Fertility and Reproduction in Male Patients with Ankylosing Spondylitis Treated with Infliximab

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ABSTRACT. Objective. To identify male patients who were treated with infliximab and had fathered healthy newborns during their management.

Methods. We reviewed medical records of men with ankylosing spondylitis (AS) who were followed up at the Rheumatology Outpatients clinic and were treated with infliximab during the period 2001-2007.

Results. We identified 4 patients with AS who had fathered 6 healthy children during infliximab treatment. One patient was also treated with small doses of methotrexate.

Conclusion. Limited data are available concerning the effects of infliximab on semen quality. Our cases provide some evidence or reassurance for male patients treated with the anti-tumor necrosis factor-α agent. Further prospective studies are necessary, however, to guide clinicians in decision-making. (First Release Dec 1 2008; J Rheumatol 2009;36:351–4; doi:10.3899/jrheum.080554)

Key Indexing Terms:
ANTI-TUMOR NECROSIS FACTOR-α AGENTS
INFLIXIMAB
MALE FERTILITY

Anti-tumor necrosis factor-α (TNF-α) agents are currently used in the treatment of rheumatoid arthritis (RA), psoriatic arthritis (PsA), ankylosing spondylitis (AS), psoriasis, and Crohn’s disease1-4. There is still insufficient evidence related to the risks associated with the use of anti-TNF-α agents in pregnancy. Infliximab, adalimumab, and etanercept belong to category B of the US Food and Drug Administration (FDA) classification. Category B means no evidence of risk in humans. However, 3 cases of VACTERL syndrome (vertebral abnormalities, anal atresia, cardiac defect, tracheoesophageal, renal, and limb abnormalities) have been reported, one with etanercept use5 and 2 with infliximab6. Thus, anti-TNF-α agents should be avoided in pregnancy whenever possible4. The role of TNF in the male gonad has been investigated7-16. Its implication in testicular functions such as spermatogenesis and in the interactions between immune system and spermatogenesis support the notion that TNF-α has important regulatory properties8,9. TNF-α released by spermatids is detected by Sertoli cells and may serve as a paracrine factor regulating spermatogenesis8. Another study showed that expression of the Fas ligand, a known inductor of testicular apoptosis, was downregulated by TNF-α. Thus, in the seminiferous tubules germ cell-derived TNF-α may regulate the level of Fas ligand controlling germ cell apoptosis10. In addition, human peritubular cells, which are able to secrete potent signaling molecules, are regulated by TNF-α11. Studies of the effects of TNF on human sperm motility and apoptosis in vitro showed that TNF-α produced sperm chromatin and DNA damage in a concentration- and time-dependent manner12-14. These findings may explain the reduction of fertility secondary to upregulated production of TNF-α in men with urogenital infections14 and inflammatory conditions13. Further, in vitro studies showed that exposing spermatozoa to pathological concentrations of TNF-α can result in significant loss of their functional and genomic integrity, which can be reversed by infliximab15. On the other hand, in vitro studies demonstrated that the beneficial effects of TNF-α in the rat seminiferous epithelium can be blocked by infliximab16. No other anti-TNF-α agents have been known to affect male or female reproductive processes. Limited data also exist concerning the effects of infliximab on semen quality17. The effect of infliximab on male fertility has not been clarified. The aim of our study was to describe male patients who were treated with infliximab and had fathered healthy infants during their management.

MATERIALS AND METHODS
We reviewed medical records of 85 men with AS who were followed at the Rheumatology Outpatient Clinic from 2001 until 2007. All patients fulfilled the modified New York criteria for AS18. Sixty-five patients were treated with infliximab. The treatment schedule and the results have been...
RESULTS
There were 65 men with AS, with mean age 33.5 ± 5.4 years and mean disease duration 14.8 ± 6.5 years.

We identified 4 men with AS who had fathered 6 healthy newborns during their treatment (Table 1). All patients responded well to infliximab therapy without adverse events. Infliximab infusions were given every 8 weeks in all patients and the number of infusions ranged between 10 and 31 when they had fathered children. Luteinizing and follicle-stimulating hormones as well as testosterone were not measured because there was no serum available. No unhealthy infants were observed in this cohort. None of our male patients required fertility assistance. Three healthy children were born during the followup period in the cohort of the 20 patients not receiving infliximab. Two patients in the infliximab group were lost from followup.

Patient 1. A 30-year-old man was diagnosed with AS in 2004. He had oligoarthritis and axial involvement since 1995 and he was taking NSAID. Infliximab was started in March 2004. The dosage was 5 mg/kg (approximately 350 mg) in a loading dose of Weeks 0, 2, 6, and every 8 weeks thereafter. In August 2005 methotrexate (MTX) was added to his treatment because of high disease activity. Three months later, he was in clinical remission. In March 2006 his wife became pregnant while he was receiving the 14th infusion of infliximab. In December 2006 his wife gave birth to a healthy boy. The patient continues his medical treatment, while his wife gave birth to a second healthy boy in July 2008.

