The influence of biological sex and body mass index on the response to and duration of TNFα inhibitor treatment in patients with rheumatoid arthritis: a retrospective cohort study

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Contents

Abstract

Objective: To study the association between biological sex and tumour necrosis α (TNFα) inhibitor response, to investigate the modifying effects of body mass index (BMI) on TNFα inhibitor treatment response and to study differences in drug survival and reasons to stop anti-TNFα treatment in patients with rheumatoid arthritis (RA).

Method: TNFα inhibitor-naive RA patients treated with TNFα inhibitors were included in this retrospective cohort study. The primary endpoint was the difference between Disease Activity Score 28 with CRP (DAS28-CRP) at the start of TNFα inhibitor treatment and after 3-12 months (ΔDAS28-CRP). Multivariable linear regression was used to determine differences in ΔDAS28-CRP. A sub-group analysis based on BMI was done to determine effect modification of BMI on ΔDAS28-CRP. Drug survival was analysed using the log rank test. Differences in reasons to stop TNFα inhibitor treatment was analysed using chi-square.

Results: A total of 203 patients, 143 females and 60 males, were included. ΔDAS28-CRP did not differ significantly between the two groups when corrected for lean body mass (LBM) ($p = 0,082$). This was also the case after stratification (BMI ≥ 30 kg/m^2 $p = 0,874$; BMI < 30 kg/m^2 $p = 0,096$). Differences in drug-survival were not significant ($p = 0,236$). Differences in reasons to stop anti-TNFα treatment were not significant ($p = 0,116$).

Conclusion: Biological sex seems to not have an association of TNFα inhibitor treatment response in patients with RA. We do however see a trend towards females on average having a worse TNFα inhibitor treatment response than males. This finding can possibly be attributed to a small study population.

Samenvatting in het Nederlands

Doelstelling: Het bestuderen van de associatie tussen geslacht en tumor necrosis α (TNFα) remmer respons, het onderzoeken van de modificerende effecten van body mass index (BMI) op TNFα remmer respons en het bestuderen van de verschillen in tijd op behandeling en redenen om te stoppen met anti-TNFα behandeling bij patiënten met reumatoïde artritis (RA).

Methode: In deze retrospectieve cohortstudie werden TNFα remmer-naïeve RA-patiënten geïncludeerd die werden behandeld met TNFα-remmers. Het primaire eindpunt was het verschil tussen de Disease Activity Score 28 met CRP (DAS28-CRP) bij aanvang van de behandeling met TNFα remmers en na 3-12 maanden (ΔDAS28-CRP). Multivariabele lineaire regressie werd gebruikt om verschillen in ΔDAS28-CRP te bepalen. Een subgroep analyse op basis van BMI werd uitgevoerd om het effect van BMI op ΔDAS28-CRP te bepalen. De tijd op behandeling werd geanalyseerd met behulp van de log rank test. Verschillen in redenen om te stoppen met TNFα remmers werden geanalyseerd met behulp van chi-kwadraat.

Resultaten: In totaal werden 203 patiënten geïncludeerd, 143 vrouwen en 60 mannen. ΔDAS28-CRP verschilde niet significant tussen de twee groepen wanneer er gecorrigeerd werd voor spiermassa ($p = 0,082$). Dit was ook het geval na stratificatie (BMI ≥ 30 kg/m2 $p = 0,874$; BMI < 30 kg/m2 $p = 0,096$).

Verschillen in tijd op behandeling waren niet significant (p = 0,236). Verschillen in redenen om te stoppen met anti-TNFα behandeling waren niet significant (p = 0,116).

Conclusie: Geslacht lijkt geen verband te hebben met de respons op TNFα remmers bij patiënten met RA. Wel zien we een trend dat vrouwen gemiddeld een slechtere TNFα remmers respons hebben dan mannen. Deze bevinding kan mogelijk worden toegeschreven aan een kleine onderzoekspopulatie.

Introduction

Rheumatoid arthritis (RA) is a progressive, immunoglobulin G (IgG) mediated autoimmune disease. The synovial tissue of the joints is being attacked and broken down by the own immune system, causing chronic inflammation. This leads to swollen, red joints and severe pain during movement which can be impairing to the patient's quality of life (1).

For every hundred people living in the West, at least one person will be affected by RA. The majority of these patients are female, with a female-male ratio of three to one (1). A possible explanation for this female bias is the role of sex hormones in regulating immune reactions.
Oestrogens have a pro-inflammatory effect: e.g. they stimulate the production of IgG and pro-inflammatory cytokines like IL-6 and TNFα. (2) (3). Androgens have the opposite effect and stimulate anti-inflammatory cytokines like IL-10 (2) (4).
There is some evidence that RA patients have a high oestrogen/androgen ratio in their serum and synovial fluid, leading to an increased production of pro-inflammatory cytokines like TNFα. These activate aromatase, an enzyme which converts androgens to oestrogen. This leads to a skewed oestrogen/androgen ratio upholds pro-inflammatory cytokine production and inflammation (5).

