FDA INSIGHTS

Inside the Gore TAG Device Advisory Hearing

On January 13, 2005, a panel voted to recommend approval with conditions for Gore's TAG Thoracic Endoprosthesis. The device could be the first approved in the US for the endovascular treatment of thoracic aortic aneurysms.

BY MATT PESOTSKI, ASSOCIATE EDITOR

Physicians and patients in the US are now a considerable step closer to having an endovascular option for treating descending thoracic aortic aneurysms, after an FDA Circulatory System Devices advisory panel (Table 1) voted to recommend approval with conditions for W. L. Gore & Associates' (Flagstaff, AZ) TAG Thoracic Endoprosthesis. The data presented and the panel's recommendation and conditions will now be considered by the FDA, who will work with Gore to see that the conditions are met and ultimately decide whether to approve the device. If approved by the FDA, the Gore TAG will be the first device approved in the US for this indication.

THE OPEN PUBLIC SESSIONS

The impression left by the testimonies given during the open public sessions is that the overwhelming majority of physicians in the vascular community are strongly in favor of the approval of a thoracic endoprosthesis. Several physicians who currently have only the option of performing open surgical repair of descending thoracic aneurysms, a procedure associated with significant morbidity and mortality, strongly urged the panel to recommend approval of this device. Most, if not all, of the physicians who spoke have also implanted investigational endovascular grafts made by Gore and other manufacturers, and they each expressed confidence that endovascular technology was a significant step forward in patient care. No physician spoke against approving the device.

Rod White, MD, opened the public session by discussing the groundbreaking work that is currently underway in the Lifeline Registry, which has now been expanded to evaluate outcomes analyses for all vascular procedures. (Look for a detailed update on the Lifeline Registry in our upcoming March 2005 issue.) Dr. White also expressed the greatly improved level of patient care that approval of a thoracic endograft would bring, citing his experience with both surgical and endovascular procedures. Greg Sicard, MD, President of the Society for Vascular Surgery, echoed these points, stating that the introduction of this technology would dramatically decrease perioperative mortality and morbidity.

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Also noteworthy in the open public sessions were the addresses of J. Michael Tuchek, DO, and Bill Tinker, a patient who had undergone an endovascular repair using the Gore TAG device. Dr. Tuchek began by providing the obligatory conflict of interest, stating that he was an investigator for an ongoing trial evaluating a potentially competing thoracic endoprosthesis developed and manufactured by Medtronic, Inc. (Santa Rosa, CA). Despite his work involving a competing product, Dr. Tuchek urged approval based on his knowledge of thoracic endografting and applauded the efforts of Gore and the physicians involved in the trial. He did, however, recommend that the approval be restricted only to high-volume centers where thoracic specialists perform a large number of aneurysm treatments.

Mr. Tinker informed the panel and the audience members that several years ago, he underwent an open repair of an abdominal aortic aneurysm, and that more recently he had been a patient in the clinical trial of Gore's thoracic endograft. He described in detail the impact on quality of life each procedure had, saying that even after a successful open surgical repair, he was significantly limited in his everyday activities for a long period of time. Conversely,

after his endovascular thoracic repair, he was able to resume normal activity much sooner and with more confidence in his health. To illustrate, Mr. Tinker said that for months after his open procedure, he always drove in the far right lane because he lacked confidence in his arterial stability; however, after endovascular treatment of his thoracic aneurysm, he immediately felt comfortable in the fast lane.

DATA PRESENTATIONS

After one of the hearing's two open public sessions, representatives from Gore and investigators from the clinical trials gave the Sponsor Presentation. R. Scott Mitchell, MD, of Stanford University, and Michel S. Makaroun, MD, of the University of Pittsburgh Medical Center, served as National Principal Investigators for the clinical trials of the Gore TAG device and presented information regarding device design, the elements of each phase of the clinical trial, and its results. After a round of questions from the panel, the floor was turned over to the FDA reviewers, who provided their evaluation of the device and the clinical trial design and data.

Dorothy B. Abel, one of the FDA's lead reviewers, began the FDA Summary; Andrew Farb, MD, provided the FDA's review of the clinical data, and Gary L. Kamer, a mathematical statistician for the FDA, presented the relevant statistical considerations.

Trial Design and Device Considerations

The trial was conducted in three phases: feasibility, pivotal, and confirmatory. In the single-arm, 28-patient feasibility study, there were no deployment failures or intraoperative deaths, and through 1 year of follow-up (n=19), the rates of paraplegia and stroke were each 0%, and renal failure and myocardial infarction were each 3.6%. Long-term results at 60 months (n=11) included no ruptures or migrations, nine fractures, six endoleaks, five incidences of aneurysm enlargement, one revision, and one conversion.

