SHORT COMMUNICATION

Interleukin-17 and - 23 Inhibitors Associated with Direct Effects on Depressive Symptoms in Psoriasis: A Register Study

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Psoriasis is associated with anxiety and depression (1). The mechanisms underlying this association are unclear, but probably reflect signs (2) and symptoms (3) of the disease, and systemic inflammation (4).

Targeted immunomodulators in psoriasis can be grouped into 5 classes, based on mode of action (MoA): tumour necrosis factors-alpha inhibitors (TNFis), interleukin (IL) 12/23 inhibitors (IL-12/23is), IL-17 inhibitors (IL-17is), IL-23 inhibitors, and phosphodiesterase-4 inhibitor (PDE-4is). Given the association between systemic inflammation and depression, these MoAs may have distinct direct effects on depressive symptoms (5). Estimating this direct effect is important because it may help identify patients who benefit from treatment with specific MoA and could advance our understanding of the association between systemic inflammation and depression. The aim of this register analysis was to explore whether targeted immunomodulators with different MoAs had distinct direct effects on depressive symptoms in psoriasis.

MATERIALS AND METHODS

Study setting and data sources. DermaReg-Pso enrols patients in Region Stockholm who are candidates for systemic treatment for psoriasis and follows them prospectively (7). Data are collected when patients visit the clinic during standard clinical practice. Appendix S1 shows further details of DermaReg-Pso.

Outcomes: The main outcome was depressive symptoms measured using the Montgomery-Åsberg Depression Rating Scale-self assessment (MADRS-s) instrument (8). The instrument is patient reported and covers 9 domains: depressed mood, feelings of unease, reduced sleep, reduced appetite, concentration difficulties, lassitude, inability to feel, pessimism, and suicidal ideation (8). Each domain is scored between 0 and 6 for a total score of 0–54 (8). MADRS-s was evaluated as an interval scale (i.e. it was assumed that the order and the difference between 2 points on the scale is meaningful). The MADRS-s domain scores were used as secondary outcomes; these were also assumed to be interval scales. Furthermore, the Anxiety/Depression (AD) dimension from the EQ5D-3L instrument (EQ5D-3L-AD) was used as an additional outcome (9). Respondents to the EQ5D-3L-AD choose 1 of 3 levels related to anxiety/depression equivalent to "no", "some", and "major" depression. EQ5D-3L-AD was evaluated as an ordered categorical scale.

Exposures: The main exposures in this study were MoA for targeted immunomodulators in psoriasis: TNFis, IL-12/23is, IL-17is, IL-23is, and PDE-4is. TNFis comprised adalimumab, certolizumab pegol, etanercept, infliximab, and golimumab; IL-12/23is comprised ustekinumab; IL-17is comprised bimekizumab, brodalumab, ixekizumab, and secukinumab; IL-23is comprised guselkumab, risankizumab, and tildrakizumab; and PDE4is comprised apremilast.

Covariates and mediators. The study included covariates that were *a priori* considered to affect both exposures and outcome. These were: sex, age, measurement year, and highest observed Dermatology Life Quality Index (DLQI) (proxy for disease impact on quality of life; measured over the entire observation period). To account for indirect effect of treatments on depressive symptoms the following potential mediators were included: Psoriasis Area and Severity Index (PASI) to measure skin disease severity (10), an itch-visual analogue scale (VAS) to measure pruritus (11), the Psoriatic Arthritis Screening and Evaluation (PASE) questionnaire to measure joint problems (12), and the DLQI to measure health-related quality of life (HRQoL) (13).

Statistical methods. A regression model framework was used to combine data on exposures, outcomes, and covariates. Data from each visit with complete data during which a patient was treated with a relevant MoA were included in the regression models. These models were fit to assess the association between exposure (MoA) and the level of depressive symptoms.

To estimate the total and direct controlled associations between depression and specific MoAs, all observations with complete data were included in linear regression models with total MADRS-s as the outcome. Two models were used: 1 with MoAs and confounders as independent variables to study the total controlled effect, and 1 with MoAs, confounders, and potential mediators as independent variables to study the direct controlled effect. The total controlled effect is an estimate of the effect of a specific MoA relative TNFis when differences in mediators (e.g. PASI and DLQI) between MoAs are allowed to impact the estimate; the direct controlled effect is an estimate of the effect when differences in mediators are accounted for. TNFis were used as the reference MoA, given that it is the most frequently prescribed class of targeted immunomodulators in psoriasis. The interpretation of the coefficients for the different MoAs from the regression models is the difference in MADRS-s for a specific MoA relative to TNFis controlling for the covariates included in the model. Furthermore, to explore the direct controlled effect of MoAs on specific depressive symptoms for treatments that were associated with total MADRS-s scores, linear regression models were used, with the scores of each individual MADRS-s domain as dependent variable, and MoAs, confounders and potential mediators as independent variables. As a sensitivity analysis, the controlled direct effect on the EQ-5D-3L-AD from different MoAs was also estimated using an ordered logistic regression model.

