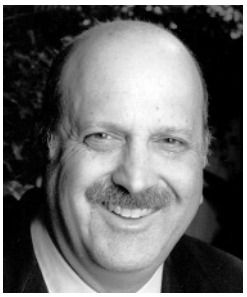
Editorial

The Use of Etanercept and Other Tumor Necrosis Factor-α Blockers in Infertility: It's Time to Get Serious




A 37-year-old white, otherwise healthy asymptomatic female corporate attorney was referred to our center by her gynecologist for consideration of etanercept therapy after the patient viewed reproductive immunology websites. Her history included a voluntary abortion at age 16 and chronic leukopenia attributed to the Epstein-Barr virus. In 1999, she underwent 4 *in vitro* fertilizations that resulted in a single, transient chemical pregnancy. Her gynecologist subsequently prescribed prednisone and low molecular weight heparin to treat the incidental finding of antiphospholipid antibodies and elevated NK cell concentrations (e.g., CD56+CD3–percentages were as high as 37.6%, with normal ranges 5–28%). When first presenting January 17, 2000, her vital signs and examination were normal. Antinuclear antibody, anti-Sm, anti-RNP, anti-DNA, C3 and C4 complement components, blood chemistry panel, rheumatoid factor, sedimentation rate, urinalysis, chest radiograph, electrocardiogram, C-reactive protein, and $ß_2$-glycoprotein were negative or normal. However, she had a positive antichromatin antibody, and anticardiolipin antibodies to isotypes IgG and IgM were positive at 25 and 38, respectively (normal < 25) at Rheumatology Diagnostics Laboratory. On May 11, 2000, she prevailed upon her gynecologist to prescribe etanercept, 25 mg biw. One month later she became pregnant. She was also treated with 81 mg aspirin daily and low molecular weight heparin (Lovenox, 30 mg daily SC). Her serologies remained unchanged during the pregnancy and NK cell levels fell to as low as 5%. Etanercept, aspirin, and heparin were discontinued at week 32. On February 19, 2001, she delivered a healthy 5 pound, 7 ounce baby boy, and mother and child remain asymptomatic as of November 2002.

Websites maintained by Dr. Alan Beer at the Chicago Medical School Reproductive Medical Program and his collaborators (http://repro-med.net/guides/enbreluse.html; http://www.repro-med.net/info/scholars.html; http://www.riala.com/pages/ria3.html) relate that etanercept "is used with reproductive immunology patients who have been found to have evidence of active NK (natural killer) cells residing in their uterine lining...Active NK cells in their uterine lining that are secreting TNF are prone to a disordered lining development...TNF produced by the NK cells of the uterus damages the DNA of the blood vessels in...the endometrium...and damages the DNA in the embryo and it fails to grow, divide and implant...Enbrel is prescribed to neutralize TNF...used for a minimum of 30 days before trying a cycle of conception... usually taken until the patient is pregnant...and until the NK assay is 50:1 or less and the NK cell numbers are 12% or below."

It is impossible to know whether or not entanercept played a role in allowing our patient's successful pregnancy; she was also prescribed heparin and asprin at the same time. Over the last few years, patients have consulted reproductive immunologists regarding the use of etanercept (Enbrel) to manage infertility, and many of these patients approach rheumatologists for their opinion. Where should a rheumatologist turn for information? The Food and Drug Administration has classified etanercept as Category B in pregnancy because there is no experience of the drug's use in this circumstance (package insert). A single case report of a patient with rheumatoid arthritis who had a successful pregnancy while taking etanercept has been published[1]. When we contacted the manufacturer of Enbrel, no additional information could be provided.

The employment of pharmacologic interventions commonly used by rheumatologists (such as corticosteroids, anticoagulants, aspirin, and intravenous gamma globulin) by non-internists who manage infertility has raised concerns about risks and benefits as well as proper informed consent[2]. The use of immune therapies to treat conditions that have been termed "subclinical autoimmunity" in healthy, asymptomatic women who have fertility problems is controversial at best. As far as we are able to determine, there are no recognized standards or board certifications that must be met or obtained for a physician to call him/herself a reproductive immunologist. How does one gauge the risk–benefit ratio in these situations and how does a rheumatologist advise his or her patient? It is conceivable (to use an appropriate term) that women or couples will often take uncertain clinical risks to fulfill a biologic prerogative; the out-of-pocket cost of etanercept most definitely needs to be taken into consideration as well. These phenomena lend a sense of urgency in the office situation when there is no option of a scientifically accepted, controlled trial of an immune

therapy to fall back upon for information to advise the patient.

There has been a surge of interest among fertility investigators relating to tumor necrosis factor (TNF)-α and pregnancy. Increased production of TNF-α has been associated with recurrent spontaneous abortions, platelet activation in early pregnancy, preeclampsia, and infertility relating to endometriosis[3–6]. Huizinga's group has recently related low TNF-α responsiveness to normal fecunditiy[7]. The rationale for using etanercept in the websites, e.g., its lowering of NK cell levels, is highly speculative and not proven. There is no generally accepted scientific evidence that elevated NK cell levels in the bloodstream cause miscarriages or that etanercept prevents miscarriages by lowering these levels. For example, Beer's group suggested that patients who miscarry have higher mean NK levels[8,9], a finding independently confirmed by Matsubayashi, *et al* [10]. However, Morikawa, *et al* reported that "peripheral NK cell activity or subsets...were not related to the cause or number of previous spontaneous abortions," a finding also confirmed by Michimata, *et al*[11,12].

It has been recognized since the early 1980s that antiphospholipid antibodies were associated with spontaneous miscarriages in patients with rheumatic disease. A large gamut of interventions including corticosteroids, antimalarials, aspirin, heparin, and intravenous immune globulin has been studied in a variety of clinical trials and circumstances[2]. Numerous etiologies, including abnormalities in the endothelium, coagulation cascade, and platelet activation, have been postulated to be pathogenetic[13,14]. The rheumatology community has led the way in clinical research into mechanisms of disease pathogenesis as well as new interventions. For example, Salmon, *et al* have shown that complement activation may play a critical role as a mediator in antiphospholipid induced pregnancy loss and thrombosis, and La Jolla Pharmaceuticals has completed a Phase 1 trial with a monoclonal antibody to an epitope of $ß_2$-glycoprotein[15,16].

Etanercept, infliximab, and adalimumab very likely could have profound effects upon the immune system that might present special pregnancy concerns, such as susceptibility to specific infections or unwanted influences upon development of the fetal immune system. The possibilities of how cytokine manipulation may affect an unborn child and her mother have not been adequately explored. Rheumatologists who manage patients with rheumatoid arthritis should be in a unique position to take the cautious high road because of their comfort (or discomfort) level as they approach TNF-α blockers or even any other cytokine treatment. Further, it is important for all practitioners to be aware of the risks to vulnerable families in giving advice that is not based on solid studies or even good evidence. There are a few websites where infertility patients can obtain unbiased, reliable information, including those of the National Infertility Association (www.resolve.org). We urge reproductive immunologists to record their experiences with innovative therapies, obtain informed consent, work with an institutional review board, and preferably use these interventions only in the context of a controlled, medical trial.

There is more than enough rationale for studying TNF-α blockers in reproductive immunology applications. Hopefully the pharmaceutical companies will see it in their interest to prospectively evaluate their products in reproductive settings before a large experience of unusable, anecdotal data is accumulated.

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