RA is treated with disease-modifying anti-rheumatic drugs (DMARDs) like tumour necrosis α (TNFα) inhibitors. TNFα inhibitors inhibit the pro-inflammatory effect of TNFα resulting in a decrease of inflammation in the joints and lessening symptoms (6).
In multiple rheumatic diseases it was found that males achieved lower disease activity scores than females after TNFα inhibitor treatment (7).
In RA specifically, females tend to have higher disease activity scores (8) (9) (10), score worse on patient reported outcome measures (PROMs) (11) (12) and are less likely to achieve and attain remission (10) (13) (11) when treated with TNFα inhibitors.

It is unknown why this difference in response to TNFα inhibitors is seen, but body composition might have something to do with this. We have seen in multiple rheumatic diseases, including RA, that having a Body Mass Index (BMI) ≥ 30 kg/m^2 was linked to having a smaller chance of having a positive response to TNFα inhibitor treatment (14) (15) (16) (17). In a study on ankylosing spondylitis, researchers saw that specifically a high body fat percentage (BFP) was linked to lower TNFα inhibitor responses (16).
Seeing that females tend to have a higher proportion of body fat than males (18), there is reason to believe that BMI might be an underlying reason for these differences in response to TNFα inhibitor treatment.

The primary aim of this study is to evaluate the differences in response to treatment with TNFα inhibitors between TNFα inhibitor-naïve, RA diagnosed males and females.
The secondary aim of this study is to analyse the modifying effects of BMI on the response to treatment with TNFα inhibitors and to determine differences in drug survival and reasons to stop TNFα inhibitor treatment between males and females.

Based on the previously mentioned results, biological sex is expected to be associated with TNFα inhibitor treatment response in RA patients. It is hypothesizes that TNFα inhibitor treatment will be less effective in female than in male patients.
Based on the previous hypothesis and previously stated literature, it is expected that BMI will be an effect modifier in the relationship between biological sex and TNFα inhibitor response.

Method

Study design

This was a single-centre, retrospective, observational cohort study.

Patient selection/Inclusion and exclusion criteria

The study population consisted of patients from Haga Teaching Hospital in The Hague, The Netherlands. These patients were (I) all diagnosed with RA, (II) were all TNFα inhibitor-naïve and (III) have first started using a TNFα inhibitor after the first of January 2017 up until May 2022.
To include these patients, the diagnosis was verified by using Diagnosis Treatment Combination codes, in Dutch "Diagnose Behandeling Combinatie - code" (DBC), or through the diagnosis "rheumatoid arthritis" in the electronic health record (EHR). The DBC-codes used to identify the patients were 0324-101 (rheumatoid arthritis) and 0324 – 117 (polyarthritis, not classified). TNFα inhibitor-use was verified by checking for mentions of infliximab, etanercept, adalimumab, golimumab or certolizumab pegol in the patient their medication list in the EHR. The starting date of TNFα inhibitor treatment was set on the date the first prescription was sent to the outpatient pharmacy of Haga Teaching Hospital.
Exclusion criteria were as follows: (I) being younger than 18 years old when starting TNFα inhibitor treatment, (II) pregnancy during the first year of TNFα inhibitor treatment, (III) being treated with a TNFα inhibitor for other indications than RA, (IV) opted out of using their data for scientific research and (V) being treated for RA in another hospital.
Baseline (t = 0) was defined as the starting date of TNFα inhibitor treatment. T = 1 was defined as the first recorded data point in the EHR three to eight months after baseline.
The board of the Haga Teaching Hospital approved the execution of this study.

Data collection

Patient selection and data collection was done using CTcue. CTcue is a software program which is able to extract patients and patient data from EHRs using machine learning and artificial intelligence. By using this tool, it was possible to extract pseudonymized patient data. In this way, the privacy of the patient was protected (19).

Data was collected by building queries in CTcue. By building queries, only specific patient data for this study was collected and patient privacy respected. The collected data included patient characteristics (biological sex, age at start of treatment, date of diagnosis, weight, height), TNFα inhibitor specific information (starting- and stopping date of TNFα inhibitor treatment, reasons to stop TNFα inhibitor treatment), presence of certain comorbidities (asthma, osteoporosis, chronic obstructive pulmonary disease, lymphoma, lung carcinoma, melanoma, smoking, heart failure, diabetes, coronary artery disease, acute coronary syndrome, atrial fibrillation, inflammatory bowel disease and psoriatic arthritis), methotrexate use and dosage, laboratory parameters (serum anti-cyclic citrullinated peptide concentration, serum C-reactive protein concentration, erythrocyte sedimentation rate) and test scores (count of swollen joints, count of tender joints, Health Assessment Questionnaire – Disease Index (HAQ) scores , Disease Activity Scores 28 with CRP (DAS28-CRP), SF-36 scores, Visual Analogue Scale (VAS) scores).

