Rheumatology Advances in Practice, 2023, **7(2)**, rkad035
https://doi.org/10.1093/rap/rkad035
Advance access publication 3 April 2023
Concise Report

British Society for Rheumatology
RHEUMATOLOGY ADVANCES IN PRACTICE
OXFORD

Clinical science

The impact of comorbidities on interleukin-17 inhibitor therapy in psoriatic arthritis: a Danish population-based cohort study

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Abstract

Objective: To investigate the influence of comorbidities on treatment response, disease activity and persistence with first-line IL-17 inhibitor (IL-17i) treatment in patients with PsA.

Methods: Patients were divided into three groups depending on the presence and/or severity of comorbidities using the Charlson Comorbidity Index (CCI). Groups were CCI 0: no comorbidities, CCI 1: one comorbidity and CCI ≥2: two or more comorbidities or one or more severe comorbidities. Outcomes in the groups were compared for treatment persistence, treatment response and disease activity.

Results: A higher CCI score was associated to an elevation in baseline CRP, swollen joint count and frequency of depression and/or anxiety. The median drug persistence in the groups were CCI 0: 1.8 years, CCI 1: 1.9 years and CCI ≥2: 1.5 years, but was not statistically significant to the CCI score. There were no significant differences in clinical response rates between the groups.

Conclusion: The presence of comorbidities was associated with increased baseline disease activity and frequency of depression and/or anxiety, but was not associated with shorter treatment persistence or lower clinical response rates in a cohort of 155 Danish patients with PsA treated with first-line IL-17i.

Lay Summary

What does this mean for patients?
Choosing the right biologic treatment for people with PsA can be problematic. It is not unusual for these patients to shuffle between multiple treatments before a satisfactory treatment is found. The first-line biologic treatment for people with PsA is usually a TNF inhibitor (TNFi). However, TNFis have been shown to be less effective in those with comorbidities (i.e. people with two or more simultaneous medical conditions) compared with those without. People with comorbidities are also less likely to continue to take the TNFi for the prescribed period of time. Since >50% of people with PsA have one or several comorbidities, we wondered if IL-17 inhibitors (IL-17is; another type of biologic drug) act in this same manner. We studied 155 people with PsA treated with IL-17is and found that, unlike TNFis, IL-17is were not less effective in people with comorbidities. Likewise, people with comorbidities were not more likely to discontinue treatment with IL-17is than those without comorbidities. Because we investigated a small group of patients, these results must be reproduced in larger groups. However, we think that these results are novel and could be an important clinical tool for quickly choosing the best biologic treatment for PsA patients with comorbidities. This would benefit patients and also minimize ineffective courses of treatment as well as societal costs.

Keywords: PsA, comorbidities, IL-17 inhibitor, treatment persistence, treatment response, disease activity

Key messages

- The first course of IL-17i was well tolerated in this nationwide PsA cohort.
- Comorbidities were not associated with shorter treatment persistence or lower clinical response rates.
- Comorbidities were associated with higher baseline disease activity and frequency of depression and/or anxiety.

Received: 7 November 2022. **Accepted:** 15 March 2023

Introduction

PsA is a chronic inflammatory condition with clinical manifestations including peripheral joint inflammation, spondylitis, dactylitis, tenosynovitis, enthesitis and skin/nail involvement [1]. One study also found that PsA patients have lower income and higher societal costs than general population subjects [2]. Additionally, several severe comorbid conditions, including cardiovascular disease, type 2 diabetes and depression, are associated with PsA [3]. Since >50% of patients with PsA have one or several comorbidities [4], it may be important to take these into consideration when choosing the appropriate therapy [5].

Over the last 2 decades, pharmaceutical treatment of PsA has evolved, especially with the introduction and expansion of new biologic DMARDs (bDMARDs) such as inhibitors of TNF, IL-12/23, IL-17 and IL-23. A previous study investigated the impact of comorbidities on disease activity, treatment response and treatment persistence in PsA patients treated with TNF inhibitors (TNFis). The study found that patients with a higher Charlson Comorbidity Index (CCI) score had greater disease activity measures at baseline and poorer drug survival. Patients with a CCI score ≥2 had shorter persistence with treatment compared with patients without comorbidities [6]. However, little is known about the interaction between PsA comorbidities and IL-17 inhibitor (IL-17i) treatment. We therefore investigated the influence of comorbidities on treatment response and disease activity in PsA patients treated with the IL-17is secukinumab and ixekizumab.

