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**Predictors of infusion reactions during infliximab treatment in patients with arthritis**

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## **Abstract**

The impact of baseline antinuclear antibody (ANA) status and usage of methotrexate (MTX) on development of infliximab related infusion reactions in patients with rheumatoid arthritis (RA) or spondylarthropathies including psoriatic arthritis (SpA) was studied. All patients with RA (N=213) or SpA (N=76) treated with infliximab in the period 1999-2005 at the Dept of Rheumatology in Lund were included. ANA was present in 28% and 25% of RA and SpA patients, respectively. Due to differences in baseline characteristics a binary logistic regression model calculating odds ratios (OR) adjusting for age, gender and prednisolone dosage was used. Altogether 21% of patients with RA and 13% of patients with SpA developed infusion reactions ( $p=0.126$ ). OR to develop infusion reactions in RA patients with baseline ANA positivity alone was 2.1. Infliximab without MTX and infliximab as monotherapy had OR 3.1 and 3.6, respectively. Combining infliximab without MTX and ANA positivity yielded an OR for infusion reaction of 4.6. Lower age at disease onset and longer disease duration were associated with infusion reactions ( $p=0.012$  and  $p=0.036$ , respectively), but not age, gender, CRP, ESR, HAQ and DAS28 at baseline. No predictors of infusion reactions were identified in SpA patients. RA patients treated with infliximab without MTX and with positive baseline ANA are at increased risk of developing infliximab related infusion reactions.

## **Introduction**

Treatment with infliximab, a chimeric IgG1 antibody specific for human tumour necrosis factor alpha (TNF) has been shown to be effective in a variety of inflammatory diseases. In combination with methotrexate (MTX), infliximab provides significant and sustained improvement in a majority of patients with rheumatoid arthritis (RA) [1,2] but also in spondylarthropathies (SpA) including psoriatic arthritis [3,4]. However, one of the clinical problems associated with infliximab treatment is development of infusion reactions. Acute infusion reactions occur within 24 hours and delayed ones develop 2-14 days after treatment initiation. Acute reactions can be true allergic i.e. IgE mediated type I reaction (anaphylactic reaction) including hypotension, bronchospasm, wheezing and/or urticaria. However, the large majorities of infusion reactions reported during infliximab treatment are characterized by more unspecific symptoms and are often classified as anaphylactoid ones; i.e. probably non-allergic [5]. A large range of symptoms such as headache, nausea, fever or chills, dizziness, flush, pruritus, chest or back pain are described in relation to infusions but do not necessarily require the discontinuation of treatment [1,2,5].

It has been shown that infliximab treatment can induce development of anti-drug antibodies leading to infusion reactions and withdrawal of the treatment [1,2]. Maini et al observed that low-dose MTX added to infliximab reduced the development of anti-drug antibodies in groups of patients suggesting that addition of MTX could possibly reduce the immunogenicity against the monoclonal antibodies [2]. Also, concomitant treatment with different

immunosuppressive agents in patients with Crohn's disease has been shown to reduce the incidence of infusion reactions [6].

In addition to development of anti-infliximab antibodies, an induction of different auto-antibodies including antinuclear antibodies (ANA) has been described during infliximab treatment in both RA and SpA patients [7,8,9,10]. Concerning ANAs, new appearances but also shift in ANA status has been detected in RA patients during treatment with disease modifying antirheumatic drugs (DMARDs) [11]. Also, treatment with TNF-blockers has been shown to lead to both induction of ANAs but also a switch from ANA positivity to ANA negativity [7-10]. The clinical significance of new appearance of ANAs has been addressed in several studies [7-11]. Cases of lupus like syndrome have been reported but in the majority of patients appearance of ANA did not have any clinical significance [7,8].

Furthermore, a correlation between ANA positivity and toxic effects of drugs i.e. some DMARDs has been previously reported [12,13]. Toxic reactions to gold compounds and penicillamine were also found to be more prevalent among RA patients with certain HLA-DR alloantigens [14] but there are insufficient data on the impact of ANA status at baseline on the risk of development of infusion reactions in relation to infliximab treatment.

A pilot study including patients with RA showed that positive baseline ANA was a risk factor for developing infusion reactions particularly when infliximab was used as monotherapy [15].

The aim of this study was to evaluate the predictive value of ANA status, MTX and other concomitant immunomodulating agents before the initiation of infliximab treatment on the development of infusion reactions during infliximab treatment in chronic arthritis patients treated in clinical practice.

