TNF-α inhibitors do not impair sperm quality in males with ankylosing spondylitis after short-term or long-term treatment

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Abstract

Objective. The aim of this study was to study the influence of active disease status and TNF-α antagonists on sperm quality in a group of AS patients.

Methods. Twenty-three active AS patients and 42 controls were recruited. Patients’ sperm samples were analysed at baseline (previous to) and at 3–6 months after TNF-α therapy (adalimumab, infliximab, etanercept) administration. Baseline assessment was made for only 20 patients, 2 of them proving to have normal fertility, 2 having a pregnant stable partner and the third having a 9-month-old child. Six patients were retested after 12 months of biologic therapy. Each patient acted as his own comparator. Results were further compared with sperm samples from age-matched controls. Sperm analysis was performed according to the World Health Organization (WHO) 1999 guidelines.

Results. Patients’ baseline assessment showed normozoospermia in 91% and oligozoospermia in 9% of patients. No significant differences in sperm quality were noticed at follow-up visits compared with baseline. Comparison to controls showed no statistically significant differences in semen quality, with some exceptions: the control group presented a higher percentage of non-progressive and immobile sperm cells and higher numbers of head and tail atypias.

Conclusion. Sperm quality in patients with active AS and after receiving short- and long-term TNF-α blocker therapy is comparable to sperm quality in healthy controls. Our study confirms that the disease process of AS does not have a major impact on sperm quality and that treatment with anti-TNF has no negative impact on sperm quality even under long-term treatment.

Key words: sperm parameters, ankylosing spondylitis, TNF-α blockers, active disease, biologic therapy, fatherhood, reproduction, fertility, spermatogenesis, treatment.

Introduction

AS a chronic inflammatory disease affecting the axial skeleton, the entheses and occasionally the peripheral joints and extra-articular organs and has a higher prevalence in males than females [1, 2]. AS develops during peak reproductive years [3]. TNF-α, a potent cytokine with proinflammatory, cytopathic, angiogenic and growth modulatory effects on different target cells, plays a central role in AS pathogenesis [4]. Treatment with TNF inhibitors has proved highly effective in patients with AS [5, 6].

Chronic inflammation of the spine and in peripheral joints influences quality of life, including sexual function and fertility status, due to the psychological impact reduced health has on all aspects of life [7]. Moreover, parents of adolescent AS patients often express concern regarding future fertility status due to disease and/or prescribed chronic drug treatment.

TNF-α also plays a role in reproduction. In the testes, TNF-α is produced by germ cells under physiological
conditions, with low levels when measured in seminal plasma. Its presence in physiologically low levels within the male reproductive tract has effects on germ cell apoptosis, peritubular cell secretion regulation and sperm survival, and thereby on fertility [8]. In inflammatory conditions, higher TNF-α concentrations are detected in seminal fluid, and adverse effects on spermatogenesis have been reported as a reduction in sperm motility, viability and motion parameters, as well as inhibition of germ cell apoptosis [9–12]. An in vitro study showed that exposure of spermatozoa to high concentrations of TNF-α can result in a significant loss of their functional and genomic integrity [13]. Treatment with TNF inhibitors (anti-TNFs) should therefore be beneficial by reducing excess TNF-α. However, several case reports of patients treated with anti-TNFs have shown negative effects on spermatogenesis [14]. In two studies, sample sizes were very small [15, 16]; a third study compared patients on anti-TNFs with controls but was not longitudinal [17].

Therefore our aim was to perform a longitudinal assessment of sperm quality in AS patients treated with anti-TNFs. The patient group was selected because of high disease activity not responding to a standard treatment protocol. Spermatograms were performed once before the start of therapy, 3–6 months after therapy onset and in six patients 1 year after treatment with anti-TNFs. Results in patients were compared with an age-matched healthy control group from the general population.

Patients and methods

Twenty-three male AS patients fulfilling the modified New York diagnostic criteria and 42 healthy men (controls) were included in a prospective study during 2010–12 (Clinical Rehabilitation Hospital and First Gynecology Clinic, Cluj-Napoca). The study was approved by the ethics committee of the Iuliu Hațieganu University of Medicine and Pharmacy, Cluj-Napoca, and informed written consent was obtained from all patients and controls. All men recruited delivered semen samples after 48 h after up to 8 days of sexual abstinence. Sperm samples, collected between 9 and 10 A.M. at each time point, were processed in the laboratory within 1 h of liquefaction time. Analysis of sperm concentration, mobility and morphology was according to current World Health Organization (WHO) definitions [18]. Measured sperm parameters within 60 min of ejaculation included sperm concentration (reference limit >20 million/ml), vitality (reference limit >50%), sperm motility (reference limit >50%) and morphology of normal forms (reference limit >15%) [18]. Definitions used included oligospermia (reduced sperm number), asthenozoospermia (reduced sperm motility) and teratozoospermia (abnormally shaped sperm cells). Abnormalities in these parameters indicate reduced sperm quality and are associated with male infertility.

