One must use extreme caution in accepting the published trial data as proof of the concept of B-cell-driven pathogenesis in multiple sclerosis. Indeed, most authors of this paper were also involved with the clinical trial of B-cell-targeted treatment with atacicept that was terminated by the sponsor because of serious worsening of disease in the treated groups (ClinicalTrials.gov NCT00642902).

The lessons from the clinical trial of natalizumab seem to have been forgotten too quickly: nearly a quarter of more than 200 patients with natalizumab-induced progressive multifocal leukoencephalopathy are dead and most of the rest are severely disabled by the drug rather then their disease. Quo vadis multiple sclerosis?

I declare that I have no conflicts of interest.

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Authors’ reply

We agree with Abhijit Chaudhuri that a phase 2 proof-of-concept study cannot provide definite evidence about the safety profile of a new compound. What we reported is that the benefit/risk profile noted over 48 weeks and in a limited number of patients was positive. Our paper concludes by underlining the need for larger and longer-term studies to better inform the benefit/risk profile of ocrelizumab.

Indeed the death of a patient is always a reason for concern, but an independent pathological review by external experts concluded that the patient who died in our study did not show any signs of viral infection. Whether the systemic acute inflammatory reaction noted in this patient had a causal relation with ocrelizumab treatment has not been established.

The lack of evidence for a dose response in this proof-of-concept study does not allow us to conclude one way or the other whether “escalation of B-cell depletion by immunotherapy alters the natural course of multiple sclerosis”. As a side note, although the primary analysis of this study did not show a clear dose response, a later post-hoc analysis indicated a dose response in patients with highly active multiple sclerosis and—together with data collected in studies of ocrelizumab in rheumatoid arthritis—suggests that ocrelizumab 600 mg might be the lowest effective dose in multiple sclerosis.

Finally, the failure of atacicept in the treatment of relapsing multiple sclerosis underlines the notion that not all B-cell-directed treatments are beneficial. Failed trials are—although regrettable—a strong stimulus for further research and for refinement of our concepts of pathogenesis and treatment. On closer inspection there are substantial differences in the mode of action of atacicept and ocrelizumab that certainly need to be discussed when the atacicept trial results are fully published.

The short-term efficacy shown in our proof-of-concept study of ocrelizumab compares well with that of other compounds used for the treatment of multiple sclerosis and certainly provides ample motivation to do larger and longer-term studies in an informative phase 3 programme to further explore the benefit/risk profile of this humanised monoclonal antibody in multiple sclerosis.

We declare that we have no conflicts of interest other than those stated in the original paper.

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Interventional cardiology and cardiac surgery in Cambodia

WHO and other international organisations decree that facilities and treatments provided by donors to developing countries should correspond to the economic realities of those countries. We would like to highlight and defend a sophisticated yet sustainable technology transfer programme that we have operated, against these principles, in paediatric cardiology and interventional cardiology in Cambodia.

The five Kantha Bopha Children’s Hospitals in Cambodia have admitted more than 1 million severely sick children over the past 20 years and treated more than 10 million sick children in their outpatient clinics. The Kantha Bopha Hospitals care for 85% of all sick Cambodian children. All treatment is free of charge.

109 100 severely sick children were admitted to hospital in 2010: 58 267 in Phnom Penh and 50 833 in Siem Reap Angkor. In the Kantha Bopha Hospitals in Phnom Penh, 376 children died (0·64%), of whom 53 (14%) had an untreatable pulmonary complication caused by a congenital heart defect. In other words, the disease with the highest mortality rate in the Kantha Bopha Hospitals is now congenital heart malformation.

But many more have died as a consequence of a heart malformation. In 2010, 272 children with severe pulmonary problems as a consequence of heart malformation had to be admitted to the intensive-care unit. 53 died (20%). The other 219 children were discharged still in...
a critical state, and their parents were told that they could not be saved. They died later at home.

This is the reason why we have installed in Siem Reap Angkor, as a logical step to reduce the mortality rate, interventional cardiology for closure of patent ductus arteriosus and atrial and ventricular septal defects, dilation of pulmonary and aortic stenoses, and cardiac surgery for more complex congenital malformations via a partnership involving the teams of the University Children’s Hospital Zurich, Switzerland; Chaîne de l’Espoir, Paris, France; and Fondation le Petit Coeur, Zurich. This strategy is based on epidemiological data and translates the will to decrease mortality in severely sick children in a sustainable way.

We declare that we have no conflicts of interest.

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