## **Materials and methods**

### *Patients*

The study population consisted of patients with RA (N=213) or SpA (N=76) treated with infliximab in the period 1999-2005 at the Dept of Rheumatology in Lund. In order to ensure that all RA patients fulfilled American College of Rheumatology (ACR) 1987 criteria [16] a systemic review of medical records was performed. The SpA included 21 patients fulfilling 1984 New York revised classification criteria for ankylosing spondylitis [17], 43 patients with psoriatic arthritis according to Moll and Wright 1973 classification criteria [18], 5 patients with inflammatory bowel related arthritis and 7 patients with undifferentiated spondylarthropathy. All patients were included in the South Swedish Arthritis Treatment Group protocol (SSATG) follow up system for monitoring of treatments by biologics [19]. The evaluations included swollen and tender joint counts, assessment of pain using visual analogue scale (VAS), patient's overall assessment (VAS), physician's global assessment (five grades), concomitant treatment with DMARDs and oral glucocorticoids. Disease activity score (DAS28) was calculated for each patient and used for disease activity grading [20].

Infliximab was given to both patient groups in dosage of 3 mg/kg at start, after 2 and 6 weeks and thereafter as a rule every 8<sup>th</sup> week as recommended by the manufacturer. The dosage could be increased or treatment intervals shortened in case of insufficient clinical response to treatment. Clinical evaluations and blood sample collection were performed directly before infusions. All adverse events, including infusion reactions, were registered and seriousness graded by one investigator. The seriousness grades were mild, moderate, serious, and life threatening, where mild was defined as self-limiting and resolved after temporary stop/slowing of infusion, moderate needed closer attention and also extended observation period and often stop of infusion, while serious involved infusion stop, respiratory symptoms/symptomatic blood pressure fall, and need of close monitoring often during a

whole day and also occasionally in ward referral. Life threatening involved intensive care treatment. An infusion reaction was defined as an adverse event occurring during infusion or within 24 hours after the initiation of infusion

#### *Determination of ANA*

ANA was analysed at initiation of infliximab treatment. In case of missing data, ANA status within a month before the treatment start was used. The measurement of ANA was performed using indirect immunofluorescence assay with HEp2 cells as substrate and anti-IgG conjugates as described earlier [21]. The analysis was done with accredited method at the Department of Clinical Microbiology and Immunology, Lund University Hospital, Lund, Sweden (accredited according to SS-EN ISO/IEC 17025). Values  $\geq 14$  units/ml corresponding to a titer of 400 were considered positive. The reference interval was based on results of measurements in healthy blood donor controls and the upper limit was determined to give between 1 - 5 % of the controls positive for ANA.

#### *Statistical analysis*

Statistical analysis and calculations were performed using SPSS 13.00 software. Due to differences in baseline characteristics, predictive values were determined using binary logistic regression model adjusting for age, gender, and prednisolone dosage. The impact of continuous variables was estimated by Mann-Whitney U-test. Differences regarding infusion reactions between RA and SpA were analysed using Fisher's exact test.  $P < 0.05$  was considered significant.

## **Results**



Altogether 213 RA patients and 76 SpA patients were treated with infliximab in the period 1999-2005. Demographics, disease characteristics, treatment characteristics and disease activity variables are provided in tables 1 and 2. The proportion of women was larger in RA than SpA patients. RA patients were older at initiation of infliximab treatment but disease duration at inclusion did not differ between RA and SpA patients. Age at disease onset was lower in SpA patients. Baseline ANA status did not differ significantly between RA and SpA patients, and there were missing data in only 12 (5.6%) of RA and 4 (5.3%) of SpA patients. Also mean HAQ, CRP and ESR differed between the two patient groups.

Infliximab was given as mono-therapy (i.e. without other DMARD) in 46 (21.6%) of RA and 31 (40.8%) of SpA patients. Among concomitant DMARDs MTX was most frequently used in both patient groups, though in a larger proportion in RA (60.6%) than SpA (46.1%). MTX dosage did not differ between the groups at start compared to at infusion reaction.

Sulphasalazine, azathioprine and other DMARDs were used less frequently in both patient groups. Mean number of previous DMARDs was 3.3 (range 1-9) and 1.9 (range 0-5) in RA and SpA, respectively. A substantial proportion of RA patients had concomitant prednisolone treatment at baseline when compared with SpA patients.

