Protocol:

Title: Gender differences in disease characteristics and biologic treatment outcomes in 1750 patients with psoriatic arthritis; a Danish natiowide registry study.

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Introduction

Psoriatic arthritis (PsA) is a chronic inflammatory disorder characterized by peripheral joint inflammation, nail involvement, enthesitis, tenosynovitis and dactylitis, as well as increased risk of extra-articular manifestations (psoriasis, uveitis, urethritis, inflammatory bowel disease) and other co-morbidities, especially metabolic, cardiovascular and psychological disorders.[1-3] During the last decades, the treatment of PsA has improved dramatically, mainly due to the introduction of biological disease modifying anti-rheumatic drugs (bDMARDs) such as tumor necrosis factor inhibitors (TNFIs).[4] TNFIs are expensive and may cause serious side effects why prescription of these drugs in Denmark is reserved for patients with ongoing, severe disease who are unresponsive to treatment with conventional synthethic (cs)DMARDs. Response to TNFIs is however insufficient in approximately 50% of patients in routine care [5]. Predictors of outcomes to TNFI therapy have been suggested to include clinical, laboratory, lifestyle-related and demographic factors although the overall evidence for specific response modifiers is limited.[6-9] A better understanding of the complex interaction between genetic/biologic and environmental factors is necessary to elaborate risk profiles and personalized treatment recommendations. A gender bias in the prevalence[10] and pathophysiology[11-13] in PsA has been suggested by recent literature and we hypothesize that gender could also play a central prognostic role in relation to therapeutic outcomes. Although some studies already support this idea, the results have been diverging emphasizing the need to further explore this research question.[14]

Objectives

To analyze gender differences in baseline characteristics including comorbidities as well as in treatment outcomes among Danish PsA patients initiating their 1st TNFI treatment course in routine care.

METHODS

Design

Observational cohort study of Danish PsA patients initiating TNFI-therapy in routine care. The study will adhere to recommendations of the STROBE statement.[15]

In accordance with Danish legislation, the registration and publication of data from clinical registries do not require patient consent or approval by ethics committees. Approval has been obtained from the Danish Data Protection Agency (BFH-2017-072, med I-Suite nr: 05725).

Sources of data

The DANBIO register and the Danish National Patient (DNPR) register will be used as data sources and cross-linked using patients' unique civil registration number. DANBIO covers > 90% of Danish adults treated with biologics in routine rheumatology care.[16,17] Patients are registered in DANBIO at initiation of therapy and followed prospectively with registrations at least bi-annually. The DNPR is a comprehensive health register that captures all somatic and psychiatric diagnoses that a patient receives from in- and outpatient secondary care units.[18] We have previously merged a DANBIO dataset with information from DNPR in order to study the impact of Charlson comorbidity index in PsA (EULAR 2017 abstract no. OP0106).
This dataset of 1750 PsA patients identified in DANBIO will be used in the present study as all relevant data is either available or can easily be calculated.

Covariates of interest

Data from DANBIO include:
Baseline (i.e. upon TNFI treatment initiation) demographics, smoking habits, body mass index, disease duration, anti-rheumatic treatments, prospective registrations of Health Assessment Questionnaire disability index (HAQ-DI), Visual analogue scale (VAS) of pain, global and fatigue, swollen and tender joint count (SJC, TJC), VAS physician, DAS28-CRP, and C-reactive protein (CRP).
Data from the DNPR include:
Hospital records reported up to 10 years before initiation of TNFi therapy as depicted in supplementary file 1. These diagnoses are used to calculate a modified Charlson Comorbidity Index (mCCI). In this study the calculation of CCI will exclude diagnoses related to connective tissue diseases as there is a considerable risk that these are not valid in our patient population. Furthermore the categorization of CCI will be according to the number of co-morbidities as follows: (I) = 0 comorbidities, (II) = 1 comorbidity, (III) >=2 without weighting severity of the disease. For presentation of comorbidity profile, we will also group the diagnoses into following

categories: Psoriasis, Extra-articular manifestations (*includes uveitis, urethritis, inflammatory bowel disease*), Mental disorders (*includes affective disorders, depression and anxiety*), Cardiovascular diseases (*includes myocardial infarction, congestive heart failure, peripheral vascular diseases and cerebrovascular diseases*), Metabolic disorders (includes diabetes mellitus I and II), Chronic pulmonary disease and Liver disease (mild, moderate or severe).

Patients

The study will include adult patients diagnosed with PsA according to their treating rheumatologist who were registered in DANBIO when initiating TNFI therapy between Jan 1st- 2000 and Jan 26th- 2015. Patients are considered non-eligible for the study if they participate in clinical studies, have erroneous baseline information, are treated with other biologics than TNFIs or are not followed in DANBIO from initiation of their first TNFI.