The patient group was tested once before the start of anti-TNF therapy. Patients were chosen because of high disease activity not responding to a standard treatment protocol for 6 months. Baseline sperm analysis was obtained for 20 of 23 patients. Three patients refused baseline assessment, two of them having a pregnant stable partner and the third having a 9-month-old child. The second sperm analysis was performed after an interval of 3–6 months after the start of anti-TNF monotherapy, including adalimumab 40 mg every 2 weeks, infliximab 5 mg/kg every 8 weeks and etanercept 50 mg/week, and included the three patients without baseline sperm assessment. Three other patients were excluded from the second sperm analysis because initiation of biologic therapy was not possible during the period of patient recruitment. Six patients with both baseline and second sperm parameter assessment were restested after 1 year of therapy (Fig. 1).

Demographic data and disease activity measurements (BASDAI, joint count, CRP, ESR) were recorded along with current laboratory screening obligatory for biologic therapy initiation (haematopoietic, liver and kidney parameters; hepatitis B and C viral markers; tuberculosis screening). The same parameters (except for viral markers and tuberculosis screening) were repeated before performing the follow-up sperm analysis. Previously prescribed therapies for AS and or other co-morbidities; the use of nicotine (smoking and/or alternative nicotine exposure modalities), alcohol or illicit drugs; exposure to toxic agents; pathology of genital tract infections and history of epidemic parotitis involving the testes in teenage or adult years were recorded.

Statistical analysis

Qualitative data were statistically summarized as percentage and associated 95% CI [19, 20]. Quantitative data were summarized as mean (s.d.) when normally distributed, otherwise median [interquartile range (IQR) (Q1 = 25th percentile and Q3 = 75th percentile)] were used. Comparisons between the patient and control groups were conducted with parametric tests (t-test) for quantitative normally distributed data, otherwise a non-parametric test was applied (Mann–Whitney test). Comparison of

**Fig. 1 Patient recruitment algorithm**

Baseline: previous to biologic therapy treatment; follow-up 1: 3–6 months after initiation of biologic therapy; follow-up 2: 12 months after initiation of biologic therapy.
the baseline and follow-up characteristics of the patient group were done by applying the t-test for paired samples for normally distributed data or the Wilcoxon test for data not following a normal distribution. The Z-test for proportions was used to compare the groups.

Statistical analysis was performed using Statistica 8.0 software (StatSoft, Tulsa, OK, USA) at a significance level of 5%.

Results

Twenty-three AS male patients [mean age 34.77 years (s.d. 9.28)] with high disease activity scores were included as a case group and 42 age-matched healthy potential sperm donors were included as a control group [mean age 34.88 years (s.d. 5.56)].

Characteristics of the patient group

Patients’ baseline assessment showed high disease activity [BASDAI mean 7.58 (s.d. 1.10) and high levels of CRP [mean 2.95 mg/dl (95% CI 2.18, 3.68)]. Twelve AS patients with exclusive axial involvement received NSAIDs only, seven patients with axial and peripheral involvement received additional treatment with SSZ and four received SSZ and MTX. The mean duration of continuous treatment with SSZ (3 g/day, 11 patients) was 24 months (s.d. 21.93) and mean duration of continuous treatment with MTX (10 mg/week, four patients, combined therapy with SSZ) was 11 months (s.d. 7.57). Baseline sperm analyses were obtained in 20 patients, whereas 3 patients refused the baseline sperm assessment for personal reasons. Except for one patient with daily use of nicotine (smoker), no other exposures to nicotine, alcohol or illicit drugs and no recall of urogenital infections/epidemic parotitis among the patients were declared.

Twenty patients started anti-TNF therapy: 14 with adalimumab [70% (95% CI 45.25, 89.75)], 2 with etanercept [10% (95% CI 0.25, 29.75)] and 4 with infliximab [20% (95% CI 5.25, 44.75)]. Three patients did not start anti-TNF therapy because costs for therapy were not covered.