A larger proportion of RA patients (21.1%) than SpA patients (13.2%) developed some kind of infusion reaction during the treatment. However, this difference failed to reach statistical significance (Fischer's exact test;  $p=0.126$ ). The treatment duration before the infusion reaction occurred was significantly shorter in SpA patients compared to RA patients (Mann-Whitney U-test;  $p=0.006$ ).

Infliximab dosage was increased in totally 21 of 45 (46,7%) RA patients and 3 of 10 (30%) SpA patients who developed infusion reactions. Among RA patients the dosage was increased

between 3 and 6 months of treatment duration in 11 patients, between 6-12 months in 7 and after 12 months in 9 patients. Corresponding number of SpA patients were 3, 2 and 0.

Infliximab dosage was increased more than once in 6 RA and 2 SpA patients. No significant correlation between increase in dosage over time and development of infusion reactions was found (Chi2 test). For comparison there were increases of dosage in 98/168 (58,3%) of RA patients and 38/66 (57,6%) of SpA not developing infusion reaction.

When applying the binary regression model, presence of ANA at treatment start and infliximab given without MTX or as mono-therapy were each identified as independent risk factors for infusion reaction in patients with RA. Furthermore, the combination of both predictors was associated with further increased risk for developing an infusion reaction.

ANA positivity at baseline and infliximab given without MTX were associated with the most pronounced risk. Consequently, RA patients without ANA at treatment initiation and receiving infliximab in combination with MTX are least likely to develop an infusion reaction (table 3 and figure1).

Concerning DMARDs other than MTX, the usage of sulphasalazine, azathioprine and all other DMARDs as a group were not found to be associated with infusion reactions in the regression model. Lower age at disease onset and longer disease duration were associated with infusion reactions ( $p= 0.012$  and  $p=0.036$ , respectively), whereas age, gender, CRP, ESR, HAQ and DAS28 at baseline did not influence this risk in patients with RA. No predictors of infusions reactions could be identified in SpA patients.

The stratification of infusion reactions according to grade of seriousness is shown in table 4. The majority of patients with RA who developed serious or life threatening reactions had

clinical symptoms suggesting type I allergic reactions (anaphylactic - urticaria, hypotension, tachycardia, obstructive lung symptoms). These reactions led to withdrawal of infliximab treatment. However, a substantial proportion of the RA patients that developed infusion reactions had reactions clinically not judged as allergic. Infusion reactions classified as moderate were mostly characterised by non-specific symptoms including headache, nausea, dizziness, fever or chills, chest or back pain, coughing or general discomfort. These did not necessarily lead to discontinuation of the treatment. Mild infusion reaction symptoms were typically transient headache, fatigue, pain in general, and the majority of these patients could continue the treatment.

Concerning SpA patients 3 patients developed infusion reactions suggesting type I allergic reactions. These reactions led to withdrawal of infliximab. Other infusion reactions were characterized by more unspecific symptoms.

## **Discussion**

The main findings in this study are that positive ANA before the initiation of treatment with infliximab and usage of infliximab without MTX in patients with RA are independent risk factors for developing infusion reactions and also that the risk is considerably increased in patients with the combination of both factors. The risk is most pronounced in ANA positive patients treated with infliximab as monotherapy suggesting that concomitant treatment with DMARDs, preferably MTX, should be encouraged before initiation of infliximab in RA patients. Concerning DMARDs other than MTX, usage of sulphasalazine, azathioprine and all other DMARDs as a group were not associated with infusion reactions.

The issue of the association between new appearances of ANA during the infliximab treatment and clinical consequences of these has been addressed in several studies [7-11]. However, to our knowledge, this is the first paper reporting the predictive value of baseline ANA for development of infusion reactions. ANA status is usually known or can be determined before the initiation of biologic treatments. Our results suggest that presence of ANA should be taken into account when infliximab treatment is considered.

The observation that combined treatment with infliximab and MTX was associated with reduced induction of anti-infliximab antibodies raised the hypothesis of reduced immunogenicity against monoclonal antibodies by concomitant MTX treatment [2]. Also, patients with Crohn's disease experienced less frequent infusion reactions if infliximab treatment was given in combination with other immunosuppressive agents [6]. Our results are in line with these reports suggesting that continuous MTX treatment should be encouraged in RA patients treated with infliximab and probably also other monoclonal antibodies.

