Pregnancy Outcomes in Couples with Males Exposed to Longterm Anti–tumor Necrosis Factor–α Inhibitor Therapies: A Prospective Study

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ABSTRACT. ***Objective.*** To examine the pregnancy achievement and outcomes in couples in which men with spondyloarthritis (SpA) were exposed to tumor necrosis factor inhibitors (TNFi).

Methods. Information about pregnancies involving fathers with SpA was prospectively collected by 6 Romanian rheumatology centers.

Results. Twenty-seven patients achieved 33 pregnancies and fathered 30 healthy children. Three elective abortions (personal reasons) and no spontaneous abortions, preeclampsia/eclampsia, stillbirths, congenital malformations, or pathologies in the children were recorded. Five patients showed normospermia before and after longterm TNFi treatment.

Conclusion. Pregnancy and child outcomes in male patients with SpA exposed to longterm TNFi therapy were reassuring. (First Release April 15 2019; J Rheumatol 2019;46:1084–8; doi:10.3899/jrheum.180588)

Key Indexing Terms:
FERTILITY MEN PREGNANCY OFFSPRING TNF INHIBITORS

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A large proportion of patients with spondyloarthritis (SpA) are affected during peak reproductive years, rendering therapy with biologic disease-modifying antirheumatic drugs (bDMARD) necessary to control active disease[1]. Recent recommendations have offered strategies for preconception counseling and treatment with bDMARD during pregnancy[2,3,4,5]. By contrast, there are still limited data available on the safety of preconception use of bDMARD in men.

Previous studies evaluating fertility, pregnancy, and offspring outcomes in smaller groups and large male cohorts exposed to bDMARD reviewed by Micu, *et al*[6] indicate no impairment of spermatogenesis by tumor necrosis factor–α inhibitors (TNFi). Outcomes of pregnancy and offspring compared to nonexposed patients or the general population have been found to be normal. Drug effects on male fertility require sperm analysis and often include a limited number of individuals[7,8,9,10,11,12]. Pregnancy and offspring outcome after male preconception exposure can be studied based on administrative registries but analysis is made mostly in a retrospective manner; data on disease activity and length of drug exposure are seldom available and pregnancy course in

partners is often not recorded[13,14,15]. Prospective data eliminate these shortcomings. The aim of our study was to examine prospectively pregnancy achievement and outcomes in men with SpA exposed to > 12 months of therapy with TNFi including the preconception period.

MATERIALS AND METHODS

Male patients with an established diagnosis of SpA[16,17] fathering children were prospectively included in the study, at 6 Romanian rheumatology centers. The study was performed between 2012 and 2017 and was approved by the ethics committee (N683/20.12.2012 and N2394/3.04.2017); informed written consent was obtained from patients.

Cases were fathers with TNFi continuous exposure > 12 months including the preconception period (defined as TNFi exposure according to standard protocols within 3 months before conception). The prospective data collection comprised demographic data, disease-related variables, pregnancy outcome in female partners, and offspring outcome. For comparison of pregnancy outcome with the general population, data were extracted from the ATLAS platform (surveillance software linking diagnosis, investigations, and medication, mainly for economic reasons) of the 1st Gynecology Clinic, Cluj-Napoca, Romania, between 2012 and 2017.

A standardized dataset was completed for each patient/couple (in case a pregnancy was identified and followed) in all participating centers. All patients had a monthly visit with the doctor for the receipt of TNFi prescription. Information about fertility treatments and pregnancy occurrence in the couple was obtained at each visit. Analysis of sperm variables before and after longterm TNFi exposure was available in 5 patients (in 3 of them, evaluation was made during a previous study[10]).

Pregnancy and offspring outcome variables were collected according to the standard protocols of the obstetrics/neonatology/pediatric units of the hospital.

Statistical analysis. The assessment of the normality of data was performed using the Shapiro-Wilk test. Descriptive statistics were performed for the continuous and categorical variables and results were expressed as mean ± SD or number of cases and percentages.

RESULTS

In the 6 centers, 202 male patients with SpA who were exposed to TNFi were identified. Their mean age was 30 (range 18–71) years. Among these, 27 men with ankylosing spondylitis (AS; positive radiographic criteria) exposed to continuous, longterm (range 12–129 mos) monotherapy with TNFi were involved in 33 pregnancies. Thirty healthy children were born and 3 elective abortions (personal reasons) were recorded.

Table 1 presents the demographic and disease-related variables in the case couples. Table 2 shows the outcome of 33 pregnancies fathered by patients compared to 12,142 pregnancies of the general population. No increase in pregnancy complications or congenital malformations occurred in cases. All children were born healthy with a weight ≥ 2500 g (range 2800–4400 g). A trend for a higher percentage of live births, cesarean delivery, and prematurity was detected in the case group. The 6 premature children were born at Week 36 of gestation (5 boys and 1 girl) with a weight range of 3300–3800 g.

