Response to Letter by Topakian et al

Response:
I am pleased with the interest shown by Topakian et al on our recent study, and I am also sure they are very interested in the field of biomarkers and the possibility of using those to guide stroke thrombolysis and not just in setting up “a relationship” with Vall d’Hebron Stroke Unit by exchanging monthly letters through Stroke.

Affairs apart, they raise some very interesting points. They suggest that some treatments such as statins might be influencing C-reactive protein (CRP) level. However, we did this analysis and no differences in CRP level existed regarding pretreatment with statins. In fact, around 20% of our patients were on statins before stroke and those had similar CRP levels than the ones who were not taking statins (0.57 mg/dL [0.22 to 0.88] versus 0.59 mg/dL [0.22 to 0.91], P = 0.99).

It is possible that the anti-inflammatory effect reported for several statins is abrogated in the acute phase of a vascular event. In fact, in a pilot study conducted by our group using statins in the acute phase of ischemic stroke, we were not able to show a decrease in CRP levels measured at several time-points after simvastatin treatment. Alternatively, it is also possible to think about the fact that stroke patients on statins having similar CRP levels than those not on statins might reflect a lack of effect of statins to control the activity of the vascular disease in those patients. Might that be the reason why they had a stroke? Perhaps nonstroke controls under statins would have much lower CRP levels than our stroke patients on statins. All that is hypothetical of course.

Topakian et al raise also several questions regarding the possibility that CRP is reflecting high mortality rates just attributable to a relationship with infections. They wonder about a relationship with temperature. We have analyzed this data and no correlation was identified between CRP and baseline temperature (r = 0.14, P = 0.36). In the same direction they argue that our cut-off to rule-out infections is too high and that perhaps our results might be quite different using lower cut-offs. They suggest 3 mg/dL, that is, including only patients with CRP below 3 mg/dL, we still identify significant differences between CRP levels regarding mortality (0.53 versus 0.80 mg/dL, P = 0.01). Interestingly, results are even better if we use lower cut-offs and we exclude patients with CRP higher than 2 (0.48 versus 0.80 mg/dL, P = 0.009), and even better if we exclude any patient with CRP higher than 1 (0.41 versus 0.73 mg/dL, P = 0.002). These results clearly suggest that CRP is doing or reflecting something beyond infections.

Of course, the selected CRP cut-point level (0.77 mg/dL) used in our article as the best predictor for mortality offers different sensitivities and specificities to predict this end point when modifying the study population using those new CRP limits: including patients with CRP <3 mg/dL, the specificity for CRP cut-point level=0.77 mg/dL is 72.6%; including those with CRP <2 mg/dL, specificity is 75% and including those with CRP <1 mg/dL, specificity is 86.5%. Moreover, we might look for new CRP values offering the best sensitivity and specificity in each of those populations; however, we believe that our option is much more realistic and perhaps in a further study it would be even better just to calculate predictive values without any kind of exclusions by high CRP levels. That would reflect daily practice.

Topakian et al have also some comments on possible CRP variability and fluctuations, so they wonder about any influence attributable to stroke onset and CRP measurement times and about the possibility of doing several CRP measurements to avoid within-individual variability.

Blood samples were obtained around 2 hours from symptoms onset (median = 110 [88 to 145] minutes). No correlation existed between CRP level and time to sampling (r = 0.07, P = 0.41). In fact, median CRP was quite similar among those patients in whom blood was obtained in the first hour (0.62 mg/dL), in the second hour (0.56 mg/dL) or in the third hour (0.56 mg/dL) after symptoms onset. Therefore, we are confident with CRP values homogeneity when obtained within the 3-hours time window.

Regarding serial measurements, authors should know that in the article to which they refer, CRP determinations were carried out at quarterly intervals over a 1-year period. When dealing with CRP as a risk factor, 2 separate measurements of CRP are adequate to classify a person’s risk level and to account for the within-individual variability, but that is not the issue in the hyperacute setting. We might expect little within-individual variability in measurements separated by minutes before deciding to treat or not to treat a patient. Moreover, we believe it might be unethical to make repeated blood sampling before tissue plasminogen activator administration.

The remaining points were addressed in the study limitations of the article. We make clear in the study that “Because the relatively small number of deceased patients in this study precludes formation of subgroups for a more detailed mortality analysis, this should be addressed in a future and larger study.” If again we are requested to hypothesize, I can say that among death patients with high CRP we have a representation of different groups of patients, those with huge infarctions, those with an extended vascular disease, involving also the heart, and those with an atherotrombotic milieu in the brain arteries, leading to reocclusion phenomena. All those groups of patients are clearly more prone to die.

In conclusion, our study supports that CRP is a useful “marker” and maybe a factor in the pathogenesis of stroke-related mortality. I still believe that some of the interindividual differences in CRP level after stroke and therefore in the mortality risk after that vascular event are in the genes of our patients. A large multicenter pharmacogenomic study (Geno-t-PA) is ongoing to answer these fascinating questions.

Disclosures
None.

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