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The Role of TNF Inhibitors in Autoimmune Diseases: A Women's Health Perspective

Considerations for Management and Therapeutic Selection for Patients Who Are Pregnant or May Become Pregnant

Autoimmune diseases are chronic conditions that present unique challenges regarding management, particularly in patients who are pregnant or may become pregnant. Over the last several decades, the treatment spectrum for autoimmune diseases has expanded significantly, with the addition of tumor necrosis factor (TNF) inhibitors. This article provides a summary of key points regarding TNF inhibitor use and safety, including in patients who are pregnant, based on recent Insights video interviews with Marla C. Dubinsky, MD; and Megan E.B. Clowse, MD, MPH. To watch the full interviews, visit ajmc.com/insights.

CLINICAL BACKGROUND ON AUTOIMMUNE DISEASES

Although some gains have been in the understanding of autoimmune diseases, the etiology and chronic nature of these conditions remain poorly grasped. According to Dubinsky, autoimmune diseases appear to arise from a combination of genetic susceptibility and environmental factors. "It is an abnormal immune reaction to what we believe is our own gut flora [in genetically susceptible hosts]," she said. "We believe that there is an environmental trigger that somehow changes the way that our genes view our host bacteria." Certain autoimmune conditions are associated with hundreds of genes, according to Dubinsky, which, combined with the fact that we have trillions of bacteria, means that isolating environmental factors to find a cure for these diseases is difficult.

Types of Autoimmune Diseases

Inflammatory Bowel Disease. Among the categories of autoimmune diseases, inflammatory bowel disease (IBD) is among the most prominent. "IBD encompasses or is an umbrella term for 2 specific disease states: ulcerative colitis and Crohn disease," Dubinsky said. She added that there are multiple types of Crohn disease. "[Research has] evolved to show that Crohn disease can actually occur anywhere, from the mouth to the anal canal; what's different versus ulcerative colitis is that ulcerative colitis

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(UC) is restricted to the colon,” she noted. “These 2 historically distinct subtypes are probably closer than we thought, especially in the fact that there’s a group of patients with Crohn disease who have disease isolated to the colon.” Dubinsky further noted that a difference between Crohn disease and UC is that the former affects all 4 walls of the bowel, while UC affects only the inner lining, called the mucosa.

The impact of IBD on quality of life is significant, according to Dubinsky. “Colon inflammation really affects someone’s life, because often they’re in the bathroom in the morning, it’s hard to get out of the house because they may run to the restroom, think that they’re finished, stand back up and have the sense that you have to still go,” she described. One factor affecting the quality of life for patients with Crohn disease is that it is a peritoneal disease, which, according to Dubinsky, differentiates it from UC. Peritoneal diseases are characterized by perianal fistulas, abscesses, ulcerations, and fissures, which often require surgery for drainage.

Inflammatory Arthritis. Another significant category of autoimmune disease is inflammatory arthritis, according to Clowse. “The most common form is rheumatoid arthritis (RA), but psoriatic arthritis is an arthritis that comes with psoriasis and ankylosing spondylitis, which is an inflammatory arthritis of the spine, and can also be found in quite a few people,” observed Clowse.

Comorbid Conditions and Quality of Life

Patients with autoimmune diseases, such as RA, often have comorbid conditions that can complicate treatment. “All of our patients are at high risk of having comorbid conditions when they have inflammatory arthritis,” Clowse noted. “We see diabetes and high blood pressure in our patients with autoimmune disease, and these patients are at higher risk of having heart disease, strokes, and myocardial infarctions later in life.” Several other patterns have emerged in patients with autoimmune diseases that would suggest that the impact of these conditions stretch well beyond clinical symptoms. “Women who have RA actually tend to have fewer children than women who don’t have RA,” Clowse explained. “Some of that is by choice, but a lot of that actually seems to be driven by the fact that they just have a hard time actually getting pregnant.”