Endpoints

The primary endpoint was defined as the difference between males and females in TNFα inhibitor treatment response. This response was assessed as the difference in DAS28-CRP (20) between t = 0 and t = 1, also known as ΔDAS28-CRP. The DAS28-CRP is an objective and clinically validated measuring instrument to calculate the disease activity in RA patients (20). DAS28-CRP < 2,6, is classified as "in remission". "Low disease activity" is defined as 2,6 < DAS28-CRP < 3,2. DAS28-CRP ≥ 3,2 is classified as having a "high disease activity"(20).

LBM and BFP were calculated for covariance. The formulas used to calculate these variables can be found in Appendix 1.

Secondary endpoints were defined as the difference between males and females in TNFα inhibitor response after stratification based on BMI. Here, ΔDAS28-CRP was also used as a measure for TNFα inhibitor response. The formula used to calculate BMI can be found in Appendix 1.

Another secondary endpoint included differences in drug survival between males and females. This was defined in months of TNFα inhibitor usage until quitting treatment or censorship of data. The reasons for patients to quit their first TNFα inhibitor used were also included. These were categorised into four categories: ineffectiveness of the drug, side effects, remission and other reasons.

To analyse how TNFα inhibitor therapy influenced disease activity and PROMs, differences in DAS28-CRP and its components, HAQ (21), SF-36 (22) and VAS scores at t = 1 between males and females were also included in the secondary endpoints.

Statistical analyses

Statistical analysis was done in IBM SPSS Statistics v. 22.0 (23). Quantitative data was tested for normality. To asses differences between males and females, t-tests were carried out for normally distributed continuous variables and described as means and standard deviation (SD). Mann-Whitney U tests were carried out for non-normally distributed continuous variables and described as median and interquartile range (IQR). For categorical and dichotomous variables differences were assessed through chi-square tests and Fisher's exact tests. These were described as frequencies and percentages in the sample groups. An outcome was labelled as significant if $p < 0,05$.

To examine the association between biological sex and ΔDAS28-CRP, multivariate linear regression models were made. Variables which differed ($p < 0,1$) between males and females were individually tested as a determinant in multivariable linear regression models together with biological sex. Variables which altered the association between biological sex and ΔDAS28-CRP ≥ 10% were put into the final multivariable linear regression model together with biological sex.

To examine if BMI was an effect modifier of the association between biological sex and TNFα inhibitor treatment response, BMI was stratified by BMI < 30 kg/m^2 and ≥ 30 kg/m^2.

A Kaplan-Meier survival curve was made to illustrate differences in drug survival. Drug survival was defined as the number of months the patient was treated with a TNFα inhibitor. Because some patients overtime were treated with more than one TNFα inhibitor, the cumulative number of months for all TNFα inhibitor treatments was used. An event was defined as a termination prescription sent to the outpatient pharmacy, which indicated that the patient will no longer be treated with the TNFα inhibitor.

Results

Patient baseline characteristics

In Table 1 the main baseline characteristics of the study population are illustrated.
A total of 235 patients were, based on the inclusion criteria, extracted from CTcue. Based on the exclusion criteria, 32 patients were excluded. The exact reasons for exclusion can be seen in Figure 1. The final population used for this study contains 203 patients. The majority of the population, 143 patients, are female. 60 patients are male.

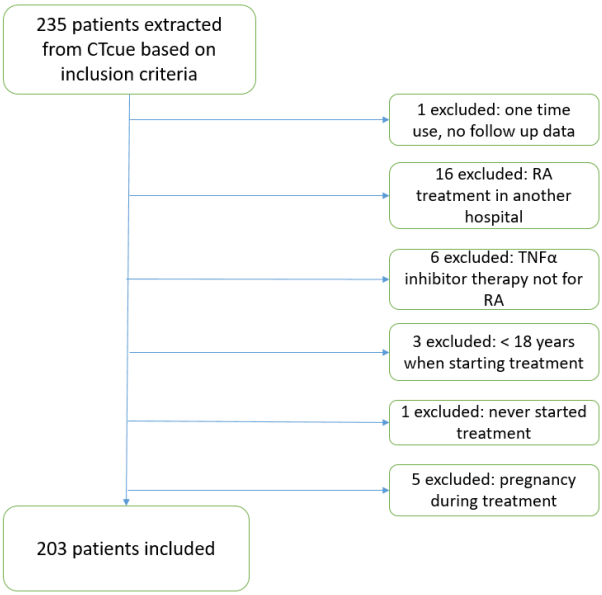

Figure 1: Flowchart of inclusion and exclusion of patients

Males and females do not differ in average age. However, there are significantly more males (86,7%) than females (72,7%) older than 50 years (p = 0,032).
There is no significant difference in BMI between the sexes. Males are significantly taller and heavier than females (both p < 0,001). In body composition, females on average have a significantly higher BFP while males have a significantly higher LBM (both p <0,001).
There are no significant differences in methotrexate (MTX) usage. The weekly dose differs between the sexes: they both have a median at 25 mg/week but females are more often prescribed lower dosages.
There are no differences in which TNFα inhibitor patients are treated with.
Males and females on average have an almost identical DAS28-CRP at baseline: 3,7 and 3,8 respectfully. However, “low disease activity” is almost twice as common with females (17,4%) than with males (8,8%). As with overall quality of life and laboratory markers, there are no significant differences between males and females.
Comorbidities screened in this study are based on ones prevalent in the general RA (24). There are two things to be noted about the RA patient population at Haga Teaching Hospital. Firstly, osteoporosis is more common in females (44,8%) than males (26,7%). Secondly, asthma is a diagnosis more than twice

as many females have than males, respectively 16,8% and 6,7%. Even though these two results are not significant (p = 0,055 and p = 0,056 respectively), we can conclude that there is a trend to be seen.