Materials and methods

Study design and setting

This was a population-based cohort study. Data on patient characteristics, treatment persistence, disease activity, treatment response and comorbidities were obtained through linkage of data from Danish health registries: the DANBIO registry [7], the Danish National Patient Register [8] and the Danish Civil Registration System [9]. In accordance with Danish legislation, the registration and publication of data from clinical registries does not require patient consent or approval by ethics committees.

Data source and participants

The DANBIO registry covers >90% of Danish adults with rheumatic diseases, including PsA, treated in routine care with bDMARDs [7]. The Danish National Patient Register is a key health register that covers somatic and psychiatric in- and outpatients in all hospitals. Internationally, the Danish National Patient Register is considered one of the most comprehensive of its kind [8, 10]. The Danish Civil Registration System contains individual-level updated information on migration and vital status on all persons residing in Denmark since 1986 [9]. Adult PsA patients registered in the DANBIO who initiated their first IL-17i treatment between the years 2015 and 2022 were included in the study, and data on medication history, current medication status, disease activity and treatment response were obtained.

Combining data from the two registries, 155 patients were eligible for the study. Information on the presence of somatic or psychiatric comorbid conditions before patients initiated their first IL-17i treatment was obtained from the Danish National Patient Register. The Charlson Comorbidity Index (CCI) is a well-known and validated index for measuring comorbidity disease status [11, 12]. In our analysis, the CCI score was based on comorbidity diagnoses registered up to 10 years prior to the date of IL-17i treatment initiation. The registration periods were made by consensus in the author group.

Outcomes

Drug survival and treatment response were evaluated as achievement of the American College of Rheumatology 20%, 50% and 70% improvement criteria (ACR20, ACR50 and ACR70, respectively), the EULAR good response and the EULAR good-or-moderate response and calculated in accordance with ACR and EULAR publications [13, 14]. Skin outcome data were not sufficient for analysis.

Statistical analysis

Demographic and descriptive data are shown as median and interquartile range (IQR) or mean and S.D. In Table 1, *P*-values represent the possibility of the differences in outcomes among the groups being coincidental and were assessed with Kruskal–Wallis one-way analysis of variance. The influence of CCI status on treatment persistence was assessed by Kaplan–Meier plots and Cox proportional hazards regression analyses. The responses (ACR20/50/70, EULAR good response, and EULAR good-or-moderate response) were calculated as observed, but also by use of the Lund Efficacy Index (LUNDEX) method. IL-17i persistence in years was used as the underlying time scale and covariates were tested for proportional hazards. In all statistical tests, *P*-values <0.05 (two-sided) were considered statistically significant.

Results

Baseline data

A total of 155 patients were included in this study. The cohort was followed for a total of 332.1 person-years and the median follow-up time was 1.8 years (IQR 0.44–3.63). The distribution of patients in each group was CCI 0, $n = 94$; CCI 1, $n = 45$; and CCI ≥2, $n = 14$, and the groups had a median follow-up time of 1.8 years, 1.9 years and 1.5 years, respectively.

Demographics and baseline disease characteristics are shown in Table 1. Patients with higher CCI scores generally had a tendency towards higher BMI, disease activity measures, PsA-related diseases and methotrexate co-medication at baseline. However, the only statistically significant baseline measures that were associated with a higher CCI score were CRP ($P = 0.046$) and swollen joint count ($P = 0.046$). The distribution of depression and/or anxiety was also statistically significant, with the highest occurrence in the group CCI 1 followed by CCI ≥2. Disease duration represents the time since the first recorded diagnosis of PsA. Patients on methotrexate co-medication were receiving methotrexate before it was decided to add an IL-17i.

Impact of CCI score on treatment response

Treatment response rates (ACR20/50/70) at 3 and 6 months revealed no significant differences between the CCI groups, neither as observed or LUNDEX-corrected (data not shown).

Table 1. Baseline characteristics according to CCI status of patients with PsA (*N*=155)

