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THE IMPACT OF COMORBIDITIES ON EFFECT AND DISCONTINUATION OF TUMOUR NECROSIS FACTOR INHIBITOR THERAPY IN PSORIATIC ARTHRITIS: A POPULATION-BASED COHORT STUDY

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BACKGROUND

Psoriatic arthritis (PsA) is a chronic inflammatory disorder associated with skin psoriasis (1). The clinical presentation of PsA is typically characterised by peripheral joint inflammation, nail involvement, axial skeleton disorders, enthesitis, tenosynovitis and dactylitis (2). Furthermore, PsA is associated with several severe comorbidities such as cardiovascular diseases, diabetes, and depression and anxiety (1, 3). Over 50% of the patients have more than one comorbidity (4).

During the last decades, the treatment of PsA has markedly improved, especially due to the introduction of the biological therapies such as tumour necrosis factor inhibitors (TNFi) (3, 5). TNFis effectively reduce symptoms of inflammation, improve quality of life and slow progression of joint damage (3). However, due to the complexity of PsA, adequate treatment is still challenging and about 50% of patients with PsA, experience failure of TNFi treatment within a year (5, 6). Given the heterogeneity of PsA, the treatment should be individualised and based on potential response modifiers (7, 8). Previous studies have shown that predictors of achieving a clinically relevant TNFi treatment response in PsA are male sex, younger age, short time of disease duration, low Health Assessment Questionnaire (HAQ) score, absence of enthesitis, a higher number of swollen joints, and a higher C-reactive protein (CRP) level at baseline (9-11). Lower treatment response rates have been observed among older patients, female sex, obese patients, current smokers, patients with a higher HAQ score at baseline and concurrent corticosteroid use (8, 12-14). Whether the number and severity of somatic and mental comorbid diseases have an effect on TNFi treatment response in patients with PsA is sparsely investigated (15). A cohort study of 596 PsA patients found no statistically significant association between presence of any of 17 selected comorbidities (16 somatic comorbidities and depression) at baseline and achievement of the European League Against Rheumatism (EULAR)-response (12). In the study, data on past and current comorbidities were obtained by use of questionnaires and the comorbidities were assessed by a composite measure, not a weightened score. Since the comorbidities of PsA influences morbidity and mortality, the relationship between presence of comorbidities and treatment response needs further investigation (4).

Research in rheumatoid arthritis (RA) has shown that treatment adherence can be interpreted as a measure of effectiveness, safety and tolerability (16). The most common reasons for treatment discontinuation of TNFis in RA are ineffectiveness and adverse events, but the treatment

adherence may be influenced by a number of other factors (16). Fore example, studies in RA have shown that higher physician global scores, higher RA Disease Activity Index scores, and a higher number of TNFis used previously are associated with premature discontinuation of TNFi (17), while conventional synthetic disease modifying antirheumatic drugs (csDMARD) use prior to TNFi treatment start and beliefs in the necessity of the medication, predicted lower risk of treatment discontinuation (18). Furthermore, a study in RA patients showed that psychological distress is independently associated with poorer TNFi treatment adherence (19). The amount of research in reasons for treatment discontinuation in PsA is more sparse. As in RA, the most common reason for discontinuation of TNFi treatment is lack of efficacy and to lesser extent adverse events (20). Previous studies have identified predictors of TNFi treatment adherence in PsA and found that male sex (20), longer duration of PsA (21), concomitant methotrexate treatment (6, 20, 22), and higher level of CRP (6, 20) were associated with a longer treatment continuation, whereas lower treatment continuation rate was associated with female sex (15, 22), older age (23), higher body mass index (BMI) (21), and higher baseline disease activity (21, 22). However, only few studies have assessed the potential impact of somatic and mental comorbidities on treatment adherence in PsA (24). A study of a previously mentioned British PsA cohort found that the presence at baseline of any of 17 pre-specified comorbidities was associated with significantly higher drug discontinuation rates due to adverse events (15). Also, studies of patients with skin psoriasis have found associations between the presence of comorbidities and a significantly shorter treatment adherence rate than patients without comorbidities, but the studies did not show results for PsA patients only (25, 26).