Table 1: Patient characteristics at baseline (t = 0)

Variable	**Females (n = 143)**	**Males (n = 60)**	**p-value**	**Missing data ***
Biological sex - count (%)	143(70,4)	60(29,6)		
Age - yr	57,4 ± 15,2	60,3±10,4	0,114	
Age ≥ 50 - count (%)	104(72,7)	52(86,7)	0,032	
Weight - kg	73,3 ± 17,9	85,9 ± 15,0	< 0,001	13
Height - cm	165,3 ± 7,9	179,5 ± 7,7	< 0,001	15
Body Mass Index - kg/m2	26,9 ± 5,9	26,6 ± 3,9	0,704	15
Body Mass Index ≥ 30 kg/m2 - count (%)	31 (21,7)	10 (24,4)	0,417	
Body Fat Percentage - %	40,4 ± 7,8	29,7 ± 4,7	< 0,001	15
Lean Body Mass - kg	48,4 ± 7,0	63,7 ± 7,5	< 0,001	15
Duration of rheumatoid arthritis until TNFα inhibitor treatment - months	26,0 (10,0 - 77,0)	20,5 (9,0 - 68,0)	0,309	
Time between measurement DAS28-CRP score at t = 0 and t = 1 - months	5,0 (4,0 - 7,0)	6,5 (4,0 - 9,8)	0,187	80
Medication				
MTX in combination with TNFα inhibitor usage - count (%)	86(60,1)	39(65,0)	0,516	
Weekly MTX dosage during TNFα inhibitor usage - mg	25,0 (15,0 - 25,0)	25,0 (20,0 - 25,0)	0,035	78
First TNFα inhibitor used - count (%)			0,270	
Adalimumab	58(40,6)	31(51,7)	0,146	
Etanercept	73(51,0)	28(46,7)	0,569	
Infliximab	3(2,1)	1(1,7)	1,000	
Golimumab	1(0,7)	0(0,0)	1,000	
Certolizumab pegol	8(5,6)	0(0,0)	0,108	
Scores				
Count of swollen joints ‖	4,0 (2,0 - 7,0)	3,0 (2,0 - 7,0)	0,535	23
Count of tender joints ‖	5,0 (2,0 - 8,0)	3,0 (2,0 - 6,0)	0,104	22
Health Assessment Questionnaire - Disease Index score ∫	1,0 (0,4 - 1,4)	0,5 (0,1 - 1,1)	0,072	135
DAS28-CRP score**	3,7±1,1	3,8±1,2	0,534	25
Disease activity based on DAS28-CRP:			0,308	25
Remission - count (%)	21 (17,4)	10 (17,5)		
Low disease activity - count (%)	21 (17,4)	5 (8,8)		
High disease activity - count (%)	79 (65,3)	42 (73,3)		
SF-36 score †	52,0 (36,5 - 79,5)	74,0 (50,5 - 83,0)	0,160	152

Variable	Females (n = 143)	Males (n = 60)	p-value	Missing data *
Visual Analogue Scale score ‖‖	55,1±25,3	51,3±24,3	0,347	25
Baseline laboratory markers				
Serum anti-cyclic citrullinated peptide - U/ml	46 (2,0 - 143,8)	26,5 (1,0 - 209,5)	0,908	103
Serum C-reactive protein above ULN - count (%) ∫∫	33(23,7)	21(35,0)	0,101	4
Serum C-reactive protein - mg/l	5,0 (2,0 - 10,0)	4,0 (2,0 - 13,0)	0,972	4
Erythrocyte sedimentation rate - mm/hour	16,0 (8,0 - 34,0)	14,0 (5,0 - 29,0)	0,377	3
Comorbidities - count (%)				
Asthma	24(16,8)	4(6,7)	0,056	
Osteoporosis	64(44,8)	16(26,7)	0,055	
Chronic Obstructive Pulmonary Disease	15(10,5)	8(13,3)	0,560	
Lymphoma	0(0,0)	1(1,7)	0,296	
Lung carcinoma	2(1,4)	3(5,0)	0,153	
Smokers	28(20,4)	13(21,7)	0,201	
Melanoma	11(7,7)	2(3,3)	0,352	
Heart failure	6(4,2)	2(3,3)	1,000	
Diabetes	20(14,0)	7(11,7)	0,657	
Coronary artery disease	26(18,2)	10(16,7)	0,796	
Acute coronary syndrome	18(12,6)	8(13,3)	0,885	
Atrial fibrillation	12(8,4)	5(8,3)	0,989	
Inflammatory Bowel Disease	8 (5,6%)	1 (1,7%)	0,286	
Psoriatic Arthritis	10 (7,4)	5 (8,3)	0,772	

Plus-minus values represent means ± SD

Non-normally distributed values are represented as median (Q1 - Q3)

Count and percentages are depicted as the amount and percentage of patients within the same sex who are afflicted by the stated variable.