All 20 patients receiving anti-TNFs were in remission [21] after 3 months of anti-TNF treatment, with a significant reduction of the BASDAI [mean 1.53 (s.d. 1.15)] and CRP [median 0.40 (Q1–Q3 IQR 0.28–0.63)]. The BASDAI was significantly lower after 3 months of treatment compared with baseline [paired Student’s t-test: mean of the difference 6.14 (95% CI 5.56, 6.72), \(P = 4.48 \times 10^{-10}\)]. CRP was also significantly lower after 3 months of treatment compared with baseline (Wilcoxon test: Z-statistic = -3.922, \(P = 8.77 \times 10^{-5}\). Maintenance of remission was present at the 12-month follow-up [mean BASDAI 0.40 (s.d. 0.52) and median CRP 0.50 (Q1–Q3 IQR 0.40–0.60)] for all 20 patients receiving biologic therapy.

Sperm characteristics at baseline, after 3 months of treatment and at 12 months of anti-TNF therapy are presented in Table 1. Except for oligozoospermia in two patients (9%) exposed only to NSAIDs, no other sperm abnormalities were present. No significant differences in sperm parameters were noticed at follow-up compared with baseline (supplementary Table S1, available at Rheumatology Online).

Control group sperm characteristics

In the control group of 42 potential sperm donors, 30 (71.42%) had normospermia, 5 (11.90%) had normoasthenozoospermia, 4 (9.52%) had oligozoospermia and 3 (7.14%) had oligoasthenozoospermia. No teratozoospermia was detected in the control group. Detailed sperm parameters are presented in Table 1.

When semen analyses in patients at baseline and at follow-up were compared with controls, no statistically significant differences were noticed, with some exceptions—the control group presented a higher percentage of non-progressive and immobile sperm cells and greater numbers of head and tail atypias. Comparison between the two groups is presented in Table 1.

Six patients (five with axial involvement and one with both axial and peripheral joint involvement) tested at baseline and follow-up 1 and treated with adalimumab (five cases) vs infliximab (one case) showed normozoospermia both in high disease activity status as well as after 3–6 months of biologic therapy. This subgroup showed normal sperm parameters after 12 months of biologic therapy (follow-up 2).

Discussion

Our study is the largest prospective study monitoring sperm parameters in patients with active AS prior to and after 3–12 months of anti-TNF therapy and presents for the first time extended experience after exposure to adalimumab (14 patients). Exposure of 20 patients to three different types of anti-TNFs did not have a negative impact on sperm quality after 3–6 months and in 6 cases after 12 months of treatment. This contrasts with case reports that describe a reduction in sperm number and motility, teratozoospermia and a reduction in normal oval forms after infliximab or adalimumab exposure [14–16]. However, these observational studies, which included fewer than 10 patients without a longitudinal design and without a control group [14–16], do not allow assignment of observed sperm pathology to treatment since abnormal spermatograms are seen in a large proportion of healthy men [22]. The study of Villiger et al. [17] comparing non-exposed with anti-TNF-exposed patients with SpA found better sperm quality in patients under anti-TNF treatment, in line with our observations.

In the three patients in our study who did not have a baseline sperm assessment, fertility was intact since all three men had either a pregnant partner or a 9-month-old child at the time of study recruitment. The differences in our results compared with other studies could be due to differences in patient selection (age, type of SpA, disease onset, dominant axial or peripheral involvement) or treatment protocols [10, 14, 16]. Indeed, our results with predominantly normal sperm parameters in active AS patients raises the question of whether TNF-α levels expressed at an active inflammatory state are really impairing sperm quality. Furthermore, it was not clear whether
Table 1: Comparison of sperm quality and parameters in patients and controls