Other factors related to autoimmune diseases, such as treatment, may have an impact on quality of life, as well. “It can be hard if [a patient is] taking a lot of prednisone, which causes weight gain, so working hard to maintain a healthy weight is important. Increasing exercise is also really important to keep

[the] heart and bones healthy,” Clowse said. This can also be particularly challenging for those with inflammatory arthritis. “It’s not that you want to just go out and exercise every day; it’s really about finding exercises that work for you, that work with your body, that can be adapted to your lifestyle,” she added.

TREATMENT CONSIDERATIONS AND THE UTILITY OF BIOLOGIC THERAPIES

Autoimmune diseases are chronic conditions that present several challenges regarding management, according to Clowse. “We don’t have a medicine that we can give you that will just make the disease go away and stay away forever,” she said. Instead, Clowse noted, most available medications manage symptoms. Nevertheless, research has also focused on identifying agents that address the underlying disease. “All of our data that have been collected over the years have really been driven by medications, so that’s what we know the most about: which medications can control inflammation, which are best at it, which work best for different diagnoses, how long to use them, et cetera,” she said.

Nonbiologic Therapies

For IBD, Dubinsky groups treatments into biologic and nonbiologic categories. Agents included in the latter category include fast-acting corticosteroids, which are particularly useful for UC, given the urgency to control symptoms. “Especially [for patients who are hospitalized], intravenous steroids are sometimes the only [agents] that can control symptoms when someone’s going to the restroom every half an hour or is up all night because they’re having constant spasm of their rectum giving them urgency,” she said.

The drawback of steroids are adverse effects, according to Dubinsky. “Steroids do not go after the biologic [roots] of the disease; they are [like] Band-Aiding the inflammation,” noted Dubinsky, who characterized mesalamine-based products similarly. Mesalamines are not approved for Crohn disease and yet, according to Dubinsky, they are still often used as first-line agents, which she believes is “unacceptable.”

Safety has been an obstacle for certain immunomodulators in general, according to Dubinsky. “Particularly in people above the age of 60 or 65, an increased risk of lymphoma has been shown with use of immunomodulators,” said Dubinsky, who noted that young people may also have increased safety risks. “These thiopurines are associated with an increased risk of lymphoma in [individuals] under 25, especially males,” she said.

Biologics

In the biologic category, TNF inhibitors are the most prominent agents. “TNF inhibitors are a class of medications that have now been on the market for 20 years and have really revolutionized the management of inflammatory arthritis,” noted Clowse. Typically administered as an injection or infusion, TNF inhibitors work in a very unusual way, she said. “We don’t really understand why some people respond [to TNF inhibitors] and why others don’t, but I think of them, from an effectiveness standpoint, as fairly interchangeable,” Clowse explained. “When you look at the drug trials that have been done, all of them are shown in a similar range to get people into decreased disease activity and into remission.”

Over the past 2 decades, the expanding spectrum of biologics has changed the course of treatment of autoimmune diseases, noted Dubinsky. “[Since] infliximab [became] the first TNF inhibitor approved for Crohn disease, we had it approved for UC in 2005, then we had adalimumab approved for Crohn in 2007,” she observed. Approvals of adalimumab and certolizumab for both Crohn disease and UC followed later, Dubinsky continued. “And then we moved in 2014 to a very exciting space, which was the antitrafficking biologics, or monoclonal antibodies, and that’s vedolizumab. And then in 2016 we had ustekinumab, which is another cytokine target that goes after the IL-12 and IL-23 pathways,” Dubinsky said. More recently, a small oral molecule known as tofacitinib, approved for RA in 2012, was granted approval for UC.

Delivery mechanism is an important consideration regarding treatment selection. According to Dubinsky, infliximab has an advantage over other agents because its safety and efficacy profile is better defined. “The intravenous administration of infliximab has become the gold standard, because of its weight base, because we understand the pharmacokinetics, because it’s been out for 20 years, and because we have a lot of dosing flexibility,” she noted. For these reasons, many physicians have confidence in dosing strategies for infliximab, Dubinsky explained.