One patient switched owing to loss of efficacy from longterm therapy with adalimumab (ADA) to etanercept (ETN) 2 months before conception; he reached remission again at conception time. Two men changed preconception TNFi exposure in subsequent pregnancies: 1 from ADA to ETN and 1 from infliximab (IFX) to ETN. One patient stopped IFX 2 months prior to conception; all other patients followed a continuous TNFi regimen. Five patients presented normospermia both before TNFi therapy initiation and after 12 months of treatment with standard doses of ADA (Table 3). In this subgroup, 7 pregnancies were achieved, with 5 children and 2 elective abortions (personal decision; not because of malformations).

DISCUSSION

To our knowledge, our study is the first real-life prospective study in fathers exposed to TNFi demonstrating no negative effect on pregnancy and child outcomes when TNFi were administered over the long term, including the 3 months prior to conception.

Sperm analysis of 5 patients before and after longterm exposure to ADA showed normospermia in all patients who fathered 5 healthy children. This confirms previous studies in patients with AS and psoriatic arthritis in which no impairment of spermatogenesis was found after short-term and longterm exposure to IFX, ETN, and ADA[9,10,11,12]. Several of these studies showed impaired spermatogenesis before initiation of a TNFi and normalization of the spermatogram during treatment[9,11,12].

The absence of sperm alterations under TNFi therapy is reassuring; however, it neither confirms fecundity nor the absence of chromosome alterations in germ cells. Normal fecundity needs to be confirmed by pregnancy achievement in the couple, and this depends on both male and female factors. Twenty-six couples included in our study achieved 32 pregnancies within 1 year of the intention of reproduction, indicating normal fecundity. Normal fecundity during TNFi therapy has also been recorded in retrospective case series[7,8].

Three recent registry-based studies investigated pregnancy outcomes fathered by men with rheumatic, gastrointestinal (inflammatory bowel disease), and dermatologic diseases exposed to TNFi. They found no increased adverse pregnancy or child outcomes compared to nonexposed, disease-matched, or nondiseased controls[13,14,15].

A nationwide study identified 372 children fathered by men treated at least once with TNFi (all types, unknown dose and administration frequency, monotherapy or combined with conventional DMARD). Regardless of the paternal disease and the type of combination therapy administered to the father, no statistical difference was identified between exposed and nonexposed pregnancies for congenital abnormalities, preterm birth, and small for gestational age[15].

Prospectively collected registry data evaluating clinical safety outcomes in patients with Crohn disease (biannual records) identified 59 pregnancies (42 with gestational and 17 with pregestational exposure) in partners after paternal exposure to at least 1 infusion of IFX (median: 3 infusions

Table 1. Demographics and disease-related variables in patients and partners.

Variables	Fathers	Mothers
Race, white	27	27
Age at conception, yrs (min;max)	34.6 ± 5.5 (24;47)	29.5 ± 3.2 (20;35)
Diagnosis		
Axial involvement in AS	19 (70.3)	0
Axial and peripheral involvement in AS	8 (29.6)	0
PsA^	0	1 (0.4)
Disease duration at conception, yrs	10.6 ± 5.7	4 (1 mother)
Abnormality at laboratory screening or imaging at conception	0	0
In remission at conception (BASDAI)	26 (96.3)	NA
TNFi dosage and exposure		
ADA, 40 mg/2 weeks	12 (36.4)	0
ETN, 50 mg/1 week	14 (42.4)	0
IFX, 5 mg/kg/8 weeks	7 (21.2)	0
TNFi therapy duration, mos	42.6 ± 26.0	0
Other therapies		
NSAID*	14 (43.8)	1 (0.4)
SSZ (+ NSAID)	0	0
MTX	0	0
Fertility treatments	0	0
Exposure to smoking, illicit drugs, toxic agents, drinking habits		
Smoking	3 (11.1)	0
Drinking habits, occasional	27 (100)	0
Illicit drugs exposure	0	0
Toxic agent exposure	0	0
Medical history/comorbidities		
History of genital tract infections	0	0
Epidemic parotitis involving testis in teen years/adulthood	0	–
Cystitis during pregnancy§	–	6 (22)
Varicocele	0	–
Other comorbidities	0	0
Desire to conceive	26 (96.3)	NA

Values are mean ± SD or n (%) unless otherwise specified. ^ Onset of PsA in 1 mother preconception. *Very rare exposure to NSAID (1–2 times/mo). § The partners of male patients were monitored 3 times during pregnancy. AS: ankylosing spondylitis; PsA: psoriatic arthritis; BASDAI: Bath Ankylosing Spondylitis Disease Activity Index; TNFi: tumor necrosis factor inhibitors; ADA: adalimumab; ETN: etanercept; IFX: infliximab; NSAID: nonsteroidal antiinflammatory drugs; SSZ: sulfasalazine; MTX: methotrexate; NA: not available.

for gestational and 1 for pregestational exposure). Regardless of the disease activity at conception, no significant differences of pregnancy and child outcomes were observed compared with a nonexposed disease-matched group for the proportion of live births, spontaneous or elective abortions, preterm birth, healthy infants, or congenital abnormalities, or extended hospitalization of newborns. The majority of the partners' outcomes resulted in live births with healthy children across the exposure groups[14]. The data are in line with the results of our study analyzing reproduction after longterm exposure to TNFi in male patients.