A recent systematic review of causes of treatment discontinuation in immune-mediated inflammatory diseases including psoriasis, spondyloarthritis and RA found an association between poorer emotional well-being, especially depression, and non-adherence (24). Reasons for this association may be that affective disorders such as depression and anxiety impair cognitive function and energy, which may affect patients' willingness and motivation to follow the physician's treatment recommendations (24, 27). Furthermore, positive beliefs and confidence in a good treatment effect are associated with greater adherence and as depression often causes a feeling of hopelessness it may be more difficult to obtain positive expectations (24, 27). Finally, a well-established social network and family contacts contribute to a greater treatment adherence. Patients with depression often experience social isolation and withdrawal from family and friends,

who would otherwise support the continuation of the medical treatment (27). The impact of psychological distress on treatment adherence is of particular importance, because depression is generally a treatable condition (19).

The Charlson Comorbidity Index (CCI) is a well-known and validated index for measuring comorbidity disease status (28, 29). It was originally developed to predict the 1-year mortality in medical patients based on comorbidity data obtained from hospital records. It is a weighted score of 19 different comorbidities, selected and weighted according to their potential influence on mortality, and the sum of the index score is an indicator of disease burden (30). An index of comorbidity level has the advantage of bringing several comorbidities into a single numeric score, which is beneficial when using medical registries (31). The CCI has been adapted to administrative databases that record medical diseases using the International Classification of Diseases 10th revision (ICD-10) (28, 31) and it is the most widely used comorbidity disease index (28).

The impact of somatic and mental comorbidities on treatment effect, disease activity and treatment adherence in patients with PsA is sparsely investigated. We hypothesise that I) the presence of severe comorbidities, weighted according to the CCI, and II) the presence of mental comorbidities will both be associated with poorer TNFi treatment adherence and response.

Objectives

The objective of this study is to investigate whether PsA comorbidities, assessed by use of the CCI, are associated with disease activity, treatment response and treatment adherence in patients with PsA treated with their first TNFi. Furthermore, we will assess whether depression and/or anxiety have an influence on the treatment effect and adherence.

METHODS

Protocol

Methods of the analysis will be specified in advance and documented in this study protocol. The protocol is in line with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement (32).

Study Design and Setting

The study is a population-based cohort study investigating the impact of comorbidities on treatment effect, disease activity and treatment discontinuation in PsA patients treated with their first TNFi. Data on patient characteristics, treatment adherence, disease activity and comorbidities will be obtained through linkage of data from Danish registries: The DANBIO register, the Danish National Patient Register (NPR) (33) and the Danish Psychiatric Central Research Register (PCRR) (34).

Data Source

The DANBIO register is a national database, which covers > 90% of Danish adults treated in routine care with biologics by cause of rheumatic diseases, including PsA. Physicians are recommended to report data prospectively in an online database system at least twice per year or when medication is changed. According to the Danish legislation, the registration and publication of data from clinical registries do not require patient consent or approval by ethics committees. DANBIO provides information on demographics, treatment, disease characteristics and disease activity. However, information on spinal disease and entheses status is sparsely registered in the DANBIO (35).

NPR is a key Danish health register, which was established in 1977. At this time, the NPR covered only somatic inpatients and information on activities in psychiatric wards were recorded in a separate register, the PCRR, founded in 1969. In 1995, the PCRR became an integrated part of the NPR. The NPR is increasingly used as a source register for more specialised Danish health register and from year 2000 the payment of public as well as private hospitals via the Diagnostic Related Group (DRG)-system has been based on the NPR. Danish hospitals are financed via tax revenue and have been run by the regions since 2007. However, the private healthcare sector in Denmark has been expanding in the 2000s and full in- and outpatient contact registration of the private healthcare sector in Denmark have been mandatory since 2003. Thus, today the NPR covers somatic and psychiatric in- and outpatients in all hospitals and internationally the NPR is considered to be one of the most comprehensive of its kind. The data reported to the NPR can be divided into two types: administrative data and clinical data. The administrative data include identification of the patient, identification of hospital ward, date and time of activity. The clinical data include diagnoses and surgical procedures (33, 34).

