Response to ‘Correspondence on ‘Historically controlled comparison of glucocorticoids with or without tocilizumab versus supportive care only in patients with COVID-19-associated cytokine storm syndrome: results of the CHIC study” by Charles

We read the letter from Charles1 2 regarding our CHIC (COVID High-intensity Immunosuppression in Cytokine storm syndrome) study.3 Charles clearly expresses his disappointment in the methodology chosen for our study (a quasi-experimental study with a matched historical control group) and in the positive results of our immunosuppressive strategy. Charles claims that it is disappointing to see false positive results of tocilizumab while subsequent studies have shown negative results.

We certainly respect an opinion that differs from ours, but we take the liberty to gently disagree with the bold statements made. First is the chosen methodology. Indeed, as we have acknowledged in our paper more than once, a randomised controlled trial (RCT) is in principle the preferred study design when assessing the efficacy and safety of a new treatment. Still, we should not ignore the context of a pandemic, with a very high initial hospital mortality, at a time when supportive treatment (ie, lack of treatment) was the only alternative. Our colleagues in the hospital, including internists such as the author, pleaded strongly against not treating half of the patients. We are proud that we have listened to them and have refrained from a placebo-controlled RCT (at that time). We still emphasise that we have improved patients’ outcomes and have saved lives.

More importantly, though, the components of the immunosuppressive treatment strategy we have chosen have been thoroughly tested in RCTs and have proven efficacy, which in our opinion proves our right in retrospect. This brings us to the second part of the criticism, in particular the efficacy of tocilizumab in COVID-19. It is true that some early trials have yielded negative results for tocilizumab, but these trials were not without methodological concerns: not including severely ill patients and not restricting the population to patients with hyperinflammation, namely those with a rationale for immunosuppression, are among these concerns.4 Nevertheless, the results of other thoroughly conducted RCTs have in the meanwhile been released and have formally confirmed the efficacy of tocilizumab in patients with severe COVID-19 pneumonia.5 6 As said, we find it reassuring that the quasi-experimental strategy that we have adopted in the early hectic phase of the pandemic has now been confirmed in RCTs, although diced into pieces.5–7 It was only recently, and after these confirmations in RCTs, that for example the national Dutch guidelines for the treatment of COVID-19 have issued a recommendation in favour of treatment with tocilizumab.8 Also the English National Health System issued a favourable interim position statement.9

One last remark remains: RCTs have highest possible levels of internal validity. Their external validity (‘which patients should actually be treated?’) often falls short and is easily ignored by the general public, which is urgently waiting for a treatment for all. We have always stipulated that ‘our’ immunosuppressive strategy is intended for the minority of patients with COVID-19 who are sickest and have clear signs of hyperinflammation. In those, we and others have shown, it contributes to better outcomes and to saving lives.

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