

Response to Interleukin-17A Inhibitors According to Prior Biologic Exposures: A Danish Nationwide Study

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Whether response to an interleukin (IL-17) inhibitor is different in patients with previous exposure to an IL-17 inhibitor compared with patients with exposure to biologics with other cytokine targets remains to be elucidated. Therefore, the aim of this study was to assess whether previous exposure to an IL-17A inhibitor was associated with worse response than exposure to (an)other biologic(s). All patients in the DERMBIO register treated with an IL-17A inhibitor (secukinumab or ixekizumab) were included. With an absolute Psoriasis Area and Severity Index (PASI) ≤ 2 as response, the proportion of responders treated with IL-17A inhibitors was assessed in patients previously treated with another IL-17A inhibitor and compared with patients with previous exposure to (an)other biologic(s), using a χ^2 test. In total, 100, 93 and 83 patients with previous exposure to an IL-17A inhibitor and 414, 372 and 314 patients with previous exposure to (an) other biologic(s) were assessed after 3, 6 and 12 months, respectively. No differences in the proportion of patients achieving PASI ≤ 2 were observed between the 2 groups after 3 months (54% vs 57%, $p = 0.59$), 6 months (70% vs 66%, $p = 0.42$) and 12 months (69% vs 60%, $p = 0.14$). In conclusion, when treating patients with IL-17A inhibitors the cytokine target of the previous biologic does not appear to affect the response.

Key words: psoriasis; biologics; IL-17; secukinumab; ixekizumab; switch.

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Based on data from clinical trials, interleukin (IL)-17 inhibitors are among the biologics for treating moderate-to-severe psoriasis with the best efficacy and show a good safety profile (1–3). Patients in the real-world have more comorbidities and have often received more treatments than those participating in clinical trials (4). In addition, patients who have previously been treated with biologics with a similar cytokine target as the

SIGNIFICANCE

This study examined whether patients who were previously treated with an interleukin-17A inhibitor responded differently to another interleukin-17A inhibitor compared with those who had been treated with other biologics. The study included patients treated with secukinumab or ixekizumab. After 3, 6 and 12 months, no significant difference was found in the proportion of patients achieving a good response (Psoriasis Area and Severity Index ≤ 2) between those with prior exposure to interleukin-17A inhibitor and those with exposure to other biologics. In conclusion, prior exposure to an interleukin-17A inhibitor does not appear to affect the response when treating patients with interleukin-17A inhibitors.

investigated biologics have often been prohibited from participating in clinical trials. In general, real-world studies report lower responses in those with previous biologic exposure compared with biologic-naïve patients for IL-17 inhibitors (5–11). Whether the cytokine target of previous biologics affects the response to the current biologic has not been well-investigated, and as multiple biologics target the IL-17 cytokine family, it is important to assess whether a class effect exists, e.g. failure of one IL-17 inhibitor leads to failure of another. Few smaller studies have indicated that previous treatment with one IL-17 inhibitor does not appear to affect the efficacy of another IL-17 inhibitor (12–23). However, these studies often lack information on the reasons for discontinuation of previous anti-IL-17 treatment (12). In addition, whether response to an IL-17 inhibitor is different in patients with previous exposure to an IL-17 inhibitor compared with exposure to (an)other cytokine target(s) remains to be elucidated.

This study examined the effectiveness of IL-17A inhibitors (secukinumab and ixekizumab) in a real-world nationwide setting according to cytokine targets of prior exposure to biologics.

MATERIALS AND METHODS

The study was approved by the Danish Data Protection Agency (ref. VD-2018-286). In Denmark, approval of an ethics committee is not required for register-based studies.

Patient selection

All patients in DERMBIO (24–34) with a treatment series with an IL-17A inhibitor (secukinumab or ixekizumab) between April 2015 and October 2019 were eligible for inclusion.

