Possible Role of Biological Agent on Characteristics of Sperm in Patients with Spondiloarthritis

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Abstract

Background: The role of TNF-α and TNF-α antagonists on seminal fluid parameters in men is controversial. TNF-α is a cytokine had a wide range of cellular effects. In testis, "TNF-α is produced by germ cells and it has a role in the regulation of spermatogenesis".

Objective: to study the effect of biological agent on sperm quality in a group of spondyloarthritis patients

Patients and Methods: A prospective study was carried out in Baghdad teaching hospital during the period starting on 1st of January 2013 till the end of October 2013 .All semen samples of (60) spondyloarthritis patients and controls (60) was collected by masturbation after (72) hour of sexual abstinence. The semen samples was examined with regard to sperm concentration, motility, and morphology, according to WHO 1999 guidelines.. Results were compared with controls

Results: According semen parameters such as Volume, PH, Count, Motility Morphology in two groups of spondyloarthritis there were no significant differences noticed between TNF blocking agents and semen parameters when compared to controls group on(baseline) but after (40 weeks), Regarding motility and morphology significant differences (P<0.001) were found between cases and healthy controls.

Conclusion: Biological agents **(**infliximab&enbrel) had no affect on seminal fluid parameters such as volume, PH and sperm concentration, but it decreased motility of sperm and percent of normal morphology

Key words: Sperm, Biological agent, Semen, arthritis, TNF.
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Introduction

Spondyloarthritis is a heterogeneous group of diseases that have the same clinical, pathogenic, and hereditary features, such as psoriatic arthritis and ankylosing spondylitis (AS) [1]. Bone ankylosis and chronic inflammation of the enthesis were the main characteristic of the spondyloarthritides, the most common clinical presentations are sacroiliitis, enthesitis, iritis, oligoarthritis, psoriasis, and inflammatory bowel [2].

The prevalence rate of spondyloarthropathy is between 0.1% and 2.5%, while incidence rate ranges from 0.3 to 7.3/100,000 inhabitants per year disease [2]. 'Tumor necrosis factor-alpha (TNF-α) is a proinflammatory cytokine that plays a major role in the pathogenesis of a group of diseases such as rheumatoid arthritis, psoriasis and psoriatic arthritis, inflammatory bowel diseases and many other rheumatologic and dermatological conditions'. It is connected to the cell surface

in its precursor transmembrane form (tmTNF-α) and is librated from cells after cleavage as soluble TNF-α (sTNF-α). Both forms are biologically active, and bind to either of the two receptors, TNF receptor one and TNF receptor two [3]. Tumour necrosis factor-alpha (TNF-α) is a potent cytokine made by neutrophils, activated lymphocytes, natural killer cells, and activated macrophages [4].Inside the testis, TNF-α is secreted by germ cells and activated interstitial macrophages [5,6]. TNF-α concentration are usually low in seminal plasma (<10 pg/mL), but tend to raise in conditions such as inflammation, There are very few data in the literature regarding fertility in Spondyloarthritis patients treated with biological agents, but we can conclude indirect evidence from some studies .The effect of biological agents on semen parameter in men is controversial. Some study reported that biological agent did not affect semen parameter such as "volume, sperm concentration, or forward progression", but that it decrease sperm motility and affect the morphology [7]. However, sperm motility and membrane integrity had higher level in the samples incubated with TNF-α plus infliximab than in the samples treated with TNF-α or infliximab alone [8,9].This study was designed to evaluate the role of biological agent on seminal fluid parameters in patients with Spondyloarthritis

Patients and Methods

A total of 60 semen samples randomly selected from patients with Spondyloarthritis on biological agent and 60 semen sample from healthy controls in Baghdad teaching hospital for a total duration of 10 month starting on 1st of January 2013 till the end of September 2013 .Age range at the time of study was between 23-40 years old with mean ±standard deviation (28±1.4).

Semen samples from Spondyloarthritis patients and controls were collected by masturbation after 72 hour of sexual abstinence. The samples were assessed with regard to semen parameter such as sperm concentration, motility, and morphology [10]. Semen analysis was performed according to the guidelines of the World Health Organization [11].

Statistical analysis

All data analyzed by using the available statistical package of SPSS-20 (Statistical Packages for Social Sciences- version 20). Data were presented in simple measures of mean, standard deviation, Using analysis of variance test for difference between means, significance was considered when the (P value ≤0.05).

Results

As shown in table (1) 30 patients (25%) was taking remicade and 30 patients taking enbrel (25%) The distribution of study samples (patients on remicade and enbrel) and compared with 60 healthy controls (50%).

Table (1): Distribution of study samples (patients on remicade and enbrel) and health controls.

