Anti-TNF, Birth Defect Link Debate Continues

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Data from a Food and Drug Administration registry suggesting an increase in birth defects among women treated with etanercept and infliximab have rekindled controversy over use of tumor necrosis factor blockers in pregnancy.

However, conflicting preliminary data from an ongoing study by the Organization of Teratology Information Specialists (OTIS) argue that anti–tumor necrosis factor agents are safe for this population.

Dr. Christina Chambers, a coinvestigator on the OTIS study, said it was alarmist to recommend avoiding anti-TNF agents in pregnancy, and said that reviews of the FDA adverse events database are "inherently biased." Based on her group's results, she said, "We're not able to draw any conclusions that suggest that we are seeing any specific pattern of defects, whether major or minor, based on the children that have been evaluated so far."

Dr. John J. Cush, who is not involved with either of these studies, said in an interview that "the FDA database serves an important role." However, he agreed that the database has incomplete and biased data.

"There is no reason or convincing data to emphatically deny effective anti-TNF therapy to patients who need it to control their disease, either before or during pregnancy," he said.

Neither the American College of Rheumatology nor the European League Against Rheumatism have any guidelines concerning treatment during pregnancy, added Dr. Cush, director of the clinical rheumatology program at Baylor Research Institute in Dallas.

The review of the FDA adverse events database, led by Dr. John D. Carter, involved more than 120,000 adverse events for all entries between 1999 and 2005. A total of 41 children with 61 congenital anomalies born to 40 different mothers who were taking a TNF antagonist during pregnancy were recorded (J. Rheumatol. 2008 Dec. 15 [doi:10.3899/jrheum.080545]).

Overall, 22 of these mothers took etanercept at some point in pregnancy; 19 took infliximab. "In all 41 cases, the TNF-α antagonist was considered the 'primary suspect' as the cause of the birth defect," wrote Dr. Carter of the division of rheumatology at the University of South Florida, Tampa.

Ongoing studies do not indicate any pattern of birth defects, but a recent FDA database review cites 41 children with congenital anomalies born to mothers taking anti-TNFs.

A total of 34 different types of birth defects were seen, 19 of which were part of the VACTERL spectrum (vertebral abnormalities, anal atresia, cardiac defect, tracheoesophageal, renal, and limb abnormalities). "Since congenital anomalies are present in 3%-5% of all live births, and VACTERL occurs in 1.6/10,000 live births, you would expect to see [about] 1.6 cases of VACTERL association in every 300-500 children born with congenital anomalies," wrote the authors. "We have now seen 2/42 (4.8%) cases of VACTERL" (including 1 case outside of the study period).

In an interview, Dr. Chambers took issue with the VACTERL findings, noting that to include a case as part of the VACTERL spectrum they must exhibit at least three of the seven defects in the spectrum—not just one. And though the authors emphasize that 24 of 41 children (59%) "had one or more congenital anomalies that are part of VACTERL," only 1 was diagnosed with the pattern of associated birth defects within the original study period, said Dr. Chambers.

Dr. Cush pointed out that there are currently no studies that address the potential effects of stopping anti-TNF therapy before pregnancy, though it could be hazardous. Furthermore, the lack of alternative therapies that approximate the effect of anti-TNFs on disease means that clinicians may have to lean on palliative agents such as prednisone and NSAIDs, "both of which also pose potential harms to mother and child."

Dr. Carter did not declare any conflicts of interest. Dr. Chambers said she did not have any personal conflicts, but OTIS receives grant funding from nine drug companies, two of which make anti-TNFs. Dr. Cush has served as a consultant or adviser to, or received grant money from, multiple drug companies, including the makers of anti-TNFs. ■

Both Specialties Can Benefit

Collaboration *from page 1*

ing their rheumatology colleagues. But there are not enough medical dermatologists in academia now. There are not enough of them in private practice."

She added that residencies and fellowships in both specialties are poorly funded by most hospitals because dermatologists and rheumatologists "don't fill hospital beds, and hospitals still view their sweet spot as filling as many hospital beds as possible. Therefore, when hospitals secure Part A Medicare funding, they'd rather pay for a cardiology fellow than a rheumatology fellow or a dermatology resident."