Patients were categorized into 2 groups according to biologic exposure: (i) patients with previous IL-17A inhibitor exposure (secukinumab or ixekizumab); and (ii) patients with biologic exposure other than IL-17 inhibitors. Patients with previous exposure to an IL-17A inhibitor were grouped according to the reason for discontinuation of previous IL-17A inhibitor: treatment failure vs reasons other than treatment failure. Treatment failure was defined as primary failure or secondary failure. Primary failure was defined as failure to achieve Psoriasis Area and Severity Index (PASI) ≤ 4 or PASI75 after 3 months, or discontinuation of treatment before or at the 3 months visit due to lack of efficacy. Secondary failure was defined as achieving PASI ≤ 4 and/or PASI75 after 3 months and stopping treatment afterwards due to loss of effectiveness, or for patients without a recorded PASI after 3 months of treatment, stopping treatment beyond the 6-month visit due to lack/loss of efficacy.

Outcomes

The effectiveness of the IL-17A inhibitors was assessed by response criteria based on absolute PASI comparing patients with previous IL-17 inhibitor exposure with patients with biologics exposure other than IL-17 inhibitors. The primary outcome was an absolute PASI ≤ 2 after 3, 6 and 12 months, respectively. Secondary outcomes were the proportion of patients achieving PASI = 0 and PASI ≤ 4 after 3, 6 and 12 months, respectively. Tertiary outcomes were based on relative reductions of PASI; PASI75, PASI90 and PASI100. Lastly, the proportion of patients achieving DLQI = 0/1 was assessed.

Responder imputation

As the data originate from the real-world and patients might have missing data/visits due to multiple reasons, including lack of effectiveness, lack of registration, visits at other times than scheduled, etc., different methods were used to analyse data. The primary model was constructed using a modified last observation carried forward (LOCF) approach: patients who stopped treatment prior to the evaluation point (month 3, 6 and 12) due to lack of effectiveness were considered non-responders, for the rest of the patients the last observation was carried forward to the evaluation point and the response was based on this value.

As subanalyses and for meta-data the following approaches were used: as observed (AO), LOCF, non-responder imputation (NRI), and a modified AO approach, where patients who stopped treatment prior to the evaluation point (month 3, 6 and 12) due to lack of effectiveness were considered non-responders and the rest of patients were analysed AO.

For all models, only patients with long enough follow-up were considered, e.g. only patients starting treatment 3, 6 and 12 months before database lock, were considered for analysis at the relevant time-points.

Statistical analysis

For continuous data, means with standard deviations (SD) and medians with interquartile ranges (IQR) were reported, and for categorical outcomes, numbers with percentages were presented. For normally distributed data an unpaired *t*-test was used to assess differences between groups, and for non-parametric data Mann–Whitney test was used. For categorical outcomes χ^2 or Fisher's exact tests were used to assess differences between groups.

The effectiveness of IL-17A inhibitors was assessed and compared in different groups: (i) patients with previous ex-

posure to IL-17A inhibitors vs patients with previous exposure to (an)other biologic(s) than IL-17 inhibitors; (ii) patients with treatment failure to previous IL-17A inhibitors vs patients who stopped treatment due to other reasons than treatment failure of previous IL-17A inhibitor; (iii) primary failure vs secondary failure to previous IL-17A inhibitor. The outcomes were assessed for IL-17A inhibitors overall and for the individual drug.

The association between previous exposure to biologics and response to drug was assessed for the primary outcome (PASI ≤ 2 after 3, 6 and 12 with a modified-LOCF approach) in a sensitivity analysis using logistic regression. The odds ratios (ORs) are presented as crude, partially adjusted and fully adjusted. The partially adjusted model included drug, and the fully adjusted model included additional adjustment for sex, age, weight and number of previous therapies (1 vs > 1).

All data management and statistical analyses were performed using SAS software version 9.4 (SAS Institute Inc., Cary, NC, USA).

RESULTS

Baseline characteristics

In total, 581 treatment series with an IL-17A inhibitor were included, of which 151 series were with ixekizumab and 430 treatment series with secukinumab. Of the included patients, 121 were previously exposed to another IL-17A inhibitor, and 460 had previous exposure to (an)other biologic(s) than an IL-17 inhibitor (**Table I**). Most of the patients with previous exposure to IL-17A inhibitors were treated with ixekizumab and were previously exposed to secukinumab, whereas most patients exposed to a biologic with another mechanism of action were treated with secukinumab (Table I). Patients

