exchange. However, the symptoms re-occurred on Nov 1, 2015, and were treated with a higher methylprednisolone dose. Due to logistical difficulties, a follow-up MRI was not done until April 18, 2016, but this MRI revealed several contrast-enhancing lesions, including some with ring-enhancing characteristics (data not shown). In view of her continued clinical and paraclinical disease activity, the patient was treated with rituximab on June 2, 2016, after which her symptoms improved, and she has since stabilised as determined by clinical and MRI measures.

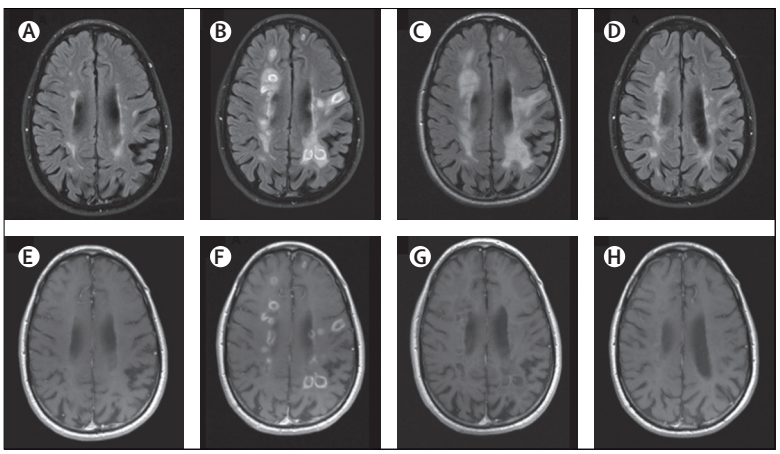

Figure: **MRI findings in a patient with multiple sclerosis after alemtuzumab treatment**
Flair sequences and corresponding contrast-enhanced T1-weighted images at the time of medication switch to alemtuzumab (A, E). Follow-up MRI performed 5 months later, showing multiple ring-enhancing lesions (B, F). Lesion restitution after plasma exchange, immunoadsorption, and rituximab initiation (C, G). Further improvement was noticeable 5 months after rituximab treatment (D, H).

These two patients might represent the first recognised cases of severely exacerbated CNS inflammation after alemtuzumab therapy in multiple sclerosis. Our findings of marked improvement of the patients after plasmapheresis and rituximab therapy indicate a predominantly B-cell-driven pathology. Alemtuzumab-dependent, B-cell-mediated autoimmune diseases have been identified for several tissues other than the CNS.[3] The exacerbated inflammation seen in our patients is consistent with the time frame in which B-cell repopulation and peripheral expansion occur following alemtuzumab treatment. Thus, it remains to be determined if the disease observed in these two patients after treatment is due to worsening of multiple sclerosis or to the development of secondary CNS-directed autoimmunity. Notably, a rare genetic or infectious aetiology was not found, as evaluated by whole genome analyses (data not shown), suggesting that further cases might be identified, and that apparent relapses after alemtuzumab treatment should be promptly evaluated by MRI for the presence of ring-enhancing lesions. A specific rescue therapy comprising plasma exchange with consecutive B-cell depletion can then be initiated to help prevent irreversible disability.

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