ZonMW Vidi grant from The Netherlands Organization for Scientific Research and by a fellowship from Janssen Biologics. Drs. Trouw, Huizinga, and Toes have submitted a patent application for the use of anti-CarP antibodies as a diagnostic test.

Carol Ann Hitchon, MD, FRCPC, MSc
University of Manitoba
Winnipeg, Manitoba, Canada
Hester Koppejan, MSc
Leendert A. Trouw, PhD
Tom J. W. Huizinga, MD, PhD
René E. M. Toes, PhD
Leiden University Medical Center
Leiden, The Netherlands
Hani S. El-Gabalawy, MD, FRCPC
University of Manitoba
Winnipeg, Manitoba, Canada

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Power and confounding in diffuse alveolar hemorrhage secondary to antineutrophil cytoplasmic antibody–associated vasculitis: comment on the article by Cartin-Ceba et al

To the Editor:

We read with interest the article by Cartin-Ceba et al (1) regarding the efficacy of plasma exchange and other medications in a cohort of patients with diffuse alveolar hemorrhage secondary to antineutrophil cytoplasmic antibody–associated vasculitis (AAV). Prudence must be exercised when utilizing observational studies to evaluate the effect of intervention (2). Many different factors other than the intervention being evaluated can determine outcomes. The application of any of the statistical strategies proposed to correct for this possible confusion requires as much accuracy as possible. Otherwise, conclusions drawn may prove counterproductive for patients.

We believe that several of the authors' conclusions warrant comment and should be considered with caution before extrapolation to clinical practice. In regard to the likelihood of patients receiving or not receiving plasmapheresis, the authors never explain how they evaluated the appropriateness of the propensity score they developed. An important component of any propensity score analysis is examining whether the propensity score model has been adequately specified (3). The use of this analytic technique requires having a large sample size and should ideally be based upon a large number of variables; these conditions were not met in Cartin-Ceba and colleagues' study.

Unadjusted confounding may still exist if unmeasured factors influenced treatment selection. Therefore, using fewer variables in the propensity score model reduces the likelihood of effective adjustment for confounding. Although the propensity score may be used to assemble comparable study groups, the quality of matching depends on the quality of the propensity score model, which, in turn, depends on the quality and size of the available data and how the model was built (4). A propensity score can be included as a covariate in the multivariate analysis; however, this is generally considered to be the least preferred option (3,5). Additionally, even if developed properly, propensity scores fail to correct for unmeasured confounding and unknown factors. For these reasons, one cannot conclude that plasmapheresis is not of any use, as Cartin-Ceba et al suggest.

Absence of significant differences in data can be attributed to small sample size (6,7). If differences were not detected with the use of plasmapheresis, was it because there were no actual differences or because there was not enough statistical power to detect any differences? The clinical trial of plasmapheresis in AAV published by Jayne et al (8) included more than twice the number of patients included in this observational study.

It is even more striking that no attempt was made to correct possible confusion caused by the nonrandom assignment of treatment with cyclophosphamide versus rituximab. This is especially noteworthy because, from Table 5 in the article by Cartin-Ceba et al, it is clearly evident that the patients who received cyclophosphamide had major renal involvement and were older than the rituximab group. If observational data obtained from routine clinical practice are examined to compare the outcomes in patients treated with different therapies, the observed differences in outcome will be the result of both differing patient traits and treatment choice, making it difficult to delineate the true effect of one treatment versus another (4). Why was a propensity score not used to compare patients who received rituximab versus those who received cyclophosphamide? It seems important to also rule out any cohort effect when considering whether the patients treated with rituximab were enrolled at a later time in the 16-year study, when clinical practices may have improved.

Finally, we consider it essential to know the conflicts of interest of the authors, which we were unable to locate in the report. Conflicts of interest matter a great deal for determining scientific independence, especially when drawing conclusions for or against any therapeutic intervention.

Mauricio Restrepo-Escobar, MD, MSc
Johanna Hernández-Zapata, MD
Universidad de Antioquia
Medellín, Colombia

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Reply

To the Editor:

We thank Drs. Restrepo and Hernández for their interest in our recent study and agree with them that the results of observational studies should be interpreted with caution. We clearly acknowledged the limitations of our study in the published article, including but not limited to the retrospective design, small sample size, and bias in the use of plasma exchange. Most of the limitations outlined in our article are inherent to retrospective observational studies, and to expect that a small retrospective observational study will change clinical practice is naive and was by no means the intention of our study.

In regard to the comparison made to the study by Jayne et al (1), we would like to point out that although the cohort included more patients than in our study, only 31 of 137 (23%) presented with diffuse alveolar hemorrhage in that study; moreover, it is now well documented that despite initial short-term benefits of plasma exchange for renal recovery, there were no beneficial long-term clinical outcomes associated with the use of plasma exchange in the study population (2).

Drs. Restrepo and Hernández also raised concerns regarding the use of a covariate adjustment propensity score to account for the imbalance observed in patients treated with plasma exchange (those in whom symptoms were more advanced). Although there appears to be a preferred hierarchy (matching being favored more than stratification over covariate adjustment) in terms of the effectiveness of balancing, we were not able to find adequate matching pairs based on the propensity score and would have lost a significant number of patients from our cohort in the analysis. Furthermore, stratification with such a small sample size was difficult to accomplish and only a small number of strata would have been created, defeating the purpose of stratification for improving bias reduction. We would like to emphasize the importance of accurate specification of the propensity score model utilized in our study. We were able to identify that, conditional on the propensity score, treated and untreated subjects had similar distributions of baseline covariates as assessed using both quantitative and qualitative measures (weighted conditional standardized difference and quantile regression models, respectively) (3).

Another inquiry was made regarding the imbalance between patients treated with rituximab versus those treated with cyclophosphamide for induction of remission. We respectfully disagree with Drs. Restrepo and Hernández concerning the need to perform a propensity score analysis for the choice of induction of remission based on differences in baseline characteristics, particularly their statement that patients who received cyclophosphamide had major renal involvement as compared to those treated with rituximab. Table 5 of our article very clearly demonstrates that there were no statistically significant differences between those treated with rituximab and those treated with cyclophosphamide in regard to active renal disease, need for new renal replacement therapy, creatinine level, or glomerular filtration rate. There also was no cohort effect, as we evaluated whether there was a difference in the main outcomes (development of respiratory failure, hospital length of stay, and mortality) in the first half of the study compared to the second half. The majority of the patients were seen during the more recent period, i.e., 48 (66%) were seen