* Missing refers to amount of patients from whom we were unable to find data for the particular variable mentioned

‖ A total of 23 specific joints are examined on tenderness and swollenness. The higher the amount of tender or swollen joints, the higher the disease activity.

∫ The Health Assessment Questionnaire Disease Index score ranges from 0 to 3: the higher the score, the higher the overall patient disability

** The DAS28-CRP score ranges from 0 to 9,4: the higher the score, the higher the disease activity.

Remission equals DAS28-CRP < 2,6

Low disease activity equals 2,6 ≤ DAS28-CRP ≤ 3,2

High disease activity equals DAS28-CRP > 3,2

† The SF-36 score ranges from 0 to 100: the lower the score, the higher the overall patient disability

‖‖ The Visual Analogue Scale ranges from 0 to 100: the higher the score, the higher the overall patient disability

∫∫ ULN has been set on 10 mg/L serum

Abbreviations: MTX = methotrexate

Primary and secondary endpoints

As can be seen in Table 2, there is no significant difference in ΔDAS28-CRP between males and females (p = 0,108). Females have an average ΔDAS28-CRP of 0,9 while males 1,4. Of the 203 patients in this study population, 80 are missing a ΔDAS28-CRP. This is equal to about 40% of the study population.

When looking at only DAS28-CRP at t = 1, males and females do not differ significantly either. Males on average score a 2,6 while females score a 2,8 (p = 0,452).

Table 2: Primary and secondary results at t = 1

End point	Females (n = 143)	Males (n = 60)	p-value	Missing *
Primary end point				
ΔDAS28-CRP †	0,9 ± 1,1	1,4 ± 1,6	0,108	80
Secondary end points				
DAS28-CRP score ‖	2,8 ± 1,1	2,6 ± 1,1	0,452	69
Disease activity based on DAS28-CRP:			0,284	69
Remission - count (%)	46 (48,4)	24 (61,5)		
Low disease activity - count (%)	17 (17,9)	7 (17,9)		
High disease activity - count (%)	32 (33,7)	8 (20,5)		
Visual Analogue Scale score ∫	37,9 ± 23,1	29,9 ± 18,1	0,041	79
SF-36 score **	77 (58,0 - 84)	59 (45,5 - 80,5)	0,315	187
Health Assessment Questionnaire - Disease Index score ††	0,9(0,5 - 1,3)	0,4 (0,1 - 0,9)	0,113	178
Count of tender joints ‖‖	2 (0,0 - 5,0)	1,5 (0,0 - 4,0)	0,420	90
Count of swollen joints ‖‖	1,0 (0,0 - 3,0)	1,0(0,0 - 2,0)	0,359	97
Serum C-reactive protein - mg/l	3,0 (1,8 - 7,0)	3,0 (2,0 - 6,8)	0,736	53

Plus-minus values represent means ± SD
Non-normally distributed values are represented as median (Q1 - Q3)
Count and percentages are depicted as the amount and percentage of patients within the same sex who are afflicted by the stated variable.
* Missing refers to amount of patients from whom we were unable to find data for the particular variable mentioned
† ΔDAS28-CRP is the difference between DAS28-CRP at baseline (t = 0) and t = 1.
‖ The DAS28-CRP score ranges from 0 to 9,4: the higher the score, the higher the disease activity.
Remission equals DAS28-CRP < 2,6
Low disease activity equals 2,6 ≤ DAS28-CRP ≤ 3,2
High disease activity equals DAS28-CRP > 3,2
∫ The Visual Analogue Scale ranges from 0 to 100: the higher the score, the higher the overall patient disability
** The SF-36 score ranges from 0 to 100: the lower the score, the higher the overall patient disability
†† The Health Assessment Questionnaire Disease Index score ranges from 0 to 3: the higher the score, the higher the overall patient disability
‖ ‖ A total of 23 specific joints are examined on tenderness and swollenness. The higher the amount of tender or swollen joints, the higher the disease activity.

At baseline almost the same percentage of males and females have a DAS28-CRP score indicating "remission" (respectively 17,5% and 17,4%). At t = 1 however, this changes to more males (61,5%) being in "remission" than females (48,4%). More males (73,3%) than females (65,3%) score a DAS28-CRP > 3,2 at baseline. At t = 1, this observation is the other way around: more females (33,7%) than males (20,5%) have scores indicating a "high disease activity". Even though we do see some differences in DAS28-CRP at t=1, these differences are not significant (p = 0,284).
As for the separate components for calculating DAS28-CRP, females on average report their overall health as significantly worse than males (VAS 37,9 and 29,9 respectively, p = 0,041). In tender- and

swollen joint count, they do not differ significantly from each other (p = 0,420 and 0,359 respectfully). Males and females have an equal CRP median of 3,0 mg/l (p = 0,736).
When looking at PROMs, HAQ and SF-36 scores are not significantly different between the sexes (p = 0,113 and p = 0,315 respectfully). Especially with PROMs, a big portion of the study population have missing data. Only 25 patients reported a HAQ-DI score and merely 16 patients reported a SF-36 score at t = 1.
There is no significant difference between males and females in time between the measurement of t = 0 and t = 1 DAS28-CRP scores (p = 0,187).