The pivotal phase was a nonblinded, nonrandomized, controlled study of 140 Gore TAG subjects and two groups of open-surgical control patients: a historical control (n=50) and a concurrent control (n=44). The safety endpoint was defined as the proportion of subjects who experienced one or more major adverse events (MAEs) through 1 year posttreatment; the safety null hypothesis was that the proportion of subjects who experienced one or more MAE through 1 year was equal in the study and control groups; the alternate hypothesis was that the proportion of subjects who experienced one or more MAE through 1 year was less in the study group than in the control. Adverse events were classified as "Major" if they required therapy or minor hospitalization (<48 hours); required major therapy, unplanned increase in level of care, or prolonged hospitalization (>48 hours); permanent adverse sequelae; or death. "Minor" adverse events were defined as requiring no therapy, no consequence; or requiring nominal therapy, no consequence (including overnight admission for observation only).

The safety outcomes from the pivotal phase favored the group treated with the Gore TAG device, with a 42% rate of one or more MAEs versus 77% in the control group. Even worst-case estimates that considered all patients with

TABLE 1. PANEL ROSTER

- William H. Maisel, MD, MPH, Brigham & Women's Hospital, Boston, MA (Acting Chairperson)
- Mitchell Krucoff, MD, Duke University Medical Center, Durham, NC
- Sharon-Lise Normand, PhD, Harvard School of Public Health, Boston, MA
- Charles R. Bridges, MD, Pennsylvania Hospital, Philadelphia, PA
- L. Henry Edmunds, Jr, MD, University of Pennsylvania, Philadelphia, PA
- Thomas B. Ferguson, MD, Washington University School of Medicine, St. Louis, MO
- Kenneth W. Johnston, MD, University of Toronto, Toronto, Canada
- Joanne Lindenfeld, MD, University of Colorado Health Sciences Center, Denver, CO
- Norman S. Kato, MD, Cardiac Care Medical Group, Encino, CA
- Gary G. Nicholas, MD, Lehigh Valley Hospital, Allentown, PA
- John C. Somberg, MD, American Institute of Therapeutics, Lake Forest, IL
- Clyde Yancy, MD, University of Texas Southwestern Medical Center, Dallas, TX
- Judah Z. Weinberger, MD, PhD, Columbia University, New York, NY
- Michael Morton, Medtronic, Inc., Cardiac Surgery Group, Fort Worth, TX (Industry Representative)
- Linda Mottle, Peoria, AZ (Consumer Representative)
- Garetta Wood, Rockville, MD (FDA Executive Secretary)

no 12-month follow-up visit favored the study group. Also, whereas four patients suffered paraplegia/paraparesis/spinal neurological deficit in the study group, 13 cases in the control group resulted in this complication.

> ". . . results such as procedural blood loss, length of ICU and hospital stay, and time to return to normal activity all favored the Gore TAG group."

The efficacy endpoint was defined as the proportion of subjects treated with the Gore TAG who were free from a major device-related event through 1 year. Because the efficacy of the Gore TAG was expected to be less than that of surgical repair, the FDA and the sponsor agreed to an analysis plan in which the device would need to show superior safety. Freedom from major device-related events in the study group was 94%. A worst-case analysis of the 10 TAG subjects who had no 1-year follow-up resulted in a freedom-of-event rate of 87%. Secondary endpoint results, such as procedural blood loss, length of ICU and hospital stay, and time to return to normal activity all favored the Gore TAG group. Average ICU stays were 1 day in the study group versus 3 days in the control, and average hospital stays lasted 3 days versus 10 days, respectively.

After enrollment in the pivotal phase, a number of fractures were observed in longitudinal spines designed to provide longitudinal stiffness during deployment. These fractures, which occurred at a rate the FDA reviewers considered relatively high, rarely resulted in adverse events: worldwide, only five of the 44 were associated with endoleak, and one with aneurysm enlargement. As a result, despite producing clinical results that were favorable when compared to the surgical control, Gore decided not to submit a planned PMA to address the fracture issue while maintaining clinical performance.

Engineers from the company made no changes in the fundamental design of the Gore TAG, but the longitudinal spine was removed. To maintain the stiffness provided by the spine, the graft material was strengthened; the wire frame stent was bonded to the graft material in a uniform manner, whereas the previous design had unbonded portions of the wire frame to accommodate the longitudinal spine. Presenters illustrated that the graft material was made axially stiffer and less permeable by replacing several layers of the original reinforcing film with layers of an additional stronger, less-permeable ePTFE/FEP film.

The confirmatory study, designed to determine the safety and efficacy of the modified Gore TAG device, enrolled 51 patients in the study arm and maintained the surgical control group of the pivotal phase. The safety endpoints were similar to those of the pivotal phase, only the evaluations were of 30-day outcomes rather than 1-year. The proportion of patients with one or more MAEs at 30 days was 12% in the study group versus 70% in the control. Two patients had no 30-day follow-up and when factored in a worst-case scenario, the rates were 16% versus 12%. There were no deaths in the study arm, versus 6% in the control; there were also no ruptures in the study arm. Efficacy outcomes included no subjects experiencing one or more major device-related events, and no deployment-related events; six subjects had minor endoleaks. Secondary outcomes also favored the Gore TAG group over the surgical control, with lower incidences of procedural blood loss, shorter ICU and hospital stays, and faster return to normal activity on average. No wire fractures were observed in the modified devices at 30 days.