Treatment duration

Treatment duration will be calculated as the number of days individual patients maintain treatment with their first TNFI. Start date is defined as the first given dose, and stop date as the first missed dose. All observations are censored 25th of May 2015. Patients without visits since 1st of January 2015 who are not registered with a stop date in DANBIO will be considered "lost to follow-up" and censored at the date of their last visit. Temporary treatment interruptions (e.g. due to surgery or infections) of less than 3 months are allowed. Reasons for discontinuation of treatment is reported in DANBIO in prespecified categories and will be summarized as 1) Lack of effect or 2) Adverse events 3) Disease remission or 4) Other reasons.

Treatment Response

Disease activity will be reported at baseline and after 6 months' treatment. The baseline visit will be defined as the time interval from 30 days prior until 7 days after TNFI start date, and the 6 months' follow up will be defined as a visit between week 18 and 32.

Response outcomes

Primary and secondary outcomes:

The primary outcome will be achievement of a EULAR good or moderate response after 6 months' treatment.

Secondary outcomes will be EULAR good response and American College of Rheumatology 20/50/70% improvement (ACR20/ACR50/ACR70).

Exploratory outcomes will be achievement of low disease activity according patient-reported and clinical measurements; inspired by items and threshold values of the Minimal Disease Activity definition provided by Coates[19] each of following criteria will be applied:

1) *Minimal Joint Activity:* Tender joint count ≤1 and Swollen joint count ≤1

2) *Minimal Patient-Reported disease activity*: Patient pain VAS ≤ 15 mm and Patient global disease activity (VAS) ≤ 20 mm and Health assessment questionnaire disability index (HAQ-DI) ≤ 0.5.

The proportion of female and male responders according to primary, secondary and exploratory outcomes will be reported both 'as observed' (completer analyses) and as LUNDEX adjusted response rates. By applying the LUNDEX tool[20], it is possible to integrate information on response and drug persistency in one measurement and thereby resemble 'intention to treat' strategy. By doing so, we acknowledge that early withdrawal of treatment is also incorporated as lack of treatment response (despite absence of follow up data).

Finally, we will report the change in single disease parameters (0-6 months) including VAS fatigue, global, pain and VAS physician, HAQ-DI, CRP, DAS-28 CRP.

Statistical Methods

Data analyses will mainly be performed in SPSS, version 22 (SPSS Inc., Chicago, IL, USA) and to a lesser extent in R v.3.4.0 and STATA. In the primary analyses, no imputation of missing baseline data will be performed. Demographic and descriptive data will be presented as median and interquartile ranges (IQR) or means and standard deviations. Variables will be compared between genders by independent t-test, Mann-Whitney U test or chi-square. P-values less than 0.05 (two-sided) will be considered statistically significant.

The influence of gender on treatment persistency will be assessed by Kaplan-Meier plots and Cox proportional hazard regression analyses, while the impact of 6 month responses will be analyzed by logistic regression. The regression models will be designed as follows:

Model 1: Analyzes the impact of gender on 6 month's treatment response (according to EULAR

good or moderate, EULAR good, ACR 20/50/70 criteria) as well as on TNFI persistence adjusting for age (continuous, years).

Model 2: Analyzes the impact of gender on 6 months response criteria and TNFI persistence when controlling for a priori selected confounders including: Age (continuous, years), Disease duration (continuous, years), Swollen joint count (0-28), Tender joint count (0-28), CRP (≥10 or < 10 mg/L), VAS pain (continuous 0-100), smoking (dichotomous, current/not current), obesity (dichotomous yes/no), hospital records of mental disorders (dichotomous, yes /no), TNFI start year (dichotomous, 2000 – 2005; 2006 – 2015) and mCCI (0, 1, >=2). Furthermore, the model will analyze if the impact of gender on outcomes is modified by the level of age, disease duration, obesity, mCCI or smoking status by including their interaction terms, using EULAR good-or-moderate response as the dependent variable in logistic regression.

Covariates will be tested for collinearity which is considered acceptable if correlation coefficients are less than 0.5 (Pearson or Spearman) and the Variance Inflation Factor (VIF) values are greater than 2. The assumption of proportional hazards will be tested in the Cox regression model by formal test of Schoenfeld residuals in STATA. Covariates that do not fulfill the requirement of proportional hazards will not be included in the Cox model.

Sensitivity analyses

Sensitivity analyses will be performed to further explore the impact of gender on TNFI treatment outcomes.

1. Gender differences in reasons for TNFI withdrawal: We will study if the frequency of stopping due to *adverse events* and *lack of efficacy* differ between genders. Furthermore, we will explore if gender predicts TNFI persistency when using in turn 1) lack of efficacy and 2) adverse events as the stop reasons, treating other reasons as censored in the Cox model. The confounders included in these analyses will be as described previously (model 1 and 2 above).