<table>
<thead>
<tr>
<th>Sperm analysis</th>
<th>Case group</th>
<th>Comparison statistics (P-value)</th>
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<tbody>
<tr>
<td></td>
<td>Baseline (n = 20)</td>
<td>Follow-up 1 (n = 20)</td>
</tr>
<tr>
<td></td>
<td>Sperm Normozoospermia, % (95% CI)</td>
<td>91 (70, 100)</td>
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<tr>
<td></td>
<td>Oligozoospermia, % (95% CI)</td>
<td>9 (0.25, 30)</td>
</tr>
<tr>
<td></td>
<td>Last intercourse, median (IQR), days</td>
<td>5 (4–5.5)</td>
</tr>
<tr>
<td></td>
<td>Semen volume, median (IQR), ml</td>
<td>3 (2.4–4)</td>
</tr>
<tr>
<td></td>
<td>pH, median (IQR)</td>
<td>8 (8–8)</td>
</tr>
<tr>
<td></td>
<td>Liquefaction time, median (IQR), min</td>
<td>13 (10–23)</td>
</tr>
<tr>
<td></td>
<td>Sperm concentration, median (IQR), millions/ml</td>
<td>40 (30–60)</td>
</tr>
<tr>
<td></td>
<td>Non-progressive, mean (IQR)</td>
<td>61.21 (11.08)</td>
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<tr>
<td></td>
<td>Rapid and slow progressive, mean (S.D.)</td>
<td>25 (0–31.3)</td>
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<td></td>
<td>Immobile, mean (S.D.)</td>
<td>19.32 (17.65)</td>
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<tr>
<td></td>
<td>Round cells, median (IQR), millions/ml</td>
<td>40.47 (10.44)</td>
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<tr>
<td></td>
<td>Sperm cell motion, %</td>
<td>57.44 (9.93)</td>
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<tr>
<td></td>
<td>Normal, mean (S.D.)</td>
<td>43.47 (10.44)</td>
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<tr>
<td></td>
<td>Atypical sperm cells, mean (S.D.)</td>
<td>60 (35–75)</td>
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<tr>
<td></td>
<td>Atypical head, median (IQR)</td>
<td>30 (25–45)</td>
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<tr>
<td></td>
<td>Atypical intermediate part, median (IQR)</td>
<td>2.5 (0–20)</td>
</tr>
</tbody>
</table>

Case group: sperm quality and sperm parameters in patients, baseline vs follow-up 1 (3–6 months after start of anti-TNFs) and follow-up 2 (12 months after start of anti-TNFs); n = sample size. Control group: sperm quality and sperm parameters in controls. Comparison statistics: sperm quality and sperm parameters; comparisons between case and control groups. aZ-test for proportions (Z-statistics). bWilcoxon test for case group and Mann-Whitney test for comparison between cases and controls. cJust two determinations. n.a.: no data in this category, absence of non-progressive sperm cells in the sperm analysis. dPaired samples t-test for case group and independent sample t-test for comparison between cases and controls.

TNF-α inhibitors do not impair sperm quality.
any possible influence depends on TNF-α levels present in the seminal fluid or on exposure time. Data on gonadal function in active and inactive AS patients are scarce and contradictory. Sperm abnormalities have been described in AS patients not treated with DMARDs [22, 23] as well as during treatment with SSZ, MTX and TNF-α inhibitors [15, 16, 24–29]. A systematic review evaluated nine papers where expectant fathers had used TNF-blocking agents shortly before conception. Reports were frequently insufficient due to lack of a prospective design and a control group [28]. To differentiate the effects of the disease process from drug-related effects in a chronic inflammatory disease is important. Therefore assessment of sperm quality must be performed both before the start of drug therapy and after a period of drug exposure in the same subject. In clinical practice the influence of disease activity on spermatogenesis alone is often difficult to assess because patients rarely have drug-free intervals. Likewise, inclusion of a control group is mandatory because reduced sperm quality is also present in healthy men [22], as confirmed by our study detecting a higher percentage of oligozoospermia, non-progressive and immobile sperm cells as well as a higher number of atypical sperm cells in the control group.

Limits of the study

The absence of data regarding nicotine (smoking/alternative nicotine exposure modalities), alcohol, illicit drugs or urogenital infection exposures in controls did not allow comparison of the impact of these potential negative factors on sperm quality between the two groups. The presence of just one smoker in the patient group with zero exposure to other harmful factors would indicate that patients lead a healthier lifestyle due to medical advice, with subsequent better sperm quality even during active periods of disease. Another limitation of the study is represented by the fact that none of the patients exposed to TNF-α blockers (tested at baseline and follow-up) fathered a child during the study period, so normal fertility must be assumed based on the observed normal sperm parameters [18].

Conclusion

Our study confirms that the disease process of AS does not have a major impact on sperm quality and that treatment with anti-TNFs has no negative impact on sperm quality, even under long-term treatment [17, 26, 31, 32]. Patients can be reassured that no harm to gonadal function occurs during treatment with TNF inhibitors such as adalimumab and infliximab.

Supplementary data

Supplementary data are available at Rheumatology Online.

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