Characteristics	CCI 0 ($n=96$)	CCI 1 ($n=45$)	CCI ≥2 ($n=14$)	*P*-value
Demographics				
Female, *n* (%)	53 (55)	29 (64)	7 (50)	0.62
Age, years, mean (S.D.)	45.2 (11)	44.8 (11.5)	49.1 (11.2)	0.446
BMI, kg/m^2, mean (S.D.)	27.2 (4.5)	27.6 (5.6)	30.5 (6.1)	0.465
Disease-related characteristics				
PsA disease duration, years	3 (1–9)	5 (1–11)	5 (2.75–6.25)	0.234
Tender joint count (of 28)	7 (2–14)	6 (3–11.25)	14 (6.25–22.75)	0.159
Swollen joint count (of 28)	2 (0–5)	2 (0–6)	4 (0.75–11.75)	0.039
DAS28-CRP (0–10)	4.7 (3.68–5.4)	4.75 (3.40–5.45)	5.85 (5.03–6.15)	0.689
CRP, mg/L	6 (2.75–12)	11 (4–28.75)	11.5 (3.5–22.5)	0.047
HAQ-DI (0–3)	1 (0.63–1.5)	1.25 (0.88–1.81)	1.75 (1.25–2.25)	0.398
VAS patient global (0–100 mm)	73 (53.3–88)	69 (62.25–80.75)	89.5 (73.25–97.75)	0.775
VAS pain (0–100 mm)	61 (47–76.75)	68 (53–76.5)	80 (66.25–97)	0.656
VAS fatigue (0–100 mm)	70 (50.5–80)	74 (64.5–83.5)	94 (80–98.5)	0.914
VAS doctor's global (0–100 mm)	27 (20–40.75)	34 (22.75–60.25)	43.5 (32.75–46.25)	0.475
DAPSA28	41.9 (27–58)	50 (22.5–70)	71.3 (57.8–75)	0.433
Methotrexate co-medication, *n* (%)	52 (54)	25 (56)	10 (71)	0.410
Depression and/or anxiety, *n* (%)	1 (1)	4 (9)	1 (7)	0.027

Values are presented as median (IQR) unless stated otherwise. Registration of comorbidities was initiated 10 years prior to the date of onset of IL-17i treatment. Comparisons were assessed by Kruskal–Wallis/analysis of variance or chi-squared/Fisher's exact test.
DAS28-CRP: 28-joint DAS with CRP; HAQ-DI: HAQ Disability Index; VAS: visual analogue scale; DAPSA28: Disease Activity in Psoriatic Arthritis using 28 swollen and tender joint counts.

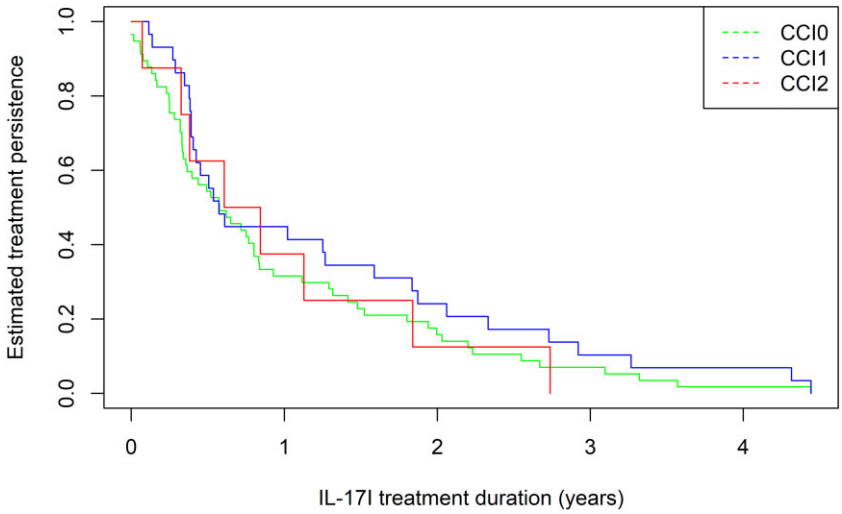

Figure 1. Kaplan–Meier plot of IL-17i persistence in patients with CCI scores of 0, 1 or ≥2

Impact of CCI score on treatment persistence

Treatment persistence estimates drawn in Kaplan–Meier plots are shown in Fig. 1. The different CCI groups show no statistically significant differences in treatment persistence ($P=0.48$) according to Fig. 1.

The multivariate Cox regression also did not show any statistically significant differences in treatment persistence between the different CCI groups. The listed demographics, disease-related characteristics, smoking, methotrexate co-medication and depression and/or anxiety did not have a statistically significant effect on treatment persistence (data not shown).

Discussion

In this cohort study of 155 PsA patients, we found that CCI scores had a significant impact on baseline CRP, swollen joint count and frequency of depression and/or anxiety, correlating with earlier findings [6, 15]. However, we also found that a CCI score of either 0, 1 or ≥2 had no significant impact on treatment persistence or treatment response to IL-17i, which is in contradiction to other studies examining the impact of comorbidities in PsA patients being treated with TNFi [6, 15].

These findings could suggest that the examined IL-17is, secukinumab and ixekizumab, have a weaker interaction with the pathologies of the included comorbidities than TNFis. Even though TNF-α was first thought to be an anti-cancer compound, it has since been associated with multiple pathophysiologies, including cancer, neurological diseases, cardiovascular diseases, pulmonary diseases, autoimmune diseases and metabolic diseases, i.e. several pathophysiologies of the comorbidities used to calculate our CCI scores. This is in agreement with the findings in studies by Ballegaard *et al.* [6] and Saad *et al.* [15] and could perhaps be part of the reason

why PsA patients with a higher CCI score may respond more poorly to TNFi in terms of treatment response and treatment persistence, although this is just speculation.