In Table 3 the results from the univariate and multivariate linear regression are shown. Females have a lower ΔDAS28-CRP than males: the difference between them is on average 0,4 points (unstandardized coefficient B = -0,406). When testing for covariates, which change this relationship between ΔDAS28-CRP and biological sex > 10%, we found that weight (female sex unstandardized coefficient B = -0,484), LBM (female sex unstandardized coefficient B = -0,639) and HAQ (female sex unstandardized coefficient B = -0,316) are covariates.
Because LBM and weight display multicollinearity, LBM was chosen to be one of the variables in the final multivariate linear regression model.

Table 3: Multivariate linear regression analysis results: comparing the influence of biological sex together with possible covariates on ΔDAS28-CRP

Variable	**Unstandardized coefficient B (95% CI)**	**p-value**	**n**
Female sex	-0,406 (-0,902 - 0,090)	0,108	123
Female sex	-0,38 (-0,885 - 0,124)	0,138	123
Age ≥ 50	0,169 (-0,386 - 0,723)	0,548	
Female sex	-0,484 (-1,024 - 0,057)	0,079	118
Weight	-0,005 (-0,019 - 0,010)	0,524	
Female sex	-0,427 (0,942 - 0,087)	0,103	117
BMI	-0,006 (-0,051 - 0,039)	0,800	
Female sex	-0,419 (-1,043-0,205)	0,186	117
BFP	-0,001 (-0,035 - 0,033)	0,952	
Female sex	-0,639 (-1,361 - 0,082)	0,082	117
LBM	-0,014 (-0,047 - 0,020)	0,415	
Female sex	-0,406 (-0,904 - 0,092)	0,109	123
Weekly MTX dosage during bDMARD usage	-0,001 (-0,022 - 0,019)	0,902	
Female sex	-0,316 (-1,220 - 0,587)	0,484	46
Health Assessment Questionnaire score	0,071 (-0,515 - 0,658)	0,808	

Variable	Unstandardized coefficient B (95% CI)	p-value	n
Female sex	-0,411 (-0,917 - 0,094)	0,110	123
Asthma	0,043 (-0,681 - 0,768)	0,906	
Female sex	-0,388 (-0,886 - 0,111)	0,126	123
Osteoporosis: prophylactic treatment	0,536 (-0,225 - 1,297)	0,166	
Osteoporosis: yes	0,09 (-0,398 - 0,578)	0,716	

Dependent variable: ΔDAS28-CRP
n is the amount of observations in every model

More than half of the study population (135 patients) are missing a baseline HAQ and even more (178 patients) at t = 1. Because of this, HAQ was not put into the final multivariate linear regression model. The final multivariate linear regression model consists of biological sex and LBM as independent variables and ΔDAS28-CRP as dependent variable. When corrected for LBM, the difference in ΔDAS28-CRP between the sexes increases: instead of 0,4 points, they now on average differ 0,6 points (p = 0,082). Even though this is not a significant result, we can see that there is a trend towards females having a lower ΔDAS28-CRP.

Results from population stratification based on BMI can be seen in Table 4. It appears that, when stratified by BMI, the difference between males and females in ΔDAS28-CRP is close to zero (female sex unstandardized coefficient B = -0,091, p = 0,874) in the BMI ≥ 30 kg/m^2 group.
In the group with a BMI < 30 kg/m^2, ΔDAS28-CRP difference between males and females increased slightly (female sex unstandardized coefficient B = -0,469, p – 0,096). The BMI < 30 kg/m^2 group contains almost five times as much patients than the BMI ≥ 30 kg/m^2 group.

Table 4: Multivariate linear regression analysis results, stratified by BMI

Stratified by	Variable	Unstandardized coefficient B (CI 95%)	p-value	n
BMI < 30 kg/m^2	Female sex	-0,469 (-1,023 – 0,085)	0,096	103
BMI ≥ 30 kg/m^2	Female sex	-0,091 (-1,278 – 1,096)	0,874	20

Dependent variable: ΔDAS28-CRP

As seen in Figure 2, males and females do not differ significantly from each other in drug survival (p = 0,236, Log Rank test). The median drug survival for males and females is 56,0 (CI 95% 40,1 – 71,9) and 52,0 (CI 95% 32,7 – 71,3) months respectfully. The mean drug survival for males and females is 46,6 (CI 95% 39,5 – 33,6) and 42,9 (CI 95% 37,9 – 49,0) months respectfully.