We found no association between baseline ANA status and usage of MTX and subsequent development of infliximab related infusion reactions in patients with SpA. However, this finding must be interpreted with caution due to limited statistical power. In our study, concomitant treatment with MTX was used to a lesser extent in patients with SpA compared to RA probably because MTX is not a prerequisite in SpA patients. Furthermore usage of infliximab as a monotherapy more frequently in SpA (48,9 % vs 21,6% table 3) could be one possible explanation for the significant shorter treatment duration at the moment of infusion reaction (4,3 months and 11,5 months for SpA and RA, respectively )

Additionally, more RA than SpA patients developed infusion reactions during the treatment. However, no significant difference in frequency of infusion reactions was observed between RA and SpA patients, possibly also reflecting the problem of statistical power. Provided that the same underlying mechanism is responsible for development of infusion reactions in both RA and SpA, the usage of infliximab as monotherapy in a large proportion of SpA patients may have contributed to the non-significant difference.

In case of insufficient clinical response after 3 months infliximab dosage could be increased. In a substantial proportion of both RA and SpA patients infliximab dosage was increased over time but no clear association between increased dosage and infusion reactions could be detected.

A further interesting observation in this study is the unexpected high frequency (25%) of ANA positivity at baseline in SpA patients. In a recently published review article by De Rycke et al which includes an overview of the studies investigating autoantibody profile during treatment with infliximab, ANA was detected in between 4 and 17% of SpA patients before the initiation of the treatment [9]. One possible explanation might be the use of different methods for detecting ANA. An advantage of international guidelines for clinical use of immunofluorescence assay for determination of ANA is that comparisons of the results from different studies should be possible [18]. The method applied in our study is accredited and used as routine at Lund University Hospital. The prevalence of ANA in 27.9 % of our RA patients is comparable to that in the literature [9].

The mechanism explaining the association between ANA positivity and infusion reactions remains unknown. Immunological mechanisms are thought to be responsible for many of the toxic reaction to some DMARDs [12,13,14]. Furthermore, Panayi et al found a positive correlation between HLA-DR phenotypes and toxic complication of some DMARDs [14].

The findings of increased risk of developing infusion reactions in ANA positive RA patients in our study support the plausibility of underlying immunogenetic mechanisms of drug related side effects.

One weakness of this work is that determination of anti-infliximab antibodies was not performed. In a previously published study including infliximab treated patients with Crohn's disease development of anti-infliximab antibodies of IgG type was found to be associated with increased risk of infusion reactions [6]. Our pilot study on development of anti-infliximab antibodies and infusions reactions in selected patients with RA [22], showed that anti-drug antibodies were mostly of IgG and not IgE type in spite of clinical symptoms indicating type I allergic reactions. The clinical relevance of measuring these antibodies is currently being investigated.

In summary, RA patients with ANA present at treatment initiation with infliximab and treated without MTX are at increased risk of developing infusion reactions. The possible protective effects of other DMARDs than MTX against such infusion reactions remain to be studied.

## **Conclusion**

RA patients treated with infliximab without MTX and with positive baseline ANA are at increased risk of developing infliximab related infusion reactions. Both positive ANA at baseline and not usage of concomitant methotrexate contributed to the development of infusion reactions in infliximab treated rheumatoid arthritis patients.

### **Competing interests**

The authors declare that they have no competing interests.

### **Authors' contributions**

MCK was responsible for data analysis and interpretation and wrote the manuscript.

LL contributed to the collection of data, interpretation and preparation of the manuscript.

GS contributed to the idea and to the critical revision of the article. LT was responsible for laboratory analysis.

TS contributed to the critical revision of the manuscript and supervised the study.

PG was responsible for the planning of the study and contributed to data analysis, interpretation, and preparation of the manuscript and supervised the study.

All authors read and approved the final manuscript.

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Table1: Demographic characteristics of the patients, ANA status at baseline and characteristics of the infusion reactions

	<b>Rheumatoid arthritis (N=213)</b>	<b>Spondylarthropathies (N=76)</b>
	<i>mean ± SD</i>	<i>mean ± SD</i>
Age at inclusion (years)	55.9 ± 14.0	45.0 ± 13.1
Age at disease onset (years)	43.2 ± 15.2	31.9 ± 13.1
Disease duration at start (years)	12.6 ± 10.0	13.1 ± 11.0
Treatment duration at infusion reaction (months)	11.5 ± 9.6	4.3 ± 4.3
Number of previous DMARDs	3.3 ± 1.7	1.9 ± 1.1
	<i>N (%)</i>	<i>N (%)</i>
Female	156 (73.2 %)	40 (52.6 %)
ANA positivity (yes)	56/201 (27.9%)	18/72 (25.0%)
Infusion reaction (yes)	45 (21.1 %)	10 (13.2 %)
Infusion reaction leading to withdrawal of treatment	33/45 (73.3 %)	9/10 (90%)