Registry data are derived from electronically reported administrative health records or surveillance registries. The strength of registries is collection of large amounts of data on exposure and outcome and generation of a large nondiseased comparator group. Registries often include patients with different diagnoses and pathologies that could influence pregnancy outcomes. Other shortcomings of retrospective data collection are that possible confounders such as disease activity, lifestyle factors, comorbidities, duration of drug exposure, and drug class may not be included, as well as a precise record of all medications (often only prescription data are given). By contrast, prospective clinical studies provide detailed demographic and disease- and therapy-related data but are limited by sample size.

Our study has several limitations. The number of TNFi-exposed patients and the number of pregnancies is small compared to registries, and the pregnancy outcome data could be chance findings. Enrollment of male patients into a prospective study is time-consuming because inflammatory rheumatic diseases have a lower prevalence among men compared to women[1,14]. We did not analyze a disease-matched control group. Patients with milder disease are generally less compliant with medical visits. The comparison group from the general population lacked data on fecundity and demographic data of fathers and mothers. The strength of our study is the prospective design and that the group of fathers was homogeneous regarding diagnosis, and all

Table 2. Pregnancy and offspring outcomes in patients compared to the general population^.

Pregnancy Evolution and Outcomes	Cases	General population
No. pregnancies	33	12.142
TTP < 12 mos	32 (96.9)	NA
Live births	30 (91)	9667 (79.6)
Male sex	13 (43.3)	NA
Stillbirths*	0	107 (0.9)
Gestational age at delivery, weeks	37.57 ± 1.01	NA
≥ 37	24 (80.0)	8593 (88.9)
< 37	6 (20.0)	1074 (11.1)
Type of delivery for live births		
Vaginal	28 (93.3)	9459 (97.8)
Cesarean	2 (6.6)	208 (2.2)
APGAR score	9.6 ± 0.7	NA
Weight of live newborn, g	3390.7 ± 342.6	NA
Weight > 2500 g∞	30 (100)	9566 (98.9)
Small for gestational age∞	0	101 (1.0)
Spontaneous abortion¶	0	1135 (9.4)
Elective abortion (weeks 8–9) ¶	3 (9.0)	1233 (10.2)
Preeclampsia/eclampsia	0	110 (1.1)
Congenital malformations	0	140 (1.4)
Other neonatal diseases that require prolonged stay in neonatal intensive care unit	0	18 (0.2)

Values are mean ± SD or n (%) unless otherwise specified. ^ Data from ATLAS platform (surveillance software linking diagnosis, investigations, and medication). * *In utero* fetal death after 20 weeks of gestation. ∞ Normal weight was defined as > 2500 g at term; small for gestational age fetuses were those with a weight < 2 SD adapted for gestational age and sex of the child. ¶ Spontaneous abortions were defined as clinically recognized pregnancy losses before 20 weeks of gestation; elective abortions were defined as pregnancies that were terminated on personal request for nonmedical reasons, up to 12 weeks of gestation. TTP: time to pregnancy achievement. APGAR: Appearance, Pulse, Grimace, Activity, Respiration evaluation in the newborn; NA: not available.

Table 3. Sperm variables in 5 patients before and after longterm TNFi exposure.

Sperm Analysis	P1	P1′	P2	P2′	P3	P3′	P4	P4′	P5	P5′
Volume, ml	3	2	3.5	2	3	2	1.5	3	4	6
pH	7.5	7.5	7.8	7.4	7.8	8	8	8	8	8
Liquefaction, min	10	10	5	15	10	10	10	20	20	10
Agglutination¶	–	–	–	–	–	–	–	–	–	–
Concentration (10^6/ml)	50	55	45	30	45	65	43	100	66	40
Sperm cell motility, %										
Rapid progressive	40	50	37	50	50	50	30	30	50	60
Slow progressive	20	20	30	0	15	20	35	30	10	0
Nonprogressive	0	10	0	0	10	10	0	0	15	0
Immobile	40	20	33	50	25	20	35	40	25	40
Leukocytes	0	0	0	0	0	0	0	0	0	0
Morphology										
Normal forms, %	65	60	70	60	63	55	53	70	63	50
Atypical forms (head + midpiece + tail), %	35	40	30	40	37	45	47	30	37	50
Results*	N	N	N	N	N	N	N	N	N	N

P1–5: evaluation of patient sperm variables before TNFi exposure. P1′–5′: evaluation of patient sperm variables after 12 months TNFi exposure. ¶ Agglutination is present (+) or absent (–). * Diagnosis was based on being within reference values of the World Health Organization[18]. TNFi: tumor necrosis factor inhibitors; N: normozoospermia.

received > 12 months monotherapy with a TNFi. Indeed, the followup of 5 patients with longitudinal sperm variables analysis resulting in pregnancy achievement and positive outcome strengthens the study conclusion, showing that normal sperm variables and fertility/fecundity preservation is possible in patients with SpA after longterm TNFi exposure.

The prospective analysis of the pregnancy and offspring outcomes in patients exposed to longterm TNFi therapy,

including the preconception period, is reassuring regarding reproduction capacity and the health status of the offspring. Larger prospective controlled studies are needed to confirm these findings.

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