Clinical trials: More to learn than the results

Randomized controlled trials provide the highest level of evidence for the way we practice medicine, particularly in our choice of treatment. But the results of these trials often have limited applicability to specific patients, as participants in clinical trials are not exactly the same as the patients who show up in our offices. Even beyond the exclusion and inclusion criteria of clinical trials, other factors distinguish patient outcomes in our practices from those in trials. Patients in well-conducted trials are monitored closely, and the data are meticulously collected. While we all like to think we follow our patients carefully and appropriately, I am periodically reminded how I have failed to recognize or record a specific detail. Smarter electronic medical records can help us do this better in routine practice. For now, the forced discipline of data collection in a well-conducted trial can provide a unique treasure trove of information on disease course and patient outcomes that is harder to generate in real-world practice and much harder for each of us to accurately recall. Clinical trials can provide us with insights beyond the drugs being tested.

The clinical update of giant cell arteritis (GCA) by Rinden et al in this issue of the *Journal* (page 465) reminded me of just how much of our management of this disease has, for decades, been based on retrospective studies (we owe a lot to clinicians from the Mayo Clinic for their compiled observations) tempered by our own recalled experiences, which we may at times twist a bit to fit prevailing paradigms. Several prospective interventional studies, perhaps most importantly the Giant-Cell Arteritis Actemra (GIACTA) trial,[1] evaluated the ability of the interleukin 6 (IL-6) antagonist tocilizumab to supplant the protracted use of glucocorticoids in the treatment of GCA. But I learned much more from this trial, in the form of collected clinical tidbits, than just the bottom-line abstract conclusion that IL-6 antagonism is at least a promising approach in many patients with GCA.

As teachers, we tell students to read the entire published clinical trial report, not just the abstract and conclusions. Over the years, I have been impatient with those who violated this dictum, but I now often find myself among the ranks of those who would have been targets of my disapproval. Usually, the articles that I merely skim lie outside my subsubspecialty areas of interest, as time constraints make this abridged reading a necessity for survival, but that excuse does not diminish the self-recognition of my often less-than-complete understanding of the clinical condition being reported. Delving into the nuances of GIACTA truly emphasized that point.

The external validity of any trial rests on understanding the trial's methods. In the case of GIACTA, there was much more to be learned and affirmed from the trial[1] than that 1 year of tocilizumab treatment met the primary end point of increasing the percent of patients achieving sustained remission at week 52 after a rapid 26-week tapering off of prednisone compared with placebo.

One treatment group in the GIACTA trial underwent an aggressive 6-month tapering of prednisone, while another underwent a more protracted tapering over 12

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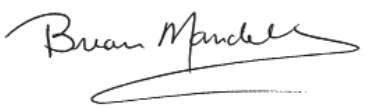
months (more in line with common practice). Patients tapered over 6 months also received either the IL-6 antagonist or placebo for the full year. The concept was that if IL-6 blockade is a correct approach, then it will maintain remission in more patients, and significantly reduce the total amount of steroid needed to control the disease, despite rapid, aggressive steroid tapering. This turned out to be correct, although more than 20% of the drug-treated patients still experienced a flare of GCA (vs 68% of the placebo-treated group).

Somewhat surprising was that almost 20% of the entered patients did not achieve an initial remission despite receiving high-dose prednisone. The traditional teaching is that if a patient diagnosed with GCA does not respond to high-dose steroids, the diagnosis should be questioned.

Another interesting facet of the study relates to the diagnosis. We are becoming more aware of the different GCA phenotypes, which include prominent polymyalgia rheumatica or constitutional features, "classic" GCA with cranial symptoms, and dominant large-vessel vasculitis (aortitis and major aortic branch disease). In GIACTA, even though imaging was not mandated, 37% of participants were enrolled based in part on imaging results (CT, MRI, angiography, or PET-CT), not on the results of temporal artery biopsy. This forces us to think more broadly about diagnosing and staging GCA, and to wonder if we should even modify our approach to other clinical challenges, including unexplained fever and wasting in older patients.

Another tidbit that came out of the study relates to the relationship between the acute-phase response and clinical flares. We already knew that a rise in the erythrocyte sedimentation rate is a nonspecific sign and does not equate with a flare. In this trial one-third of patients in the placebo group who had a flare had a normal sedimentation rate or C-reactive protein during the flare, and about one-third of patients in the placebo group were receiving more than 10 mg of prednisone. In preliminary reports of follow-up after 52 weeks of treatment,[2] patients who had achieved complete remission with the IL-6 antagonist and were off of prednisone were still not out of the woods; when the drug was discontinued, many flares continued to occur over the 2-year study extension. We have more to learn about what triggers and drives flares in this disease.

Thus, in addition to informing us of a successful "steroid-sparing" and rescue drug option for our patients with GCA, the details of this well-conducted trial both challenge and reaffirm some of our clinical impressions. Clearly, GCA must be defined for many patients as a very chronic disease, perhaps with occult vascular reservoirs, the biologic basis of which remains to be defined.



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1. **Stone JH, Tuckwell K, Dimonaco S, et al**. Trial of tocilizumab in giant-cell arteritis. N Engl J Med 2017; 377(4):317–328. doi:10.1056/NEJMoa1613849
2. **Stone JH, Bao M, Han J, et al**. Long-term outcome of tocilizumab for patients with giant cell arteritis: results from part 2 of the GIACTA trial (abstract). Ann Rheum Dis 2019; 78:145–146. doi:10.1136/annrheumdis-2019-eular.2099