Table I. Baseline characteristics of included patients

	Previous exposure to an IL-17A inhibitor (N = 121)	Previous exposure to (an)other biologic(s) than an IL-17A inhibitor (N=460)	<i>p</i> -value
Sex, male, <i>n</i> (%)	81 (66.9)	264 (57.4)	0.06
Age, years, mean (SD)	48.5 (14.7)	47.9 (14.2)	0.71
Weight, kg, mean (SD)	98.6 (26.3)	93.5 (25.4)	0.09
	Missing = 26	Missing = 63	
Body mass index, mean (SD)	30.4 (6.9)	30.4 (7.3)	0.96
	Missing = 62	Missing = 227	
Psoriatic arthritis, <i>n</i> (%)	53 (43.8)	206 (44.8)	0.85
Concomitant MTX, <i>n</i> (%)	7 (5.8)	33 (7.2)	0.59
Disease duration, years, mean (SD)	27.2 (14.3)	24.0 (12.3)	0.043
	Missing = 32	Missing = 162	
Baseline PASI, median (IQR)	5.0 (2.0-10.0)	5.0 (2.0-10.0)	0.81
	Missing = 29	Missing = 70	
Baseline DLQI, median (IQR)	8.0 (4.0-13.0)	7.0 (3.0-12.5)	0.80
	Missing = 47	Missing = 160	
Treatment			
Patients treated with ixekizumab, <i>n</i> (%)	95 (78.5)	56 (12.2)	<0.0001
Patients treated with secukinumab, <i>n</i> (%)	26 (21.5)	404 (87.8)	<0.0001
Number of previous biologics			
1	20 (16.5)	178 (38.7)	<0.0001
2	22 (18.2)	119 (25.9)	
3	26 (21.5)	69 (15.0)	
4 or more	53 (43.8)	94 (20.4)	

IL: interleukin; SD: standard deviation; MTX: methotrexate; PASI: Psoriasis Area and Severity Index; DLQI: Dermatology Life Quality Index. *p*-values < 0.05 are marked in bold.

previously exposed to an IL-17A inhibitor had been treated with more biologics than those with previous biologic exposure but naïve to IL-17 inhibitors (Table I).

Effect of interleukin-17A inhibitors in previously biologic-exposed patients

Of the included patients, 556 had follow-up time of minimum 3 months, 486 of minimum 6 months and 402 of minimum 12 months (Fig. 1). The overall proportion of patients treated with an IL-17A inhibitor who achieved PASI ≤ 2 was respectively, 56% after 3 months, 66% after 6 months and 62% after 12 months using the modified LOCF approach.

Patients with previous exposure to interleukin-17A inhibitor vs biologics other than interleukin-17 inhibitors

Of the included patients, 115, 103 and 87 with previous exposure to an IL-17A inhibitor had follow-up time of minimum 3, 6 and 12 months, respectively; and 441, 383 and 315 with previous exposure to (an) other biologic(s) than an IL-17 inhibitor had follow-up time of minimum 3, 6 and 12 months, respectively (Fig. 1). The number of patients that could be analysed using modified LOCF was 100, 93 and 83 for patients with previous exposure to an IL-17A inhibitor and 414, 372 and 314 for patients with previous exposure to an(other) biologic(s) than an IL-17 inhibitor after 3, 6 and 12 months respectively. No differences in the proportion of patients achieving PASI ≤ 2 was observed after 3 months (n: 54 [54%] vs n: 236 [57%], p = 0.59), 6 months (n: 65 [70%] vs n: 244 [66%], p = 0.42),