Based on the results of preclinical bench testing and a review of the subsequent confirmatory phase of the clinical trial, the FDA reviewers determined that the device modifications satisfactorily addressed the device deployability and the short-term risks potentially associated with the design changes. The FDA further concluded that all prespecified safety and effectiveness hypotheses were met. The statistical analyses performed by the FDA review team determined that the Gore TAG and control groups were reasonably matched in both the pivotal and confirmatory studies, with a note that some results were still being evaluated at the time of the panel hearing. The nonrandomization of the two phases was considered to be adequately addressed through appropriate analyses. The safety and effectiveness hypotheses were considered met from a statistical perspective, with the exception that the confirmatory study's effectiveness assessment was limited by the absence of an appropriately defined hypothesis comparing the two Gore TAG groups.

PANEL CONCERNS

Two hours of open committee discussion followed, during which a number of issues with regard to the study design arose, particularly pertaining to the nature of the control groups. Despite the FDA reviewers' statements regarding adequate analysis incorporating the lack of randomization and that AAA devices approved in the US were not evaluated using randomized studies, as well as statements that randomization could likely have been prohibitively difficult due to the profound morbidity and mortality associated with the surgical option and the nature of the disease, several panel members believed this to be a flaw that should have been remedied. Some panel members also argued that the two control groups were not comparable, and further, that the control groups on

the whole may not be comparable to the Gore TAG groups with respect to the timing of treatment and anatomical parameters. FDA and Gore presenters pointed out that the control groups were from the same clinical sites and were selected using the same criteria, and also highlighted the statistical data comparing the control populations that were included in the panel packs.

> "eight [panel members] voted to recommend approval . . . with certain conditions, two voted against approval, and one abstained."

Responses to these concerns were acceptable to some panelists but unsatisfactory to others, who were unwilling to accept what they considered to be significant and fundamental errors in trial design that resulted in an inability to properly evaluate the data presented. Another criticism shared by some panel members was that the relatively large number of composite endpoints was problematic because of the possibility that it could mask the relative importance of each. Several panel members recommended that future trials focus only on those events that are permanent and irreversible.

Many concerns were adequately addressed either by the sponsor or the FDA reviewers. For instance, several panelists also asked for detailed information regarding the device modifications; Ms. Abel expressed confidence in the preclinical testing methods and results and adherence to the new ISO standards regarding device integrity. Louis Smith, an engineer for Gore, also provided in-depth explanations of the modified graft material. One panelist stated that a quality-of-life assessment would have been helpful in analysis, to which the sponsor responded that it was believed the data regarding hospital stays and return to normal activity adequately assessed impact on quality of life. Dr. Makaroun sufficiently explained the system employed to classify adverse events as either major or minor, which was not originally understood by a few of the panel members.

THE VOTE

Of the 11 voting members, eight voted to recommend approval of the Gore TAG Endoprosthesis with certain conditions, two voted against approval, and one abstained. It is difficult to determine which factors most significantly influenced the votes of each panel member, but each person who approached the microphone during the open public session essentially expressed how beneficial an approval of this technology would be for patients suffering from thoracic aneurysms. The physicians' descriptions of performing surgical thoracic procedures clearly illustrated the difficulty involved and the potential for major and minor adverse events both periprocedurally and postprocedurally. Their experiences with endovascular devices such as the Gore TAG, however, were significantly less traumatic to the patient, with higher rates of procedural success and notably shorter recovery times.

Although the panel at times became fixated on what some members believed to be flawed elements in the study design, when it came time for each to vote, it appeared the words of the sponsor and the trial's investigators, the findings of FDA presenters, the first-hand account of Mr. Tinker, and the urging of the independent physicians who traveled to scenic Gaithersburg, Maryland, to plead for the device's approval had left a strong impression. During the time in which the panel members were asked to give their reasons for voting the way they did, the majority of the voting members could not overlook the probability that thoracic endografts would greatly benefit a patient population in dire need of a new treatment option, although not all were wholly convinced. Despite expressing that he indeed wished to one day see such a device available in the US, one of the two panelists who voted against approval did so due to what he considered "thin data" and "a need for much more information." In contrast, a panel member who voted in favor of approval with conditions indicated he did so because common sense outweighs perfect science.

Recommended Conditions

The specific conditions attached to the recommendation for approval as determined by the panel were as follows: First, the company must conduct a postmarket study following the current IDE protocol for a number of patients deemed adequate by the FDA for 5 years. Second, the company must work with the FDA to determine the appropriate training required before an interventionist be permitted to perform procedures using the Gore TAG. Finally, the specific anatomic inclusion and exclusion criteria from the trial should be included in the Instructions for Use.

FDA APPROVAL?

The FDA will now evaluate the information presented, the panel's recommendation, and the validity of the conditions stipulated. When the FDA announces its final decision regarding approval of the Gore TAG Thoracic Endoprosthesis, look for complete coverage in the print and online editions of *Endovascular Today*. ■