The Danish Civil Registration System (CRS) contains individual-level updated information on migration and vital status on all persons residing in Denmark since 1986. A unique ten-digit Civil Personal Register number assigned to all persons in the CRS allows for linkage of Danish registers and provide virtually complete long term follow-up (36).

Participants and Study Size

Patients will be adults diagnosed with PsA according to the treating rheumatologist, who have initiated their first TNFi treatment course in routine care. The patients will be identified through the DANBIO register, as will medication history, current medication status, disease activity, treatment effect and reasons for treatment discontinuation. We will use the NPR for identifying the comorbidities of each individual patient. A comorbid condition will be registered if the patient has one registration for the given disease in the NPR. We will assess comorbidity status of the patients 10 years before initiating TNFi treatment. All PsA patients who have been registered in DANBIO initiating their first TNFi treatment between years 2000-2015 will be included in the study. We estimate the study sample size to be about 2000 patients (8, 20).

Treatment Adherence

Treatment adherence will be calculated as the number of days individual patients maintain treatment with their first TNFi. Start date will be the date of the first given dose, and stop date will be the date of the first missed dose. Temporary treatment interruptions (e.g. due to surgery or infections) of ≤ 3 months' duration will be allowed. All observations will be censored on 25 May 2015. Among patients with no follow up after January 2015, data will be censored according to the last visit registered.

Treatment Response

Disease activity will be evaluated at baseline and after 3 and 6 months of TNFi treatment. The baseline visit will be defined as a visit within 30 days before to 7 days after initiation of therapy. The time window for the 3 and 6-month visits will be 10-17 and 18-32 weeks, respectively. If more than one visit is available for the given time window, the one closest to the time point will be selected. If the patient has no registrations for a given visit, data will be registered as missing data for this visit. Clinical response will be evaluated as achievement of the American College of

Rheumatology (ACR) 20% improvement criteria (ACR20), ACR 50% improvement criteria (ACR50), ACR 70% improvement criteria (ACR70) or the EULAR-good-response (37, 38). In case of missing data at either the 3-months' or 6-months' visit, one registration will be sufficient to characterise the patient as responder. Patients who stop therapy within the first 3 months of therapy will be considered non-responders (8, 20).

Variables

The variables are listed in Table 1. From the DANBIO database we will capture information on sex, age, disease duration of PsA, BMI, tender joint count, swollen joint count, Disease Activity Score in 28 joints (DAS28), CRP, ACR20/ACR50/ACR70, EULAR-good-response, HAQ, patient's visual analogue scale for pain, fatigue and global, and physician's global. We will also capture information about medication (drug type, year of treatment initiation, concomitant methotrexate treatment), and reason for treatment discontinuation. Reasons for treatment discontinuation are registered in DANBIO in pre-specified categories: lack of effect, adverse events, disease remission, pregnancy, surgery, cancer, death, infections, loss of follow-up and other reasons. In this study, reasons for discontinuation will be divided into four categories: I) lack of efficacy II) adverse events (infection, death, cancer), III) Remission, and IV) other (pregnancy, surgery, loss to follow-up, remission and other reasons).

The comorbidities as described in the CCI will be extracted from the NPR and identified by use of ICD-10 codes according to Thygesen et al., who have validated the CCI in the NPR (Table 1) (31). The CCI was originally developed to predict survival and assigns weights for specific diseases. Comorbid conditions with a weight of one include myocardial infarction, congestive heart failure, peripheral vascular disease, cerebrovascular disease, dementia, chronic pulmonary disease, connective tissue disease, ulcer disease, mild liver disease, and diabetes. Hemiplegia, moderate or severe renal disease, diabetes with end organ damage, any tumour, leukaemia, and lymphoma have a weight of two. Moderate or severe liver disease has a weight of three. Metastatic solid tumour and AIDS have a weight of six. The total score is calculated by adding the weights (30, 39). From the NPR we will also capture information on the presence of PsA related diseases (psoriasis, iridocyclitis, urethritis, inflammatory bowel disease).