Patient preference is another factor that comes into play, according to Dubinsky, as some patients prefer to avoid injections. “Convenience, we know, is probably number 1 for our patients,” Dubinsky noted. Often, decisions are made based on patient lifestyle and age as well, she continued. Nevertheless, disease severity and safety may represent the deciding factors in treatment selection, observed Clowse. “All TNF inhibitors really show the same risk profile for patients outside of pregnancy,” she said. “The main thing we all worry about is that taking a TNF inhibitor will reignite a tuberculosis infection. Doctors will always give you a tuberculosis test prior to giving you one of these drugs because it’s a specific infection that can be reignited in your body when you take these medications.”

“One other thing that people often will call about is that they got an injection site reaction,” said Clowse. “It’s very common, but certainly not all patients get it. When patients give themselves an injection of a TNF inhibitor, sometimes they get a red welt in the area that’s 1, 2, or 3 inches in diameter.” Other adverse effects happen very occasionally. But, according to Clowse, arguably the greatest upside “is that the data really support that TNF inhibitors do not increase the risk of cancer.”

PREGNANCY AND AUTOIMMUNE DISEASE

Certain autoimmune diseases, such as IBD, have been shown to be more common in women—particularly women of childbearing potential.

This can complicate treatment, according to Dubinsky. “When managing a patient who wants to get pregnant or will be getting pregnant or is pregnant—so she is in the preconception, pregnancy, or even the postpartum phase—[understanding] the role of inflammation and their underlying immune disease is paramount,” Dubinsky noted.

For patients with inflammatory arthritis, there is some risk of pregnancy complications, according to Clowse. “The key ones we see,” she said, “are preterm delivery, as well as babies being born a bit smaller than you would expect them to be—what we call small for gestational age.” She noted further that preterm delivery in patients with inflammatory arthritis seem to be particularly associated with cases when the disease is active in pregnancy. Those with controlled disease during pregnancy go to term more often. “Patients who are not taking medications during pregnancy if their arthritis

is active, or those whose arthritis is bad and we just can’t get it under control with pregnancy-safe medicines, tend to be the people who have more preterm deliveries,” said Clowse.

Infertility

Infertility has also been linked to autoimmune disease. According to Clowse, data over several decades have shown that women with RA appear to have a high risk of infertility. “Going back to data from the 1960s, it appears that women who had RA, had fewer children than their neighbors,” Clowse said. “We’ve done studies more recently that have shown similar information—that women with RA appear to have more difficulty getting pregnant, particularly women who are diagnosed at a younger age. For patients who are diagnosed before having children, we tend to see pretty high rates of infertility. In some studies, up to 30% to 40% of patients will have a hard time getting pregnant,” Clowse explained. Fortunately, she continued, “most women will succeed in getting pregnant, but a lot of them will actually need fertility treatment in order to achieve a pregnancy.” In patients with RA, Clowse observed that nonsteroidal antiinflammatory drugs (NSAIDs) at multiple doses per week appear to make it difficult to get pregnant. “We think it actually might be changing the way that a woman is ovulating, to some extent,” she noted.

One approach to avoid issues with fertility, according to Clowse, is to control disease activity with pregnancy-compatible medications. “We don’t let people flare ahead of time if possible. We try to avoid prednisone if we can help it [and] we also try to avoid NSAIDs, keeping women comfortable by decreasing inflammation with other drugs,” Clowse observed.

Managing Risks During Pregnancy

For patients with inflammatory arthritis who are considering pregnancy, Clowse recommends weighing disease activity and severity

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before deciding on a new treatment course. “We first take a look at how active her disease is, then we take a look at her medications, [and] then we take a look at the rest of her comorbid conditions,” Clowse said. The goal for management should be to improve or at least maintain a good level of control of the disease. “[We should] ensure that women do not live with high levels of pain and ongoing inflammation, which in particular, can cause joint destruction and long-term disability.”

During pregnancy, management of inflammation is essential, particularly in patients with IBD, noted Dubinsky. “Inflammation has been shown to impact cognitive and emotional behavior in children born to mothers with active inflammation,” she said. “We do explain to our female patients that [managing] inflammation is very important in the first trimester, because we want to minimize the risk of losing a baby,” Dubinsky observed.

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Also, another necessary focus in that first trimester is on how medications could impact the risk of congenital malformation. The fetus has undergone a great deal of development “within the first 10 weeks, so often by the time the [mother] comes to us reporting pregnancy, the baby has been exposed to the medications they were on,” she said.

