Fatigue remains a dominating symptom despite tumor necrosis factor inhibitor therapy in psoriatic arthritis: a population-based cohort study

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INTRODUCTION

Fatigue is defined as a persistent feeling of tiredness, lack of energy, and felling worn out or exhausted [7]. It is often described as a phenomenon that interferes with physical and social functions and may lead to social withdrawal and long-standing sick leave [10]. Fatigue is seen in patients with various chronic diseases, including psoriatic arthritis (PsA) [14].

PsA is an inflammatory disease characterized by inflammation of the joints, the surrounding ligaments and tendons, and skin [1,16]. Besides fatigue, it is also associated with pain [1] and a number of comorbidities, including obesity, metabolic syndrome, non-alcoholic fatty liver disease, diabetes and cardiovascular disease, with over 50% of patients with PsA having more than one comorbidity [2,3]. PsA affects approximately 0.3%-1% of the general population worldwide [12] and 20–30% of patients with skin psoriasis [2,17]. PsA patients continue to cite fatigue as one of the most challenging aspects of their disease as it decreases their quality of life [8].

Fatigue in psoriasis has been associated with the impact of the inflammatory cascade on the central nervous system. This may suggest that a pathway which relays the immune signals that underlie psoriatic disease to the brain, results in negative symptoms as fatigue [8]. This might explain why an often used treatment like tumor necrosis factor inhibitor (TNFi) targeting the inflammatory pathway should result in less fatigue [1]. Although, TNFi therapy have shown to be effective in treating PsA and improve function, quality of life, and fatigue [2,8], it still fails among half of patients with PsA treated in routine care [4]. TNFi drug efficacy trials treating ankylosing spondylitis have shown distinct results with limited to marked improvement on fatigue [5,6,9].

Existing knowledge indicate the need for further investigation into associations between fatigue, TNFi drug survival, and other patient-related factors including comorbidities.

Objectives

The objective of this population-based cohort study is to investigate the association of fatigue with disease activity and adherence to therapy in PsA patients receiving their first TNFi treatment.

METHODS

Literature search

The study is built around a literature search in the database Pubmed, from which 15 studies, that were all original articles, were selected and analyzed. A systematic search for relevant literature was conducted on two different subject matters. First a PICO search was done on PsA and TNFi collectively (figure 1). Secondly, a PICO search was conducted on the subject of fatigue and inflammatory disease, specifically looking for articles relevant to PsA and spondyloarthritis (figure 2). We chose to split the search into two categories, because a combined search on the associations between PsA patients treated with TNFi and fatigue resulted in a very limited number of articles. Correlations between the two subjects was aimed to be established, and was somewhat accomplished, by also allowing articles that described rheumatoid diseases in general to be part of the end search result. Additionally, references from relevant papers were reviewed.

figure 1:

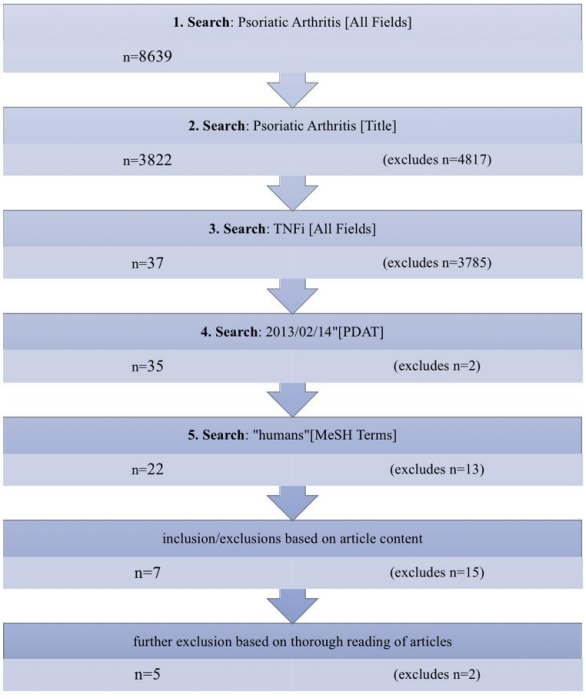
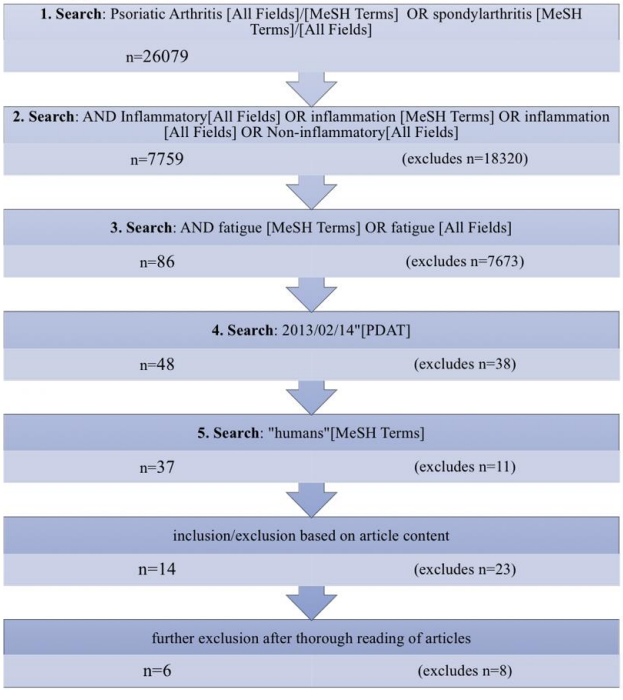


figure 2:



Study design

The study is designed as a cross sectional registry study including data on patients registered in the Danish nationwide registry DANBIO [11].

Setting & data source

Data on patient characteristics, disease activity and treatment adherence will be obtained from the DANBIO register. Information on comorbidities according to the Charlson Comorbidity Index (CCI) and psychiatric comorbidities will be obtained through linkage with the Danish National Patient Register. The data from the DANBIO registry, will in this study be generalized to represent all patients with PsA who are treated with TNFi in Denmark since only hospital outpatient clinics are allowed to give TNFi treatment and since it is mandatory to register all patients treated with biologics in DANBIO. According to DANBIO annual report from 2016 (www.danbio-online.dk) DANBIO covers 98% of all patients treated with biologics in Denmark, including Danish PsA patients.

Participants

All PsA patients registered in DANBIO from 2000 to 2015 will be identified and assessed for eligibility to analysis based on following criteria.
All patients registered in DANBIO during treatment with their first bDMARD will be identifies and considered for participation in the study. From the initial inclusions, a number of patients will be excluded based on the criteria of having participated in clinical trials, having erroneous baseline information, not followed from initiation of treatment or with no consecutive follow-up visit registration, having been treated with other bDMARDs than TNFi and patients who have not identified fatigue as a problem.
Alle patients included after exclusion criteria will be grouped and compared based on severity of fatigue extrapolated to the lower median fatigue and higher median fatigue.

Variables & outcome measures

Touch screens for patients to enter patient-reported outcome are available in every public outpatient clinic in Denmark. Fatigue is assessed by a visual analogue scale (VAS) which is a scale composed

to measure pain and fatigue (VAS pain, VAS fatigue, VAS global health) on a scale from 0-100 mm with '0' representing "no fatigue" and '100' representing "worst imaginable fatigue" [13].

Variables from DANBIO include: Gender, age, date of visits, disease duration, swollen joint count (SJC), tender joint count (TJC), C-reactive protein (CRP), health assessment questionnaire (HAQ), diseases activity assessments (DAS-28-CRP), visual analogue scales (0-100 mm VAS) for doctor's global, patient's global, and pain, treatment information on conventional synthetic disease-modifying anti-rheumatic drugs (csDMARDs) and/or biologic DMARDs (bDMARDs).

Data analysis

Data analysis will be performed in SPSS (version 25), where the data will be presented by means and standard deviations or medians and interquartile ranges. Two-sided P-values <0.05 will be considered statistically significant in all analyses. Kaplan-Meier plots, univariate and multivariate Cox proportional hazard regression analyses will be adjusted based on age and sex, and percentages of patients achieving relevant clinical responses will be calculated. Kappa statistics will be used to assess agreement between fatigue and ACR20/ACR50/ACR70 by the use of the Lund Efficacy Index (LUNDEX) method, which has the advantage of integrating clinical response and persistence with therapy in a composite value [15]. The equation for calculating the LUNDEX is:
LUNDEX=(Fraction of starters still in the study at time T)x(Fraction responding at time T)[15]
The LUNDEX adjustment is an intent-to-treat (ITT) method developed for the observational setting to account for both withdrawals from therapy and for missing response recordings at certain points of followup [15].

Ethical consideration

In accordance with Danish legislation, studies based on data from registries do not require approval by Ethics Committees. Registrations and publication of data from clinical registries do not require patient consent. Results whether positive, negative, or inconclusive will be published in relevant international peer-reviewed scientific journals with authorship determined according to the Vancouver Recommendations.

Patient perspective

The objective and study design will be discussed with a PsA patient partner after informed consent. The input from the patient partner will be integrated in the current protocol and data presentation.

RESULTS

Results will be presented as:

Table 1: Baseline characteristics according to median fatigue stratification.

Table 2: 2x2 tabel depicting correlation between STR and Fatigue, with each square including: ACR20,50,70 and VAS20,50,70.

Figure 1: Patient inclusion (flow chart).

Figure 2: Kaplan-Meier plot of the cumulative TNFi drug survival.

Figure 3: Venn-diagrams of: VAS20/ARC20, VAS50/ACR50 and VAS70/ACR70

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