Bias

In this study, data on comorbidities will be extracted from the NPR and based on ICD-10 codes recorded by physicians at in- and outpatient somatic and psychiatric care units irrespective of speciality. Thus, the results do not account for patients, who are exclusively diagnosed and treated in primary care units, which may effect the number of registrations of certain comorbidities such as mild liver disease, peripheral vascular disease and dementia (40). Data from a Nordic database similar to the NPR shows that misclassification regarding comorbidities is estimated to be less than 5% (41). In DANBIO, the clinical diagnosis for individual patients is registered according to the expert opinion of the treating physician. Generally, the use of register data for research is associated with certain limitations such as risk of missing data. However, the data completeness in the DANBIO register is generally high (42).

Patient perspective

A patient research partner has reviewed the protocol and confirmed the importance of the study from the perspective of patients. She will be involved throughout the research process.

Statistical Methods

Data analysis will be performed in SPSS, version 23 (SPSS, Chicago, IL, USA). Demographic and descriptive data will be presented by median/interquartile ranges or means/standard deviations. Groups will be compared by parametric tests (T-test, one-way ANOVA) if data follow a normal distribution, otherwise non-parametric tests (chi-square, Mann-Whitney tests, Krusal-Wallis). In all statistical tests p-values < 0.05 (two sided) will be considered statistically significant. Calculations will be based on observed data and no imputation of missing data will be performed.

The influence of CCI status on treatment adherence will be assessed by Kaplan-Meier plots and Cox regression analyses. TNFi adherence in years will be used as the underlying time-scale. Covariates will be tested for proportional hazards. Treatment responses will be given stratified according to different levels of comorbidities at baseline. The responses (ACR20/50/70 and EULAR-good-response) will be intention-to-treat corrected by using the LUNDEX-method, which is an index for comparing the long-term efficacy and tolerability of biologic therapies (43). Uni- and multivariable logistic regression analyses will be performed to investigate the impact of

CCI status on clinical response (ACR50). In the multivariate analyses the selection of confounders will be determined a priori based on clinical importance and with a maximum colliniarity of 0.3. As a minimum it will include sex, age, calendar time, life style factors (smoking, BMI), disease duration, and in the logistic regression also TNFi drugs: adalimumab; certolizumab pegol; etanercept; golimumab; infliximab. The influence of CCI status on discontinuation due to 1) adverse events or 2) lack of response will be investigated stepwise by censoring other reasons for withdrawal in Cox regression analyses. Furthermore, the following sensitivity analyses will be performed: I) Determine the impact of CCI status only 2 years before initiation of the first TNFi therapy; II) The multivariable analyses will be repeated and stratified according to TNFi drug type; III) Stratification according to mental disease diagnosis.

RESULTS

Outline (anticipated)

Figure 1: Flow chart: Patient inclusion.

Table 1: Baseline patient characteristics, disease activity and reasons for terminating TNFi treatment according to CCI status at the baseline visit.

Table 2: Impact of CCI status on treatment adherence for all TNFis and stratified by TNFi drug type, as determined by multivariate Cox regression analysis including a priori confounders.

Figure 2: Kaplan-Meier treatment adherence curves according to CCI status.

Table 3: The influence of CCI status on treatment response according to ACR and EULAR definitions: Crude LUNDEX-modified responder fractions (stratified according to comorbidities) and results from multivariable logistic regression analyses.

Timeline (anticipated)

May – June 2016: Protocol.

July 2016: Data extraction.

August – November 2016: Data analysis and interpretation.

December – January 2016: Manuscript preparation.

February 2017: Manuscript submission.