Biological agent	N0	%
Remicade groups	30	25.0
Enbrel groups	30	25.0
Controls groups	60	50.0
Total	120	100.0

Regarding semen parameters suchas Volume, PH, Count, Motility and Morphology in two groups of spondyloarthritis there were no significant differences noticed between TNF blocking agents (infliximab, etanercept). And semen parameters when compared to controls group as shown in table (2).

Table (2): Distribution of studied groups according to semen parameters on baseline.

Semen parameter	Remicade (N=30)	Enbrel (N=30)	Controls (N=60)		
	(Mean±SD)	(Mean±SD)	(Mean±SD)	(F.test)	(P.V)
Volume	2.80±.08	2.92±.04	2.50±.06	11.723	0.061
PH	7.52±.07	7.59±.07	7.65±.04	1.525	0.222
Count	51.07±1.11	52.40±1.07	55.55±.86	2.116	0.125
motility					
Grade A	61.03±1.52	61.70±1.73	58.23±1.06	2.056	0.133
Grade B	16.17±1.13	13.37±1.11	16.40±.86	2.413	0.094
Grade C	12.67±.81	12.20±.86	12.60±.56	.103	0.903.
Grade D	11.93±.73	13.90±1.03	14.18±.82	1.639	0.199
MOPHOLOGY					
NORMAL	59.17±2.35	58.00±2.19	76.18±1.50	1.450	0.239
ABNORMAL	40.83±2.35	42.00±2.19	24.07±1.46	1.478	0.232

According to seminal fluid parameter, significant differences (P<0.001) were found between studied groups by motility and morphology (higher proportion of grade D motility (totally immotile) was observed and higher proportion of abnormal morphology (table 3).

Table (3): The association of studied groups and semen parameters after40 weeks

Semen parameter	Remicade (N=30)	Enbrel (N=30)	Controls (n=60)		
	(Mean±SD)	(Mean±SD)	(Mean±SD)	(F. test)	(P.V)
Volume	2.47±.14	2.64±.15	2.60±.06	0.508	0.603
PH	7.57±.05	7.72±.05	7.64±.04	2.160	0.120
Count	49.50±1.54	50.10±1.56	55.98±1.33	59.183	0.211
motility	.	.	.		
Grade A	14.00±1.92	13.83±1.76	58.72±1.10	346.338	0.0001*
Grade B	9.33±1.19	11.17±1.24	16.17±.85	12.524	0.0001*
Grade C	28.17±2.44	25.50±2.25	12.52±.56	34.168	0.0001*
Grade D	46.33±4.15	47.33±3.89	14.02±.84	61.761	0.0001*
Morphology	.	.	.		
Normal	59.17±2.35	58.00±2.19	76.18±1.50	32.054	0.0001*
Abnormal	40.83±2.35	42.00±2.19	24.07±1.46	31.986	0.0001*

Discussion

Very few data are available concerning the possible role of biological agent on semen quality. (More than a decade of use of biological agents in rheumatology has confirmed their acceptable safety profile and very few adverse effects had been seen. However, TNFα, a pleiotropic cytokine, is important to many physiological functions and its suppression may lead to unexpected results) It has also been shown in vitro that 'TNF-α inhibits germ cell apoptosis in human seminiferous tubules effectively and dose-dependently' [12, 13].

Regarding the seminal volume, PH and sperm count there is no significant difference between patients on biological agents (remicade and enbrel) and controls groups at baseline while at 40 weeks of biological agent there were significant differences regarding motility and morphology, these results revealed that the biological agent therapy may affect sperm morphology as well as sperm motility and that the effect on morphology is dose dependent.

This result is similar to what had been reported by Mahadevan *et. al.*, who found that remicade therapy, did not affect the semen parameter such as volume, sperm concentration, and forward progression, but it decreased sperm motility and percent of normal oval forms [7]. And differ from the study done by Villiger *et. al*, who found that there was no significant difference of sperm quality between healthy controls and anti-TNF treated patients with spondiloarthritis [14]. This difference may be due to difference in sample size between two studies. The effect biological agent, such as infliximab, on semen parameter in men is controversial. One study conclude that TNF-α effectively inhibited apoptosis of human germ cells; while no significant effect of TNF-α on the activation of transcription factor, which is considered to be a mediator of TNF-α –induced survival signals, were observed [1]. Another study revealed the effects of the TNF-α in the rat seminiferous epithelium promotes cell survival and this prosurvival effect can be stopped by infliximab [15]. On the other hand, Said *et al.*, incubated sperm suspensions with different doses of TNF-α, TNF-α plus infliximab and only infliximab. Sperm quality decreased following incubation with TNF-α in a dose- and time-dependent manner. Sperm motility grading and membrane integrity were increased in samples incubated with TNF-α plus infliximab than in the samples treated with TNF-α or infliximab alone [16] .

Conclusion

Infliximab and enbrel had not effect on seminal fluid parameter such as volume, PH and sperm concentration, but it decreased motility of sperm and percent of normal morphology.

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