Phase I Antibody Risks, Trial Safety Examined

Antibody therapies are the subject of discussion on both sides of the Atlantic this year. Britain and Germany are dealing with the serious fallout of a phase I trial this spring, and U.S. regulatory agencies are working to settle issues of dosing and treatment of antibody therapies in phase I trials.

The phase I trial, using a drug developed by the German company TeGenero AG, is part of a new wave of immune system–altering antibodies being developed to treat cancer and other ailments. More than 20 other antibody therapies have either been approved for use in humans or are in late-stage clinical development, yet many scientists view these new agents as riskier than traditional antibody therapies, which do not bind to immune system targets. Despite their concern, several scientists said the problem in the British trial, which put six people in the hospital, was likely with the TeGenero drug itself rather than antibody therapies as a whole.

But antibody therapy is still under federal scrutiny. Britain has temporarily restricted phase I trials of new antibodies, regardless of their target, as well as other immune system agents.

“I think the TGN outcome has always been a concern for anybody taking a novel therapy into clinical development,” said Stephen M. Kelsey, M.D., senior group medical director of exploratory clinical development for Genentech BioOncology. “If we are prepared to do clinical trials on human beings, then we are going to have to accept that there can always be unexpected safety outcomes, which may occur with varying degrees of frequency and varying degrees of severity. What these guys met, unfortunately, was the perfect storm of very severe and very frequent.”

The British Trial

TeGenero AG, based in Würzburg, Germany, applied for regulatory approval in Britain and Germany to take their monoclonal antibody therapy, TGN1412, into phase I clinical trials. Developed to treat multiple sclerosis, rheumatoid arthritis, and some cancers, TGN1412 was designed to bind to a receptor on the surface of T cells and induce proliferation of regulatory T cells. The company received approval from Britain first and opted to start phase I trials there. On March 13, shortly after receiving the first dose of the drug, each of the six volunteers experienced cytokine release syndrome, which the company describes as “a severe inflammatory reaction with shock-like symptoms.” Cytokine release syndrome is an understood risk with other monoclonal antibodies, but it is usually uncommon and not severe. It is now included in a generic grouping of “infusion reactions”. However, similar side effects have caused fatalities, such as in a small number of patients treated with rituximab, muromonab-CD3, and alemtuzumab.

The British Medicines and Healthcare products Regulatory Agency (MHRA) completed their investigation of the incident in late May and concluded that the severe adverse events were due to an unexpected biological reaction to the drug. They found no abnormalities in the clinical trial procedure or manufacture of the drug.

The British Secretary of Health, who oversees the MHRA, has appointed an expert panel to examine how to improve the safety of “first-in-man” trials that test biological molecules that are likely to work differently in different species or that target the immune system. Until the expert panel has completed its report, the agency has restricted trials of new antibodies by requiring extra reviews for those drugs. A similar restriction has been placed on all new agents that target the immune system.

Genentech’s Kelsey and other researchers interviewed said the TGN1412 scenario probably reflected a problem with the target, the CD28 T-cell receptor, or the Fc portion of the antibody, which can trigger immune responses.

“There are biologics, and there are biologics,” said Gail Eckhardt, M.D., professor of medicine at the University of Colorado Health Sciences Center in Denver, pointing out that some antibodies block a specific receptor, whereas others, like TGN1412, are intended to activate a whole pathway or system.

“Immune responses are some of the most robust responses. So to me, it may be that when you are talking about immunomodulatory agents, that you do need to have certain [stringent] requirements.”

Eckhardt, who has run many phase I trials with both small-molecule and antibody therapies, said she hopes regulators don’t go too far.

“Going forward, you would hate to say all of the sudden, ‘We are going to clamp down on all antibodies,’ because I think there is a distinct difference between immunomodulation and antibodies that are essentially just another method for targeting a growth factor receptor.”

Antibodies and Oncology

Despite the current issues surrounding antibody therapies, these drugs are not new. In 1986, muromonab (Orthoclone OKT3) became the first monoclonal antibody therapy approved by the FDA, and in 1997, rituximab (Rituxan) became the first anticancer antibody to receive approval. Although many of these drugs have had problems—including cytokine release syndrome and reactions because the drugs were made of mouse sequences—most of the side effects can be controlled by changing the dose, slowing the infusion rate of the drug, or creating humanized antibodies. Now many of the new targeted therapies are antibodies, including cetuximab (Erbitux), bevacizumab (Avastin), trastuzumab (Herceptin), ibritumomab tiuxetan (Zevalin), and panitumumab.