Publication

The aim is to publish the obtained results in an international peer-reviewed journal with the in the protocol mentioned authors and other participating authors according to involvement. The results will be published as one or more scientific papers. Additionally, the study results will be presented at national and international professional meetings as well as to professionals and patients, who take an interest in comorbidities related to treatment in patients with PsA.

DISCUSSION

CONTRIBUTIONS OF AUTHORS

Contributions: All authors will throughout the process have access to data and contribute to study conception and design, the analysis and interpretation of data, revising the manuscript and approving the final version. CB and PH will be drafting the manuscript. LEK, LD, PH and RC will provide statistical expertise. CB and LEK take the overall responsibility for the scientific integrity of the work as a whole.

COMPETING INTEREST STATEMENT

LEK has received fees for speaking and consultancy from Pfizer, AbbVie, Amgen, UCB, Celegene, BMS, MSD, Novartis, Eli Lilly, and Janssen pharmaceuticals. TSJ has received fees for speaking and consultancy from AbbVie, Roche, and Novartis.

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TABLES

Table 1. The Baseline Demographic and Disease Characteristics of the Study Cohort.

Demographics characteristics
Number, n
Women, n (%)
Age (years)
BMI (kg/m^2)
Disease related characteristics
PsA disease duration (years)
Tender joint count (28) (no.)
Swollen joint count (28) (no.)
DAS28 (0-10)
CRP (mg/L)
ACR20 (no.)
ACR50 (no.)
ACR70 (no.)
EULAR-good-response
HAQ score (0 - 3)
VAS patient global (0 – 100)
VAS pain (0 – 100)
VAS fatigue (0 – 100)
Doctor's global (0 – 100)
PsA related manifestations, n (%)
Psoriasis
Uveitis
Urethritis
Inflammatory bowel disease
TNFi, no.
Adalimumab
Certolizumab pegol
Etanercept
Golimumab
Infliximab
TNFi initiation year, n (%)
2000 – 2004
2005 – 2009
2010 – 2015
Methotrexate co-medication, n (%)
Anxiety and/or depression (yes/no)
Reason for treatment discontinuation, n (%)
Lack of efficacy
Adverse events
Remission
Other

Abbreviations. BMI: Body mass index; PsA: Psoriatic arthritis; VAS: Visual analogue scale; HAQ: Health Assessment Questionnaire; DAS28: Disease Activity Score in 28 joints; CRP: C-reactive protein; ACR20: American College of Rheumatology (ACR) 20% improvement criteria; ACR50: ACR 50% improvement criteria; ACR70: ACR 70% improvement criteria; csDMARD: Concomitant conventional synthetic disease modifying anti-rheumatic drug.

Table 2. Weighted Index of Comorbidities (Charlson Comorbidity Index).

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

Abbreviations. Abb.: Abbreviation; AIDS: Acquired immune deficiency syndrome.

Table 3. ICD-10 Codes for the Mental and Behavioural Comorbidities of Interest.

Condition	Abbreviation	ICD-10 codes
Mental and Behavioural Disorders	MBD	F30-F34, F38-F41
Manic episode	MAE	F30
Bipolar affective disorders	BIPO	F31
Depressive episode	DPE	F32
Recurrent depressive disorder	RDD	F33
Persistent mood (affective) disorder	PMA	F34
Other mood (affective) disorders	OMA	F38
Unspecified mood (affective) disorders	UMA	F39
Phobic anxiety disorder	PAD	F40
Other anxiety disorder	OAD	F41

Table 4. ICD-10 Codes for Psoriatic Arthritis and the Related Manifestations.

Condition	Abbreviation	ICD-10-codes
Psoriatic arthritis	PSA	DM07.0, DM07.1, DM07.2, DM07.3, DL40.5
Psoriasis	PSO	L40
Uveitis	UVE	H20; H22.1
Urethritis	URE	A56.0; A56.2; N34.1; N34.2; N37.0
Inflammatory bowel disease	IBD	K50 - K51

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