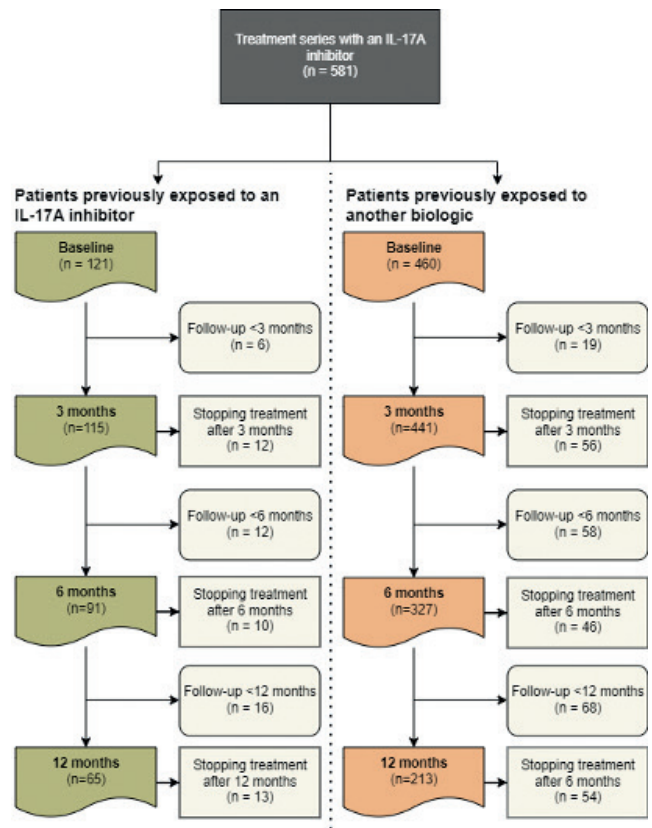


Fig. 1. Flowchart showing number of patients available for analysis at different time points IL: interleukin.

and 12 months (n: 56 [69%] vs 189 [60%], p = 0.14), respectively (Fig. 2). Similar results were observed for all other outcomes (Table SI). When analysing data using

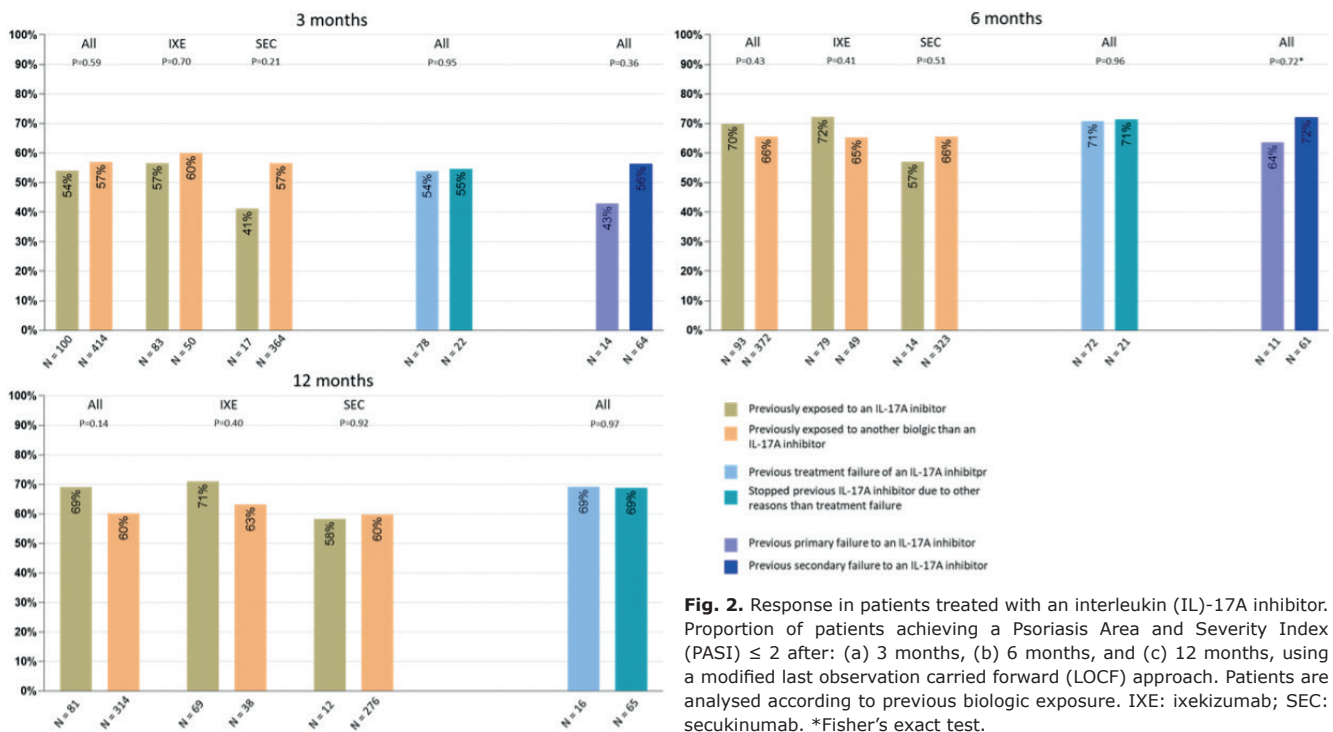


Fig. 2. Response in patients treated with an interleukin (IL)-17A inhibitor. Proportion of patients achieving a Psoriasis Area and Severity Index (PASI) ≤ 2 after: (a) 3 months, (b) 6 months, and (c) 12 months, using a modified last observation carried forward (LOCF) approach. Patients are analysed according to previous biologic exposure. IXE: ixekizumab; SEC: secukinumab. *Fisher's exact test.