Table 2: Treatment characteristics and disease activity measures at baseline and at the infusion reaction in patients with rheumatoid arthritis (RA) and spondylarthropaties (SpA)

	At treatment initiation		At infusion reaction	
	RA	SpA	RA	SpA
Number	213	76	45	10
<b>Drug treatments</b>				
	<i>N (%)</i>	<i>N (%)</i>	<i>N (%)</i>	<i>N (%)</i>
Infliximab monotherapy	46 (21.6%)	31 (40.8%)	22 (48.9%)	7 (70%)
Methotrexate	129 (60.6%)	35 (46.1%)	17 (37.8%)	2 (20%)
Sulphasalazine	33 (15.5%)	6 (7.9%)	5 (11.1%)	0
Azathioprine	10 (4.7%)	3 (3.9%)	1 (2.2%)	0
Other DMARDs	30 (14.1%)	4 (5.3%)	4 (8.9%)	1 (10%)
Prednisolone	155 (72.8%)	30 (39.5%)	38 (84.4)	6 (60%)
	<i>mean ± SD</i>	<i>mean ± SD</i>	<i>mean ± SD</i>	<i>mean ± SD</i>
Methotrexate dosage (mg/week)	17.3 ± 5.2	15.6 ± 6.8	15.4 ± 6.1	16.2 ± 12.4
Sulphasalazine dosage (g/week)	13.5 ± 2.3	15.2 ± 2.9	15.4 ± 3.1	none
Azathioprine dosage (mg/week)	745.5 ± 432.1	758.3 ± 101.0	700	none
Prednisolone (mg/week)	43.2 ± 37.8	20.5 ± 28.9	33.4 ± 29.0	11.7 ± 18.0
<b>Disease activity measures</b>				
	<i>mean ± SD</i>	<i>mean ± SD</i>	<i>mean ± SD</i>	<i>mean ± SD</i>
DAS28 *	5.4 ± 1.3	-----	5.0 ± 1.6	-----
HAQ **	1.4 ± 0.6	1.1 ± 0.6	1.3 ± 0.6	1.1 ± 0.8
CRP***	30.9 ± 33.4	21.7 ± 26.2	25.5 ± 26.3	14.4 ± 16.9
ESR#	36.8 ± 27.2	27.4 ± 23.0	37.8 ± 25.5	29.2 ± 32.1
VASpain (0-100)##	61.7 ± 22.2	61.4 ± 19.7	48.3 ± 25.7	55.9 ± 32.3

VASglobal (0-100)###	63.4±21.6	63.4±19.7	52.5±25.4	56.3±33.6
Evaglobal (0-5)†	2.3±0.6	1.8±0.7	1.9±0.9	1.8±0.6
TJC (0-28)††	8.7±7.3	5.9±6.9	7.9±7.8	6.6±8.3
SJC (0-28)†††	8.9±6.0	3.0±4.1	6.9±6.0	3.3±5.4

\*DAS28= disease activity score using 28 tender and 28 swollen joint count,

\*\*HAQ= health assessment questionnaire,

\*\*\*CRP= C-reactive protein;

# ESR= erythrocyte sedimentation rate,

##VASpain= patient's assessment of pain,

###VASglobal= patient's global assessment,

†Evaglobal= physician's global assessment,

††TJC= tender joint count,

††† SJC= swollen joint count.

Table 3: Positive predictive values for separate factors and combination of presence of antinuclear antibodies (ANA) and methotrexate (MTX) treatment for development of infusion reactions in RA patients

	Pats (N)	Odds ratio	95%CI	p
ANA positivity	56	2.1	1.04-4.29	0.040#
Infliximab without methotrexate	84	3.1	1.53-6.29	0.002#
Infliximab as monotherapy	46	3.6	1.73-7.14	0.001#
ANA pos + MTX no	26	4.6	1.61- 13.15	0.004###
ANA pos + MTX yes	30	2.2	0.74 - 6.36	0.161##
ANA neg + MTX yes	93	1.0	-	-
ANA neg + MTX no	52	3.3	1.35- 8.06	0.009###

# adjusted for age, gender and prednisolone at start

## adjusted for age, gender and disease duration

Table 4: Number of infusion reactions classified according to grade of seriousness