Patient 2. A 39-year-old man was diagnosed with AS in 2004. His symptoms had begun in 1989 with morning stiffness, oligoarthritis, low back pain, and uveitis. He started taking MTX and small doses of prednisone in 2004 and infliximab in September 2005. He discontinued MTX in October 2006 because of nausea and vomiting. He continued the treatment with infliximab with clinical improvement. His wife became pregnant while he was on the 10th infusion and gave birth to a healthy child in 2007.

Patient 3. A 34-year-old man was diagnosed with AS in 2005, while his initial symptoms presented in 1997. He was treated with NSAID. The first infusion of infliximab was in January 2005. He responded very well to the treatment and during the 14th infusion of the drug his wife became pregnant. His healthy child was born in 2007.

Patient 4. A 36-year-old man was diagnosed with AS in 2002. The disease onset was in 1999. He was treated with infliximab in March 2002. His first child, a healthy boy, was born in December 2004, while the patient was on the 18th infliximab infusion in complete clinical remission. His second child, a healthy girl, was born in October 2007 while he was on the 36th infusion of infliximab.

DISCUSSION
Fertility, reproduction, and pregnancy outcome have been studied in patients with autoimmune diseases. A decreased likelihood of ovulation as compared with the control group has been described in patients with RA19, while young adults with a history of juvenile chronic arthritis presented significantly reduced fecundity20. In addition, women with scleroderma were more likely than those without scleroderma to have adverse outcomes of pregnancy after the onset of their disease, particularly premature births and small full-term infants21. On the other hand, women with AS expect to have the same rate of fertility, course of pregnancy, and normal delivery as the healthy female population22. Men with RA had lower levels of testosterone than the healthy men, and a large proportion were considered hypogonadal23-25. In addition, rheumatoid flares appear to be associated with prolonged suppression of testicular function26. Patients with AS may have periods of decreased libido27. Further, patients with spondyloarthropathies have a certain degree of hypogonadism28. However, another study showed a small, but not significant reduction in serum total testosterone in patients with AS compared to controls29.

Infliximab is a chimeric monoclonal antibody against TNF used in patients with RA, seronegative spondyloarthropathies, psoriasis, and Crohn’s disease1-4. Allergic reactions, increased risk of infections (especially tuberculosis), autoimmune phenomena, reports of lymphoma, and demyelination disorders constitute the adverse effects of infliximab, similar to those reported with the other anti-TNF-α agents4,30.

No maternal toxicity, embryotoxicity, or teratogenicity to infliximab was observed in a murine toxicity model conducted by the manufacturer31. Rates of live births, miscar-

Table 1. Characteristics of male patients with ankylosing spondylitis who fathered healthy children during infliximab treatment.

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age, yrs</th>
<th>Disease Duration, yrs</th>
<th>Dose of Infliximab, mg/kg</th>
<th>Date of First Infusion</th>
<th>No. Infusions of 1st Child</th>
<th>During Conception of 2nd Child</th>
<th>Concomitant Therapy During Conception</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>30</td>
<td>13</td>
<td>5</td>
<td>31-3-2004</td>
<td>14</td>
<td>24</td>
<td>Methotrexate</td>
</tr>
<tr>
<td>2</td>
<td>39</td>
<td>19</td>
<td>5</td>
<td>27-9-2005</td>
<td>10</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>34</td>
<td>11</td>
<td>5</td>
<td>27-1-2005</td>
<td>14</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>36</td>
<td>9</td>
<td>5</td>
<td>6-3-2002</td>
<td>14</td>
<td>31</td>
<td></td>
</tr>
</tbody>
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riages, and therapeutic terminations do not appear to be signi-
ificantly different in women exposed to infliximab during
pregnancy compared to those not exposed to the drug32. Thus, according to the FDA guidelines, infliximab is consid-
ered to belong to category B in terms of the risk during pregnancy. According to the manufacturer’s prescribing
information, infliximab should be given to a pregnant
woman only if clearly needed33. However, there are some
reports of women with inflammatory arthropathies, treated
with anti-TNF-α inhibitors, who became pregnant and gave
birth to healthy children34.

Limited information exists concerning the effects of
infliximab on male fertility. Available data on the effects of
infliximab on semen quality come from a study in patients
with inflammatory bowel disease. Comparing pre- and post-
infusion semen measures in these patients, there was a sig-
nificant increase in semen volume after infusion with inflix-
imab, and a trend toward decreased sperm motility, while in
some patients there was a significant decrease in normal
oval forms17. Whether these findings translate into impaired
fertility is an area for further investigation.

We describe 4 male patients with AS who had no fertili-
ty problems during infliximab treatment. All patients were
in remission when their wives became pregnant. These cases
provide some evidence of reassurance for men treated with
infliximab. However, further prospective studies are neces-
sary to clarify the effects of the drug on male fertility and to
guide clinicians in appropriate counselling and therapeutic
decision-making.

REFERENCES