Parallel Specialists

Dr. Daniel E. Furst, professor of rheumatology at the David Geffen School of Medicine at the University of California, Los Angeles, also rates the current state of collaboration between specialties as poor. "Principally, it's a matter of poor communication," he said. "This includes the effect of geographic distances between offices, so colleagues really aren't close enough together so they can talk regularly and easily."

One way to optimize collaboration, he said, is to seek out parallel specialists with similar interests and be proactive in communication with them, regardless of your practice setting. "For example, I'm very interested in scleroderma but not that interested in psoriasis," Dr. Furst said. "I don't know which dermatologists in my area have those same interests. The solution might be some sort of common electronic database in which I list the things I'm interested in and they do the same. In a simple manner, we can then look for those who have common interests so we can communicate and work together. We'd also be able to send medical records and dictated notes back and forth (assuming HIPAA compliance). That's going to be very important."

Current medical record systems "have problems on that front," he said. "They'll straighten out, but we're not there yet."

Dr. Eichenfield takes an old-fashioned approach to establishing a line of communication with rheumatologists and other parallel specialists. He picks up the telephone and talks to them, a strategy he described as "highly effective for communicating information and for establishing a rapport with the physician. A consequence of that is an establishment of respect for the other physician's expertise in the topic area."

He went on to note that while it's easy to see a patient, master the information in your area of expertise, and dictate a letter to the parallel specialist relating the care you provided, "you're not going to get the exchange of information in the same way as if you pick up the phone and speak to the physician. You have tremendous gains beyond transfer of the medical evaluation and management suggestions. You establish a personal relationship with that physician and you end up hearing the thought process behind the evaluation and decision making of the other individual."

Another way to form collaborations with other specialists, he said, is to listen to patients and their families about their experiences with other physicians, as they often do much of their own "grunt work" searching for a team of care experts. "Many times they can tell you who they found who has the most interest," said Dr. Eichenfield, who also directs the eczema center at Rady Children's Hospital.

Once a dermatologist and rheumatologist establish a working relationship and begin to share patients, the strengths of both disciplines "reinforce the positive relationship between the doctors," he explained.

"Rheumatologists come to want to use the dermatologists for their diagnostic capabilities. Many times the dermatologists want to use the rheumatologists for their knowledge of systemic disease agents and for their ability to do careful systemic evaluations of diseases that present in the skin."

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He credits such partnerships with advancing the understanding and treatment of rare but serious conditions such as localized scleroderma/morphea on an international level. "We are better physicians as a direct result of collaboration," he said.

One of the missions of the Group for Assessment of Psoriasis and Psoriatic Arthritis (GRAPPA) is to foster communication between rheumatologists, dermatologists, and others who are interested in advancing care of patients with psoriasis and psoriatic arthritis. In its founding year of 2003, the group consisted of roughly 60% rheumatologists and 40% dermatologists. Today, the breakdown of its 200-plus members is more like 52% and 48%, respectively, said cofounder Philip J. Mease, a rheumatologist who practices in Seattle.

Research Partnering

One achievement has been the formation of committees composed of dermatologists and rheumatologists who carry out research projects in basic science, screening, outcome measures, and treatment.

For example, one project of the screening committee is to "develop simple screening tools that can be used, say, in the dermatology office, for recognizing when psoriatic arthritis is present, or distinguishing it from arthritis or rheumatoid arthritis, so that appropriate treatment can be initiated, either in the dermatology office or via triage to a rheumatology office," Dr. Mease explained. Researchers in Toronto, Canada, Boston, and Leeds, England, "have developed the screening tools. Through the auspices of GRAPPA, each of these tools is being tested and validated."

GRAPPA also published treatment recommendations for PsA (Ann. Rheum. Dis. 2008 Oct. 24 [doi:10.1136/ard.2008.094946]) and launched a mentorship program whereby dermatologists and rheumatologists "mentor fellows who do research projects that bridge between psoriasis and psoriatic arthritis, and present their work at our annual meeting," said Dr. Mease, GRAPPA's treasurer.

"I come back from a background of desire for collaboration between entities. It's Obama-esque. It's always been a big emphasis of mine to help foster this kind of relationship." ■

View a video interview of Dr. Furst at http://www.youtube.com/watch?v=FiwLg9xCYfc.