		<b>Infliximab dosage</b>				
	<b>Grade of seriousness</b>	<b>all infusion reactions</b>	<b>infliximab unchanged</b>	<b>infliximab increased 3-6 months</b>	<b>infliximab increased 6-12 months</b>	<b>infliximab increased 12 months</b>
RA patients (n=45)	Life threatening	2	1	1	0	0
	Serious	16	11	2	1	2
	Moderate	24	15	8	5	6
	Mild	3	1	0	1	1
SpA patients (n=10)	Life threatening	0	0	0	0	0
	Serious	6	4	1	1	0
	Moderate	2	1	1	0	0
	Mild	2	1	1	1	0

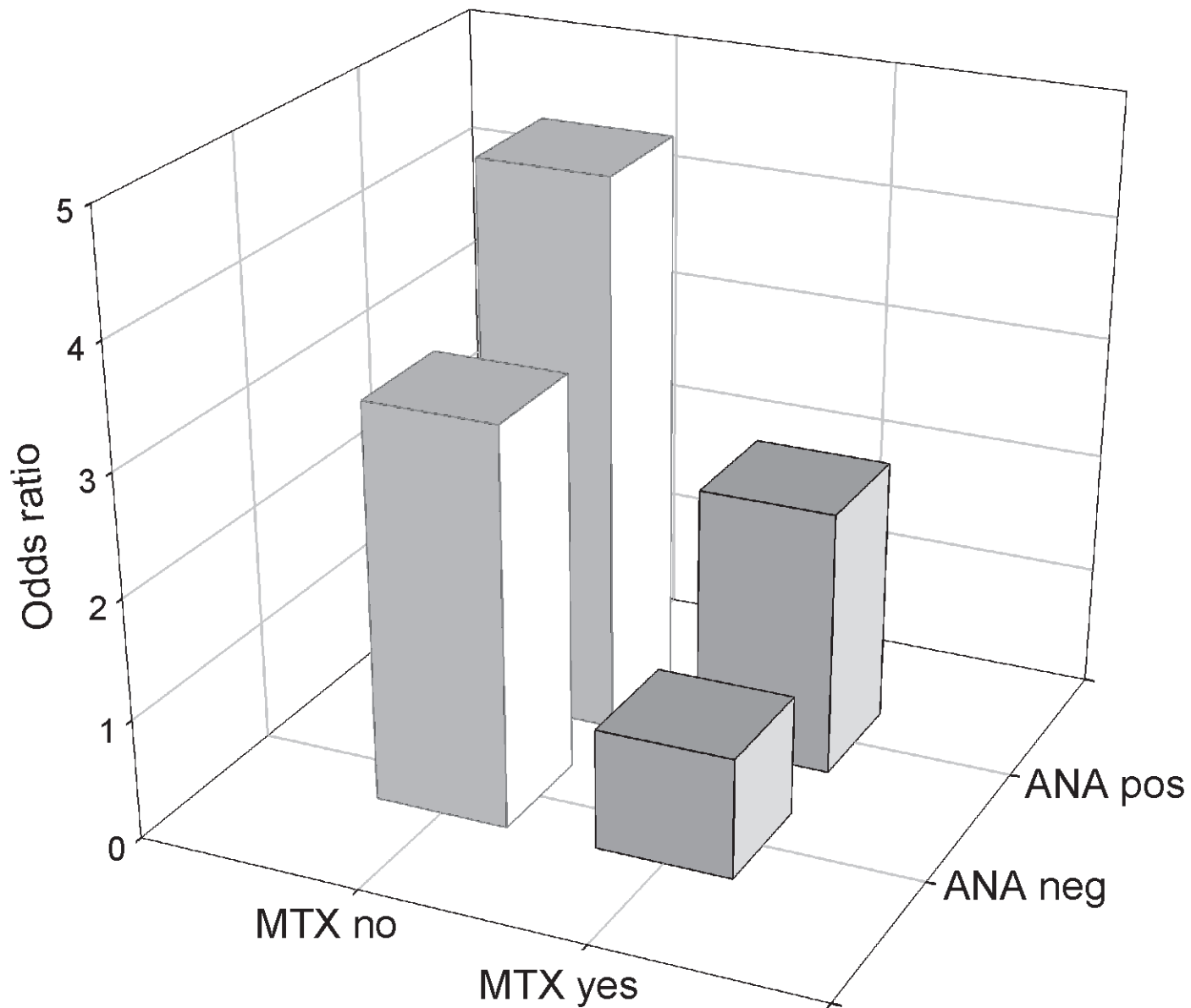


Figure 1