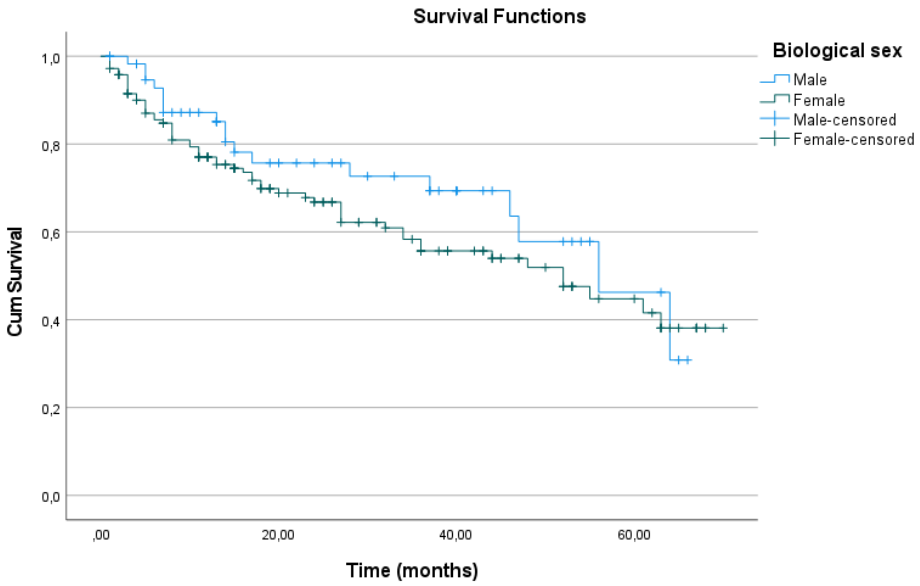

Figure 2: Kaplan-Meier curve showing total TNFα inhibitor drug survival

The reasons for patients to quit their first TNFα inhibitor treatment used, are shown in Table 5. More than three times as often females quit their treatment because of side effects (26,3%) when compared to males (8,3%), while males quit almost three times as often because of remission (16,7%) when compared to females (6,6%). These results are not significant (p = 0,116).

Table 5: Reasons to quit treatment with first TNFα inhibitor used

Reasons to terminate treatment	Males	Females	Total
Side effects	2 (8,3)	20 (26,3)	22
Ineffectiveness	16 (66,7)	40 (52,6)	56
Remission	4 (16,7)	5 (6,6)	9
Other	2 (8,3)	11 (14,5)	13
Total	24	76	100

Count and percentages are depicted as the amount and percentage of patients within the same sex who are afflicted by the stated variable.
Chi = 5,914
p = 0,116

Discussion

In this retrospective cohort study we have investigated the association between biological sex and the response to TNFα inhibitor treatment in RA patients. Based on our analysis, males and females do not differ significantly from each other in ΔDAS28-CRP.
When stratified for BMI, we do not see a significant difference in ΔDAS28-CRP between males and females.
A significant difference between males and females in drug survival and reasons to terminate TNFα inhibitors was also not found.

The contradictory outcome of our research could be explained by the small study population and a large portion of missing data. We expect a difference between males and females with a larger study population, seeing that there is a trend towards females on average having a lower ΔDAS28-CRP than males.
This difference in outcomes could perhaps also be explained by in genetic- and environmental factors. This was also argued in a large study based on the South Swedish Arthritis Treatment Group Register, where they also did not find differences in TNFα inhibitor response between males and females (25). RA is a disease which incidence, course and severity is largely influenced by genetic and environmental factors (26). Because of plausible differences in these factors between the RA population at Haga Teaching Hospital and other study populations, it is possible that our results differ from previously mentioned results.

It is unclear what the underlying mechanisms are of the plausible difference in TNFα inhibitor response between males and females as found in the previously mentioned studies. Males and females were given the same dosage and dosage form of TNFα inhibitors used and differences in volume of distribution were corrected for. Because of this, we do not expect pharmacokinetic differences to explain the differences in TNFα inhibitor effectivity.
Pharmacodynamic differences between males and females could be a possible reason, like the different effects sex hormones have on the immune system, as described previously.
When looking at data showing a high estrogen/androgen ratio in the serum and synovial fluids of RA patients, it is then logical to think that males would benefit more from TNFα inhibitors than females because of the anti-inflammatory properties of androgens (5). Straub et al. looked into this and investigated sex hormone concentration in RA patients who started TNFα inhibitor treatment. They found that after 12 weeks of TNFα inhibitor use, this sex hormone imbalance was not restored. For future research it would be interesting to look at a time period of longer than 12 weeks (27).
More research into how these pharmacodynamic differences relate to the mechanism of action of immune therapies like TNFα inhibitors is needed to be able to explain sex differences in anti-TNFα therapy effect. Results from these studies could potentially have an effect on the future of how we treat RA patients to perhaps a more sex specific approach (2).