Most of the oncology antibodies currently in development are designed to inhibit a process rather than stimulate it,
and that might be less risky than drugs that alter the body’s immune response. But even inhibitory drugs can cause problems that weren’t predicted in preclinical tests, Kelsey said. As an example, he points to the high blood pressure that some patients develop in response to bevacizumab.

As oncology researchers look for new ways to harness the immune system against cancer, the risk of serious complications may increase. For example, antibodies against the T-cell receptor CTLA-4 reverses immune system suppression caused by the cancer, but it also induces an autoimmune response in some patients. That tradeoff has to be carefully balanced, but the benefits may outweigh the risk.

“There are a number of novel agents that have been taken into the clinical trials or are being prepared for clinical trials that activate the immune system,” Kelsey said. “If [anti-CTLA4 antibodies] are a precedent, then we are likely to see more immune activators going into patients with cancer with the assumption that there will be clinical benefit.”

Without more information about what went wrong in the TGN1412 trial, many researchers hesitate to jump to any hard-and-fast conclusions. “It is hard to say what we should do differently,” said Helen Chen, M.D., senior investigator in the investigational drug branch of the Center of the Cancer Therapy Evaluation Program at NCI. “I think we will be more careful when dealing with new agents that regulate—particularly, stimulate—the immune response. But I don’t think we will do things differently for other antibodies, because we have so much experience with antibodies.”

**FDA Addresses Phase I Antibodies**

While the British government has been dealing with the fallout from the TGN1412 trial, U.S. regulators at the FDA’s Center for Drug Evaluation and Research (CDER) have been struggling with their own issues surrounding potential toxic effects in phase I antibody trials. Specifically, the agency asked an Oncologic Drug Advisory Committee (ODAC) panel to indicate whether advanced can-

cer patients who enroll in a phase I trial of antibody therapies can continue their treatment until their disease progresses or they have excessive toxicity.

Standard phase I trial design allows patients who respond to an investigational therapy to remain on the drug until their disease progresses. “The ethical thing has always been that we will continue to treat those patients until they have unacceptable toxicity or progression of their disease,” Eckhardt said.

But antibodies behave differently. Whereas the half-life of small molecules is on the order of hours, monoclonal antibodies have a half-life of approximately 3 weeks. That means one dose can hang around in a patient for months, so giving multiple doses can lead to cumulative toxicity. That possibility has led some researchers and regulators to alter their antibody trials so that patients are allowed only one or two doses, but other doctors have stuck to the traditionally accepted approach.

The FDA presented data during the ODAC meeting showing that cumulative toxic effects have been found in preclinical trials comparing antibodies to growth factor receptors. (The details regarding which antibody and which target were involved were not disclosed because the data are from investigational new drug applications.)

Anne M. Pilaro, Ph.D., a CDER toxicologist who presented several case studies on behalf of the FDA, said that 13 weeks of toxicity data should be enough to uncover these cumulative toxic effects and show that people could take the drug over long periods of time.

After hearing the evidence, the ODAC members eventually recommended that patients in a phase I trial
who were benefiting from the investigational antibody therapies—either with tumor shrinkage or stable disease as assessed by the treating physician—should be allowed to continue taking it, even if that meant that they were exposed to larger cumulative doses than had been used in preclinical studies. Also, the panel voted against requiring 13 weeks of preclinical toxicity data to prevent toxic doses before antibodies could enter phase I trials. Several committee members said that they felt this measure would have caused undue delay in bringing agents into clinical trials.

“This should settle the issue,” said Richard Pazdur, director of FDA’s Office of Oncology Drug Products in CDER. On the basis of the ODAC recommendation, phase I antibody trial design should be consistent on this point.

With that issue settled on this side of the Atlantic, researchers have to wait and see what the expert panel will find with regard to the TeGenero trial. Once those data are in, British regulators will look closely and decide what changes, if any, need to be made. And other governments might follow suit.

—Rabiya S. Tuma