The approach to treatment tends to evolve in the second trimester of the pregnancy, during which Dubinsky allows for controlled inflammation. “The baby needs to grow quite significantly, from brain growth and neurodevelopment growth [to its overall] size, [and we also] do not want a preterm delivery,” Dubinsky pointed out.

When the third trimester arrives, the good news, Dubinsky said, is that a lot of women feel very good due to a hormonal influence. “As you get further on into pregnancy, progesterone becomes a predominant hormone and it tends to have a nice effect on how our female patients feel,” she explained. Patients may begin asking if they can stop their medication.

Among pregnancy-compatible medication for women with RA or another inflammatory arthritis is hydroxychloroquine. “It’s been around for decades and has been shown to be very safe in pregnancy, with no known complications for the developing fetus,” Clowse explained. Another drug safe in pregnancy is sulfasalazine, which has been available for several decades but is not used often in inflammatory arthritis.

One agent patients with autoimmune disease must avoid during pregnancy is methotrexate. “It’s important to know that there is a much higher rate of pregnancy loss—about 40%—and a higher rate of the baby having a birth defect for patients on methotrexate,” Clowse explained. She noted that sulfasalazine can be a good substitution for patients on methotrexate who become pregnant.

In general, Clowse recommends that patients and physicians take every precaution necessary when managing inflammatory arthritis during pregnancy. “I really strongly recommend not using medications

that don’t have any kind of pregnancy safety data in women who are either considering getting pregnant right now or are not using birth control,” she stated.

The Use of TNF Inhibitors in Pregnancy

Clowse noted that available data suggest that TNF inhibitors are relatively safe in pregnancy. “No data really suggest that any of [these agents] is unsafe in pregnancy,” she said. Late in pregnancy, there is some question as to whether TNF inhibitors should be continued, because the risk of the drug crossing into the placenta increases, Dubinsky noted. “We started to explore that a little more and it ended up that if you gave the last infliximab infusion before week 30, it had the lowest rate of placental transfer and the baby had the lowest measurement of core blood level of infliximab,” said Dubinsky.

The lone TNF inhibitor that has been shown not to cross the placenta is certolizumab, noted Dubinsky. “Certolizumab is pegylated and it doesn’t have that Fc receptor that binds to the placenta for the transfer,” she explained. Because certolizumab’s structure differs from that of other TNF inhibitors, Clowse is comfortable with patients taking it through delivery. “I often actually have them skip the week of delivery, just because of infection risk, but they can really take it,” Clowse observed. “It won’t harm their baby to take the certolizumab throughout delivery and just keep taking it through lactation and breastfeeding.” Clowse generally stops other TNF inhibitors approximately 2 months before delivery, to allow time for the drug to get out of the mother’s and baby’s system. “When the baby is born, it might have a smidgeon of drug, but it won’t have any kind of level of drug that would make us really worry about the risk for infection,” Clowse noted.

There is no clear agreed-upon guideline as to exactly when to stop each TNF inhibitor, according to Clowse. “I personally pick somewhere between 30 and 34 weeks for most of them. I also negotiate that a little bit with the woman, based on how her arthritis is doing,” she noted. “We know that women who are on TNF inhibitors before and during pregnancy, if they don’t start a TNF inhibitor after delivery, they will most likely flare,” said Clowse. “I start people back on to their TNF inhibitor 1 or 2 weeks after delivery, and they can take it while breastfeeding, without difficulty,” she noted. “That really avoids the postpartum flare quite effectively.”

Regarding newer biologics, such as interleukin inhibitors, Clowse generally does not consider using these agents during pregnancy because of the limited available data. “We are still waiting for any kind of data that help us understand the safety of any of the newer biologics and, particularly, any of the newer small molecule drugs that are on the market,” Clowse added.

CONCLUSIONS

Despite the challenges of managing autoimmune diseases in patients who are pregnant or may become pregnant, TNF inhibitors represent a viable treatment option for many patients, when used appropriately. To gain more insights on the use of TNF inhibitors for autoimmune diseases, visit www.ajmc.com/insights. ■