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The Use of IL-17 and IL-23 Inhibitors in Swedish Clinical Practice: A Register-Based Analysis

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Keywords
PASI · DLQI · EQ-5D · Interleukin inhibitors · Psoriasis

Abstract
Background: Interleukin (IL) inhibitors have made *completely cleared skin* achievable for many patients with moderate to severe psoriasis in clinical trial settings. Few observational studies assess treatment response in accordance with treatment goals in guidelines. ***Objectives:*** The aim of the study was to analyze the treatment response of IL-17/IL-23 inhibitors in clinical practice and the proportions of patients that reach the treatment target of the Psoriasis Area and Severity Index (PASI) < 3 and the Dermatology Life Quality Index (DLQI) ≤5. ***Methods:*** A longitudinal, observational study based on the Swedish National Registry for Systemic Treatment of Psoriasis, PsoReg. Patients using IL-17/IL-23 inhibitors with assessments of PASI, DLQI, and EQ-5D before (maximum 6 months) and after (3–12 months) initiation of IL-17/IL-23 were included. ***Results:*** In total, 333 patients using IL-17/IL-23 inhibitors were included. Eighty percent (n = 266) received IL-17 inhibitors, and 20% (n = 67) received IL-23 inhibitors. Sixty-six percent of patients reached both PASI <3 and DLQI ≤5, 23% reached one target, and 11% reached none. The mean (SD) PASI, DLQI, and EQ-5D improvements were 6.75 (6.99), 7.14 (7.97), and 0.126 (0.296), respectively. There was no statistically significant difference in outcomes between IL-17 and IL-23 inhibitor treatment groups. ***Conclusions:*** IL-17/IL-23 inhibitors are effective in clinical practice, but there is still an unmet therapeutic need in moderate to severe psoriasis.

Introduction

The development of biologic drugs has been a central therapeutic advancement in psoriasis treatment. The recent introduction of efficient interleukin (IL)-17/IL-23 inhibitors [1], has greatly increased the prospects of completely clear skin. Several randomized controlled trials (RCTs) have proven the efficacy of IL-17 and IL-23 inhibitors [1], but complementary studies of effectiveness in clinical practice are required in order to capture heterogeneity in population characteristics, treatment regimens, and patient adherence.

An important consideration for the evaluation of psoriasis drug effectiveness in clinical practice is that, unlike RCTs, there are no "wash-out periods" that reveal the patients' un-

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Table 1. Patient characteristics in patients with IL-17 and IL-23 inhibitors

	Total	IL-17	IL-23
Patients, *n*	333	266	67
Age, mean years (SD)	49 (15)	49 (15)	47 (16)
Women, *n* (%)	125 (37)	103 (39)	22 (33)
BMI, median (IQR)	29 (6)	29 (6)	30 (6)
Waist, mean cm (SD)	106 (16)	106 (16)	105 (16)
Debut age >30, *n* (%)	94 (28)	74 (28)	20 (30)
Plaque psoriasis	274 (82)	220 (83)	54 (81)
Psoriatic arthritis	71 (21)	60 (23)	11 (16)
Nail psoriasis	66 (20)	55 (21)	11 (16)
Guttate	26 (8)	19 (7)	7 (10)
Smoking, *n* (%)	63 (19)	45 (17)	18 (27)
Risk consumption alcohol, *n* (%)	24 (7)	19 (7)	5 (7)
PASI pre-index, mean (SD)	9.06 (7.0)	8.98 (7.19)	9.40 (6.18)
DLQI pre-index, mean (SD)	10.38 (8.0)	10.3 (7.99)	10.9 (8.23)
EQ-5D pre-index, mean (SD)	0.658 (0.323)	0.655 (0.320)	0.671 (0.339)

DLQI, the Dermatology Life Quality Index; IQR, interquartile range; PASI, the Psoriasis Area and Severity Index; SD, standard deviation; BMI, body mass index

treated disease state. Traditional RCT end points, i.e., the relative measure of Psoriasis Area Severity Index (PASI), including PASI75 or PASI90, are therefore unsuitable due to the lack of "baseline" values. Instead, current treatment guidelines refer to absolute values, e.g., PASI <3 and the Dermatology Life Quality Index (DLQI) ≤5 [2–5]. However, although several studies have evaluated the real-world effectiveness of individual IL-17 or IL-23 drugs in psoriasis by PASI and DLQI [6–18], few have yet assessed the absolute values. The objective of this study was to analyze treatment response and proportions of patients that reach the treatment targets in terms of clinical and HRQoL outcomes in patients using IL-17 and IL-23 inhibitors in clinical practice.

Materials and Methods

Data Source

This study was based on data from the Swedish National Registry for Systemic Treatment of Psoriasis (PsoReg) in which patients with systemic treatment for psoriasis are enrolled at local, regional, and university hospitals, private clinics, and treatment centers managed by the patient organization. Observations reflect clinical practice; they occur when patients visit their physician, and no visits are protocol-driven.