TNFα inhibitors are just as effective in obese males as in obese females. We do however see a trend in the group with a BMI < 30 kg/m^2, where females tend to have a smaller response to TNFα inhibitor treatment than males.
Jawaheer et al. conducted a study on whether or not BMI had an association with disease activity scores and if this effect is specific to biological sex. They found that when compared to a control group with a normal BMI, being overweight and obese was significantly associated with a lower DAS28 score with

females. This result was not found in males. Although Jawaheer et al. did not specify what kind of treatment the patients had and only looked at DAS28 at one time point, it can suggest that a high BMI might be an effect modifier in TNFα inhibitor therapy response in females (28). These results were not seen in our study but perhaps this can be explained by the small sample sizes of our stratified groups.

Our results on reasons to stop the first TNFα inhibitor used match the results from a study conducted by Marchesoni et al.: the risk of discontinuing TNFα treatment is not significantly different between males and females (29). Our results also match the results from a research done with the DREAM-RA register, where they also found that ineffectiveness was the number one reason to stop TNFα inhibitor therapy followed by adverse effects (30) .

Our findings on drug-survival not being different between males and females match the results from multiple studies (31) (32).
When comparing our results with those from previous studies, it is important to note the differences in defining TNFα drug-survival. In our study, we have pooled the months of TNFα inhibitor use for every TNFα inhibitor used by the patient. In previously mentioned studies, patients were followed in only their first TNFα inhibitor used. These differences could result in different outcomes, so comparing these two should be done with caution.

One of the main strengths of this study is the use of ΔDAS28-CRP. To our knowledge, the use of ΔDAS28-CRP as a primary endpoint has only been used in a handful of studies (33) (34). One asset of using ΔDAS28-CRP is being able to see how big the relative pharmacological effect of TNFα inhibitors is, as opposed to the absolute effect which is for example measured with European Alliance of Associations for Rheumatology (EULAR) criteria (35). Another asset is that patients are their own control in the study. Because of this, differences in TNFα inhibitor response cannot be explained by a change in patient characteristics.
Another strength of this study is that our study population was clearly defined and it consists of only patients from one hospital, making our results low in heterogeneity. If our study population would consist of patients from multiple hospitals, the found differences could possibly be explained by a difference in patient populations.
The use of CTcue also made for an efficient way to conduct research with real-world data. Because of this, results from this study are possible to be extrapolated to the general RA population.

There were a few limitations to this study. The main limitation is the small study population. This is partly due to Haga Teaching Hospital changing their EHR at the beginning of 2017. All patient data before that date could not be used due to possible unreliability of the converted data. Without this issue, we could have included patients who started anti-TNFα treatment before 2017.
The small study population was also due to the fact that this was a retrospective cohort study. Because of this, we did not have control over how data was collected and consequently were faced with missing data. Of only 60% of the population we were able to calculate a ΔDAS28-CRP, resulting in a low power and a large CI. If we could have calculated ΔDAS28-CRP for a larger portion of our study population, our study power would have been higher, the CI smaller and we could have concluded with more certainty that the results from our study are not based on coincidence.
Even though BMI is used in plenty of research in order to assess body composition, it does not take differences in muscle- or fat mass distribution. This is especially of importance in RA patients, seeing

that their body composition is often skewed towards one containing more fat instead of muscle. This could be accounted for by using modern body composition imaging techniques like DXA scans (36).

Further research in the form of a prospective cohort study would be of value to further investigate the association of biological sex with TNFα inhibitor treatment response in RA patients and the role of body composition as an effect modifier in this relationship. In this way, more control can be exerted over the data collected and patients included. Perhaps it is interesting to include blood sampling and measuring sex hormone and cytokine concentrations in blood serum and synovial fluids to see if these change over a longer period of TNFα inhibitor treatment. Results from these studies could give us more insight in how anti-TNFα therapy has an effect on sex hormones and if this is related to RA disease activity. Further investigation regarding body composition in RA patients should be done using DXA scans. If it is not possible to use a DXA scan, future researchers should reduce BMI cut-off points by 2 kg/m^2 to predict BFP more accurately because of rheumatoid cachexia (37).

Conclusion

It seems that the biological sex of RA patients does not have an association with TNFα inhibitor treatment response. We do however see a trend towards TNFα inhibitor treatment response being worse in females than in males.
It also seems that BMI is not an effect modifier in the response to TNFα inhibitor therapy. There is no difference between males and females in drug survival and reasons to stop anti-TNFα therapy.

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Appendix 1

DAS28-CRP was calculated using the following formula (38):

DAS28-CRP = 0.56 * √ (tender28) + 0.28 * √ (swollen28) + 0.36 * ln(CRP+1) + 0.014 * VAS + 0,96

BMI was calculated using the following formula (39):

$$Kg/m^2 = (\text{weight in kg/height in cm}) * 10000$$

BFP was calculated using the following formula (40):

For males:

$$\% = 1{,}20 \times BMI + 0{,}23 \times Age - 16{,}2$$

For females:

$$\% = 1{,}20 \times BMI + 0{,}23 \times Age - 5{,}4$$

LBM was calculated using the following formula (41):

For males:

$$Kg = 0{,}407 * \text{weight in kg} + 0{,}267 + \text{height in cm} - 19{,}2$$

For females:

$$Kg = 0{,}252 * \text{weight in kg} + 0{,}473 * \text{height in cm} - 48{,}3$$