Given that many patients were observed more than once, all regression models were mixed effects models with patient as random effect. All analyses were performed in STATA 17.2. For exploratory purposes p-values below 0.05 were considered statistically significant.

RESULTS

There were 2,609 observations with complete data in 405 patients. Among the 405 patients, mean (standard devia-

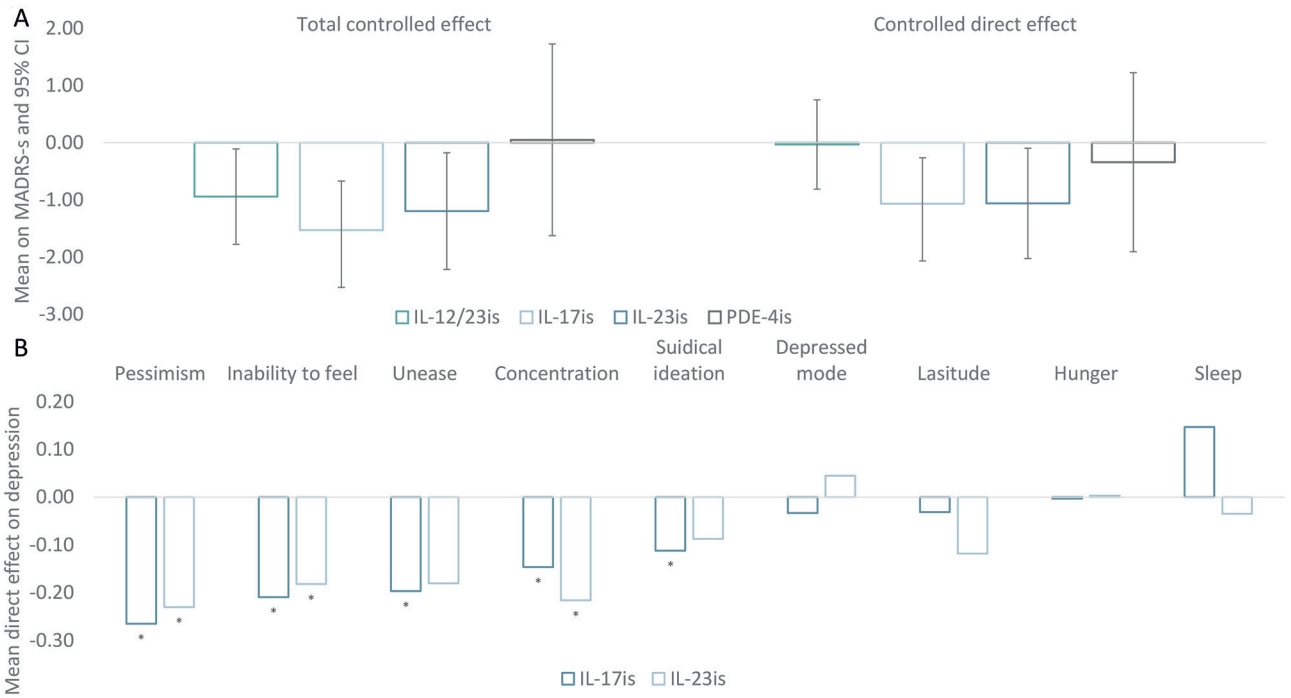

Fig. 1. Effects on total Montgomery-Åsberg Depression Rating Scale-self assessment (MADRS-s) and individual MADRS-s domains from targeted immunomodulators with different modes of action in psoriasis. (A) Total controlled and direct controlled effect on total MADRS-s scores for different modes of action. (B) Controlled direct effect on individual MADRS-s domains for different modes of action. The estimates for total and direct controlled effects were obtained from mixed effects linear regression models controlling for confounders and (for direct controlled effects only) mediators (Psoriasis Area and Severity Index, Dermatology Life Quality Index, Itch-visual analogue scale, and Psoriatic Arthritis Screening and Evaluation). 95% CI: 95% confidence interval; IL: interleukin; PDE-4is: phosphodiesterase-4 inhibitor.

tion; SD) age was 48.5 (15.5) years, 269 (66.4%) were male, and 136 (33.6%) had PsA (Table SI). The numbers of observations per MoA were 1,172 for TNFis, 661 for IL-12/23is, 540 for IL-17is, 174 for IL-23is, and 62 for PDE-4is (Table SII).

IL-12/23is, IL-17is, IL-23is were associated with a total controlled effect compared with TNFis, whereas only IL-17is and IL-23is were associated with direct controlled effects on total MADRS-s score (**Fig. 1**A, Table SIII). IL-23is were also associated with significantly reduced odds of depression measured using the EQ-5D-3L-AD (Table SIV).

In terms of individual MADRS-s domains IL7is and IL23is were associated with beneficial direct effects in the concentration, inability to feel, pessimism, unease (IL-17is only), and suicidal ideation (IL-17is only), domains of MADRS-s (Fig. 1B).

DISCUSSION

This study found that IL17is and IL23is are associated with reduced depressive symptoms compared with TNFis when controlling for confounders and mediators. This direct controlled effect on depressive symptoms may reflect their effect on systemic inflammation.