Outcome Measures

The EQ-5D-3L (hereafter EQ-5D) is a generic standardized 3-response level questionnaire that measures health status in five dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Lower EQ-5D values reflect decreased HRQoL. The EQ-5D index score was calculated using the UK utility values [19], as no hypothetical (only experience-based) values were available in Sweden.

DLQI [20] is based on ten questions on a four-point scale, assessing how the skin disease affected patients' quality of life over the last week. DLQI ranges from 0 (quality of life not impaired) to 30 (quality of life severely impaired).

PASI measures the current severity of psoriasis based on the coverage of four body areas (in percentage of affected area): head, arms, trunk, and legs. Three main signs of psoriasis are assessed: redness, thickness, and scaling [21]. The score is on a scale from 0 (no present skin disease) to 72 (theoretical maximal disease).

Inclusion and Exclusion Criteria

Patients in PsoReg that initiated IL-17/IL-23 inhibitors after 1st of January 2016 were included. Only patients with pre-index (max 6 months) and post-index (min 3–max 12 months) PASI, DLQI, or EQ-5D values were included. To maximize the overall sample size, different sample sizes for PASI, DLQI, and EQ-5D were allowed. Patients with no registered treatments or contacts and patients with pustular psoriasis, erythroderma, and/or acrodermatitis continua suppurativa were excluded.

Data Analyses

Descriptive statistics (mean, standard deviation [SD], median, interquartile range [IQR], min, max) of PASI, DLQI, and EQ-5D were presented. Wilcoxon signed rank test was used to test for differences in the pre- and post-index date. Kruskal-Wallis test was used to test for differences in the outcomes between subgroups.

Results

Patient Sample

In total, 333 patients were included; 80% ($n = 266$) used IL-17 inhibitors, and 20% ($n = 67$) used IL-23 inhibitors (Table 1). No statistically significant differences in patient characteristics were detected between the two groups ($p > 0.05$).

Table 2. Descriptive statistics of PASI, DLQI, and EQ-5D outcomes in IL-17 inhibitors

IL-17, *N* = 266	Mean	SD	Median	Q1	Q3	Min	Max	*p* value
PASI, *n* = 252								
Pre-index	8.98	7.19	7.4	4.2	12.2	0.0	50.2	<0.01
Post-index	2.36	4.67	1.1	0	2.8	0	52.7	
Change	6.62	7.08	5.8	2.15	9.8	−33.7	38.2	
DLQI, *n* = 245								
Pre-index	10.3	7.99	8	3	17	0	30	<0.01
Post-index	3.14	5.06	1	0	5	0	28	
Change	6.93	7.82	5	1	12	−19	30	
EQ-5D, *n* = 203								
Pre-index	0.655	0.320	0.725	0.620	0.848	−0.239	1.00	<0.01
Post-index	0.784	0.266	0.796	0.725	1	−0.181	1	
Change	−0.131	0.284	−0.036	−0.221	0	−1.181	−0.601	

DLQI, the Dermatology Life Quality Index; PASI, the Psoriasis Area and Severity Index; Q, quartile.

Table 3. Descriptive statistics of PASI, DLQI, and EQ-5D outcomes in IL-23 inhibitors

IL-23, *N* = 67	Mean	SD	Median	Q1	Q3	Min	Max	*p* value
PASI, *n* = 60								
Pre-index	9.40	6.18	8.05	4.8	12.75	1.2	36.8	<0.01
Post-index	2.03	2.11	1.45	0.45	2.8	0	8.9	
Change	7.31	6.61	6.15	3.1	9.85	−4.5	36.8	
DLQI, *n* = 63								
Pre-index	10.91	8.23	9	4	16	0	28	<0.01
Post-index	3.06	4.26	1	0	5	0	16	
Change	8.0	8.52	7	1	−10	10	27	
EQ-5D, *n* = 53								
Pre-index	0.671	0.339	0.796	0.620	1	−0.181	1.00	0.01
Post-index	0.779	0.274	0.822	0.691	1	−0.016	1.00	
Change	−0.104	−0.342	0	−0.204	0	−0.807	0.736	

DLQI, the Dermatology Life Quality Index; PASI, the Psoriasis Area and Severity Index; Q, quartile.

Previous Treatment

Eighty five percent of patients with IL-17/IL-23 inhibitors had previously used a non-biologic systemic agent. About 76% had a registration of previous anti-TNF use. The most common reason for discontinuing the treatment prior to the IL-17/IL-23 (among the 276 patients who had recorded reasons) was "insufficient effectiveness" (78%), followed by "other reasons" (13%) and "reported side effects" (9%).