To our knowledge, no previous study has examined the effects of comorbidities on IL-17i treatment in PsA patients, so more investigation into this subject is needed before making any conclusions about the correlation between comorbidities, treatment persistence and treatment response in PsA patients treated with IL-17i.

An important limitation of this study is the size of the analysed groups, especially in the CCI $\geq$2 group, as this group only had 14 patients, and therefore findings for this group should be interpreted with care. The somewhat short treatment persistence is also a limitation of this study, and these results should therefore be interpreted with this in mind. Unfortunately, data on 66/68 joint counts, skin disease, uveitis and inflammatory bowel disease were not available for analysis in this study. The 28-joint DAS has been shown to correlate reasonably with disease activity in the peripheral joints, but further research across multiple PsA domains would be ideal to see if there is a consistent link with the presence of comorbidities. Moreover, the Disease Activity in Psoriatic Arthritis (DAPSA) score using 28-joint counts, although inferior, has been shown to be a reasonable estimate for DAPSA [16]. Another limitation was the observational, open study design, which may have led to selection bias. These limitations may have affected our results and therefore further investigations into the subject are needed, especially before making any interpretations about the effects of comorbidities on treatment response and treatment persistence in PsA patients being treated with IL-17is.

Conclusion

In conclusion, the presence of comorbidities was associated with increased baseline disease activity and frequency of depression and/or anxiety but was not associated with shorter treatment persistence or lower treatment response rates in a cohort of 155 Danish patients with PsA treated with first-line IL-17i.

Data availability

Data used for this study can be shared with the relevant stakeholders to the extent possible under Danish law.

Authors' contributions

Conception of the work: M.B.P., L.E.K.; Design of the work: M.B.P., L.E.K.; Acquisition of data for the work: M.B.P., L.E.K.; Analysis of data for the work: M.B.P., L.E.K.; Interpretation of data for the work: All authors; Drafting of the work: M.B.P., L.E.K.; Critical revision of the work for important intellectual content: All authors; Final approval of the work to be published or presented: All authors; Participated sufficiently in the work to agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved: All authors.

Funding

Funding was received from the Minister Erna Hamiltons Legat for Videnskab og Kunst. The study is further supported by an unrestricted core grant to the Parker Institute from the Oak Foundation (OCAY-18-774-OFIL).

Disclosure statement: L.C.C. has received grants/research support from AbbVie, Amgen, Celgene, Eli Lilly, Novartis and Pfizer; worked as a paid consultant for AbbVie, Amgen, Boehringer Ingelheim, Bristol-Myers Squibb, Celgene, Eli Lilly, Gilead, Galapagos, Janssen, Novartis, Pfizer and UCB and has been paid as a speaker for AbbVie, Amgen, Biogen, Celgene, Eli Lilly, Galapagos, Gilead, Janssen, Medac, Novartis, Pfizer and UCB. T.S.J. has received fees for participation in speakers bureaus for AbbVie, Roche, Novartis, UCB and Biogen. A.E. has received research funding from Pfizer, Eli Lilly, Novartis, Bristol-Myers Squibb, AbbVie, Janssen Pharmaceuticals, the Danish National Psoriasis Foundation, the Simon Spies Foundation and the Kgl Hofbundtmager Aage Bang Foundation and honoraria as a consultant and/or speaker from AbbVie, Almirall, Leo Pharma, Zuellig Pharma, Galápagos, Sun Pharmaceuticals, Samsung Bioepis, Pfizer, Eli Lilly, Novartis, Union Therapeutics, Galderma, Dermavant, UCB, Mylan, Bristol-Myers Squibb, Horizon Therapeutics and Janssen Pharmaceuticals. J.F.M. is a consultant and/or investigator for Amgen, Bristol-Myers Squibb, AbbVie, Dermavant, Eli Lilly, Novartis, Janssen, UCB, Sanofi, Regeneron, Sun Pharma, Biogen, Pfizer and Leo Pharma. L.E.K. has received fees for participation in speakers bureaus, research grants and consultancy fees from Pfizer, AbbVie, Amgen, Galapagos, UCB, Celgene, BMS, MSD, Novartis, Eli Lilly and Janssen Pharmaceuticals. The remaining authors have declared no conflicts of interest.

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June 2022 GB-RA-JY-202205-00033