It is important to note that the controlled direct effects on depression with IL17is and IL23is observed in this study may reflect factors other than systemic inflammation; for example, the observed effects may reflect improvements in signs or symptoms of psoriasis that were not controlled for. However, the fact that the regression models fit to estimate controlled direct effects were adjusted for quality of life measured using the DLQI, suggests that such an effect is less likely, as the DLQI includes a question on stinging, burning, and skin pain.

The clinical significance of these findings is unclear. On the one hand, the relatively modest reduction in total MADRS-s scores fall below the threshold for clinically meaningful change, estimated at 3–9 points for MADRS-s (14); on the other hand, the impact on depression measured using the EQ-5D suggests that the changes may be important. In this context should be noted that most patients were not depressed, resulting in that clinically meaningful change in MADRS-s score would not be possible in many patients.

Two main limitations of this study are uncertain generalizability, and potential measurement error, given that MADRS-s and EQ-5D may not accurately measure depressive symptoms, especially as we did not account for use of antidepressants. Furthermore, the results cannot be interpreted as causal given the non-randomized observational study design.

In conclusion, this study supports the notion that IL17/IL23 pathway may be important for depression in psoriasis and that blocking related cytokines may directly reduce depressive symptoms. However, further research is

needed. Especially, a study that also measures circulating cytokines would be important to better understand the mechanistic link and therapeutic potential of anti- IL17/IL23 treatment for depression.

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Conflicts of interest: AS reports consulting fees from Abbvie and Eli Lilly, employment and consulting fees from Icon, and lecture fees from Janssen. MS reports consulting, advisory, or lecture fees from Abbvie, Janssen, Novartis, Eli Lilly, Bristol Myers Squibb, and Leo Pharma.

REFERENCES

1. Kleyn CE, Talbot PS, Mehta NN, Sampogna F, Bundy C, Ashcroft DM, et al. Psoriasis and mental health workshop report: exploring the links between psychosocial factors, psoriasis, neuroinflammation and cardiovascular disease risk. Acta Derm Venereol 2020; 100: adv00020.
2. Tee SI, Lim ZV, Theng CT, Chan KL, Giam YC. A prospective cross-sectional study of anxiety and depression in patients with psoriasis in Singapore. J Eur Acad Dermatol Venereol 2016; 30: 1159–1164.
3. Reich A, Mędrek K, Szepietowski JC. Interplay of itch and psyche in psoriasis: an update. Acta Derm Venereol 2016; 96: 55–57.
4. Koo J, Marangell LB, Nakamura M, Armstrong A, Jeon C, Bhutani T, et al. Depression and suicidality in psoriasis: review of the literature including the cytokine theory of depression. J Eur Acad Dermatol Venereol 2017; 31: 1999–2009.
5. Wang X, Li Y, Wu L, Xiao S, Ji Y, Tan Y, et al. Dysregulation of the gut-brain-skin axis and key overlapping inflammatory and immune mechanisms of psoriasis and depression. Biomed Pharmacother 2021; 137: 111065.
6. Zafiriou E, Daponte AI, Siokas V, Tsigalou C, Dardiotis E, Bogdanos DP. Depression and obesity in patients with psoriasis and psoriatic arthritis: Is IL-17-mediated immune dysregulation the connecting link? Front Immunol 2021; 12: 699848.
7. Svedbom A, Ståhle M. Real-world comparative effectiveness of adalimumab, etanercept and methotrexate: a Swedish register analysis. J Eur Acad Dermatol Venereol 2020; 34: 525–532.
8. Svanborg P, Asberg M. A new self-rating scale for depression and anxiety states based on the Comprehensive Psychopathological Rating Scale. Acta Psychiatr Scand 1994; 89: 21–28.
9. Oppe M, Devlin NJ, Szende A. EQ-5D value sets: inventory, comparative review and user guide. Springer, Berlin, Germany; 2007.
10. Fredriksson T, Pettersson U. Severe psoriasis – oral therapy with a new retinoid. Dermatologica 1978; 157: 238–244.
11. Reich A, Riepe C, Anastasiadou Z, Mędrek K, Augustin M, Szepietowski JC, et al. Itch assessment with visual analogue scale and numerical rating scale: determination of minimal clinically important difference in chronic itch. Acta Derm Venereol 2016; 96: 978–980.
12. Dominguez PL, Husni ME, Holt EW, Tyler S, Qureshi AA. Validity, reliability, and sensitivity-to-change properties of the psoriatic arthritis screening and evaluation questionnaire. Arch Dermatol Res 2009; 301: 573–579.
13. Finlay AY, Khan G. Dermatology Life Quality Index (DLQI) – a simple practical measure for routine clinical use. Clin Exp Dermatol 1994; 19: 210–216.
14. Hengartner MP, Plöderl M. Estimates of the minimal important difference to evaluate the clinical significance of antidepressants in the acute treatment of moderate-to-severe depression. BMJ Evid Based Med 2022; 27: 69–73.