Treatment Outcomes

The mean (SD) time was 25.9 (39.6) days between the pre-index PASI/DLQI/EQ-5D assessment and IL-17/IL-23 and 5.5 (2.6) months between the IL IL-17/IL-23 and the post-index assessment. Only 4 patients had discontinued their IL-17/IL-23 at post-index.

In the total patient group, mean (SD) PASI, DLQI, and EQ-5D improvements were 6.75 (6.99), 7.14 (7.97), and 0.126 (0.296), respectively. The within-group improvements in PASI, DLQI, and EQ-5D were statistically significant ($p = \leq 0.01$) in both patients with IL-17 inhibitors (Table 2) and IL-23 inhibitors (Table 3). There was no statistically significant difference in the PASI ($p = 0.368$), DLQI ($p = 0.316$), or EQ-5D ($p = 0.382$) improvements between the IL-17 and IL-23 patient groups, nor in the post-index PASI ($p = 0.239$), DLQI ($p = 0.872$), or EQ-5D ($p = 0.902$) values at post-index assessment.

Treatment Targets

Most patients with IL-17/IL-23 inhibitors (66%, n = 205) reached both treatment targets PASI <3 and DLQI ≤5, 23% (n = 71) reached one of the targets, and 11% (n = 33) reached neither target. No statistically significant difference was detected between the IL-17 and the IL-23 groups (p = 0.968).

Discussion

In this observational study, the vast majority of patients using IL-17/IL-23 inhibitors (89%) reached at least one of the treatment targets of PASI <3 and DLQI ≤5, and two out of three (66%) reached both targets. In accordance with requirements from the Swedish reimbursement authority, most patients using IL-17/IL-23 had previously used other biologic and non-biologic systemic agents. These numbers may be even higher due to the underreporting of retroactively registered treatments.

An advantage of this study is the relatively large sample of patients in clinical practice. Some limitations are inherent in this register-based design. As there were no protocol-driven visits, follow-up times and treatment durations varied. Some patients may not have reached the full treatment effect at assessment; others may have had a relapse of disease after discontinuing treatment. We only included post-index observations between 3 and 12 months to limit this. Another limitation is that overall disease severity may not be reflected in assessments based on one timepoint, as psoriasis can cause episodes of varying severity.

Patient characteristics were comparable between patients using IL-17 and IL-23. Estimating the relative effectiveness of these IL-inhibitors was, however, beyond the scope of this study. That would require larger samples so that the influence of confounding factors could be limited by matching patients.

The reductions in mean PASI (6.8) and DLQI (7.1) observed here were relatively low compared to other real-world studies of IL-17/IL-23 inhibitors. One explanation could be the limited follow-up time of mean (SD) 5.5 (2.6) months. Previously published protocol-driven observational studies of IL-17 or IL-23 with longer treatments (≥24 to ≤104 weeks) have shown reductions (mean or median) from baseline in the ranges of 7.1–15.6 for PASI and 7.5–10.9 for DLQI [6, 8, 9, 12, 16, 22, 23]. As an exception, Mala et al. [26] reported even larger reductions in both PASI (22.1) and DLQI (21.5) after 6 months with IL-23 inhibitor, possibly due to relatively high median baseline scores (PASI:24.1, DLQI:24.1) in the patient population.

This study shows that IL-17/IL-23 inhibitors are effective in clinical practice. Nevertheless, there is still an unmet need for patients with moderate-to-severe psoriasis who have tried and failed IL-17/IL-23 inhibitors. The study used data from a time when the IL-17/and IL-23 inhibitors were still new. Further research, when more data are available, should match cohorts and compare the relative effectiveness of different IL-17/IL-23 inhibitors.

Key Message

89 percent of patients with IL-17/IL-23 inhibitors reached at least one of the targets PASI <3 and DLQI ≤5.

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Statement of Ethics

This study was conducted according to the Declaration of Helsinki and approved by the Regional Ethical Review Board at Umeå University, Sweden (Dnr 2010-194-31M, Dnr 2011-286-32M, Dnr 2016-126-32M). Oral informed consent has been obtained from all participants in PsoReg. All data used in the study were de-identified.

Conflict of Interest Statement

Marcus Schmitt-Egenolf is responsible for dermatology in the project management for the national guidelines for psoriasis at the Swedish Board of Health and Welfare. Jenny M Norlin and Sofia Löfvendahl have been involved in the health economic analyses of the national guidelines. The authors have no further conflict of interest to declare.

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Author Contributions

Jenny M Norlin, Sofia Löfvendahl, and Marcus Schmitt-Egenolf contributed to the conceptional framework and the study design and equally to the analyses and the writing of the manuscript. Jenny M Norlin carried out the statistical analyses.

Data Availability Statement

The data that support the findings of this study were retrieved from PsoReg. Restrictions apply to the availability of these data under Swedish and European laws, which were used under license for the current study and are therefore not publicly available. Further inquiries can be directed to the corresponding author.

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