2. An additional logistic regression model with 6 months EULAR good or moderate response as outcome will be performed using a stepwise forward selection ‘change-in-estimate’ approach for confounder selection. The benefit of this strategy is reduced risk of overfitting while the drawback is the arbitrary cut-off for the importance of a confounding effect. In this study, covariates that change the estimate (OR) for gender with >10% when tested in the basic model of age and gender

are included for the next step. In the next stepwise maneuver, covariates are then added hierarchically according to which of them that changed the gender OR-estimate the most. The addition of these covariates is continued until the OR-estimate for gender no longer changes with more than 10%.

Following variables will be considered: Disease duration (continuous, years), Swollen joint count (0-28), Tender joint count (0-28), VAS pain (continuous 0-100), Smoking (dichotomous, current/not current), Obesity (dichotomous yes/no), TNFI start year (dichotomous, 2000 – 2005; 2006 – 2015), Type of TNFI (all 5 types), Use of methotrexate (yes/no), CRP (≥10 or < 10 mg/L), HAQ-DI (0-3), VAS fatigue (0-100), VAS global (0-100), Hospital record of: Mental disorders (yes /no), Psoriasis (yes/no), Extra-articular manifestation(s) (yes/no), Diabetes (yes/no), Cardiovascular disease (yes/no), Lung disease (yes/no), Liver disease (yes/no) and Charlson Comorbidity Index (categorical (0, 1, >=2).

3. For sensitivity, imputation of missing baseline data will be considered for the logistic regression (with EULAR good-or-moderate response as outcome).

Perspectives, strengths and limitations

While randomized controlled trials provide valuable insight into the efficacy of biologic drugs, longitudinal observational cohorts represent a unique opportunity to study real-life drug effectiveness and identify response modifying factors. Gender medicine is a highly relevant field especially within auto-immune diseases that often have a partiality to females.[21] In PsA, the impact of gender on pathophysiology and prognosis is not well established. We anticipate that this observational nationwide study will provide valuable knowledge regarding the impact of gender on disease activity and response to therapy in patients with PsA. Collecting real-life evidence is important due to the high external validity and relevance for routine care. However the risk of residual confounding and occurrence of missing data in the registers, underscores the importance of supporting findings from other studies before final conclusions can be drawn.

Supplementary table 1.

ICD-10 codes for the somatic comorbidities and calculation of Charlson Comorbidity Index.

Condition	Weight	ICD-10 codes
Myocardial infarct	1	I21;I22;I23
Congestive heart failure	1	I50; I11.0; I13.0; I13.2
Peripheral vascular disease	1	I70; I71; I72; I73; I74; I77
Cerebrovascular disease	1	I60-I69; G45; G46
Dementia	1	F00-F03; F05.1; G30
Chronic pulmonary disease	1	J40-J47; J60-J67; J68.4; J70.1;J70.3; J84.1; J92.0; J96.1; J98.2; J98.3
Connective tissue disease	1	M05; M06; M08; M09;M30;M31;M32; M33; M34; M35; M36; D86
Ulcer disease	1	K22.1; K25-K28
Mild liver disease	1	B18; K70.0-K70.3; K70.9; K71; K73; K74; K76.0
Diabetes	1	E10.0, E10.1; E10.9, E11.0; E11.1; E11.9
Hemiplegia	2	G81; G82
Moderate or severe renal disease	2	I12; I13; N00-N05; N07; N11; N14; N17-N19; Q61
Diabetes with end organ damage	2	E10.2-E10.8; E11.2-E11.8
Any tumor	2	C00-C75
Leukemia	2	C91-C95
Lymphoma	2	C81-C85; C88; C90; C96
Moderate or severe liver disease	3	B15.0; B16.0; B16.2; B19.0; K70.4; K72; K76.6; I85
Metastatic solid tumor	6	C76-C80
AIDS	6	B21-B24

AIDS = acquired immune deficiency syndrome.

ICD-10 codes for depression and anxiety.

Condition	ICD-10 codes
Mental and Behavioral Disorders	F31-F34, F38-F41
Bipolar affective disorders	F31
Depressive episode	F32
Recurrent depressive disorder	F33
Persistent mood (affective) disorder	F34
Other mood (affective) disorders	F38
Unspecified mood (affective) disorders	F39
Phobic anxiety disorder	F40
Other anxiety disorder	F41

ICD-10 codes for psoriatic arthritis and the related manifestations.

Condition	ICD-10 codes
Psoriatic arthritis	L405, M070, M071, M072, M073
Psoriasis	L40
Uveitis	H20; H221
Urethritis	A560; A562; N341; N342; N370
Inflammatory bowel disease	K50 - K51

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