NRI, it appeared that a higher proportion of patients responded to IL-17A inhibitors among those exposed to (an)other biologic(s) than an IL-17 inhibitor after 3 and 12 months for most outcomes (Table SI). This was not observed after 6 months or for any of the other responder imputations (Table SI).

Reasons for discontinuation of previous interleukin-17A inhibitor: treatment failure vs other reasons than treatment failure

Of the patients with previous exposure to an IL-17A inhibitor, 93 stopped the previous IL-17A inhibitor due to treatment failure and 28 stopped due to other reasons. Overall, with the modified LOCF approach, 100 patients could be analysed after 3 months, 93 after 6 months and 81 after 12 months. No differences in the proportion of patients achieving PASI ≤ 2 after 3 months (54% vs 55%, $p = 0.95$), 6 months (71% vs 71%, $p = 0.96$), and 12 months (69% vs 69%, $p = 0.97$) were observed between the 2 groups (Fig. 1). Similar results were observed for all other outcomes although the proportion of patients achieving PASI ≤ 4 appeared to be higher in those with previous treatment failure at all time-points (Table SII). Changing the responder imputation did not alter the results (Table SII).

Reasons for previous treatment failure IL-17A inhibitor: primary failure vs secondary failure

In total, 18 patients stopped treatment of previous IL-17A inhibitors due to primary failure and 75 stopped due to secondary failure. Overall, with the modified LOCF approach, 78 patients could be analysed after 3 months and 72 after 6 months. Response rates could not be assessed after 12 months due to the limited number of patients. Throughout the treatment course, no statistically significant difference was observed in the proportion of patients achieving PASI ≤ 2 (Fig. 2). However, more patients appeared to achieve PASI ≤ 2 (43% vs 56%, $p = 0.36$) and PASI ≤ 4 (57% vs 75%, $p = 0.18$) after 3 months in patients with previous secondary failure, although this was not statistically significant and was not observed after 6 months (Table SIII).

Sensitivity analyses

Sensitivity analyses were performed for PASI ≤ 2 using a modified LOCF approach after 3, 6 and 12 months. Here, no association between previous exposure to biologics (IL-17 vs (an)other biologic(s)) and response to treatment with an IL-17A inhibitor was observed (Table SIV). Similarly, no association was observed between the previous reason for drug discontinuation (failure vs other reasons than failure) or for treatment failure (primary vs secondary failure) and response to treatment with an IL-17A inhibitor (Table SIV). This was observed for the crude

analyses and for the adjusted analysis. Of the explaining variables only body weight seemed to influence the response (data not shown).

DISCUSSION

This nationwide register-based study of 581 patients treated with IL-17A inhibitors with previous biologic exposure, observed that 56%, 66% and 62% of the patients achieved PASI2 after 3, 6 and 12 months using a modified LOCF imputation. No differences were found in response regarding the cytokine target of the previous biologic or the reason for discontinuation of the previous IL-17A inhibitor.

In phase 3 clinical trials, the proportion of patients with previous exposure to biologics achieving PASI75, PASI90 and PASI100 were 88%, 68% and 37% after 3 months in patients with psoriasis treated with labelled doses of ixekizumab (35). The corresponding proportion of patients with PASI75, PASI90 and PASI100 in real-world studies are generally reported to be similar or lower (5, 8, 18). However, clinical trials and real-world studies differ in several settings. The follow-up time in real-world studies is often incomplete and handling of patients with incomplete follow-up time is not always clear. Furthermore, patients are seen more often and at specific time-points in clinical trials. Thus, missing values in clinical trials more likely represent a non-responder; consequently, non-responder imputation is often opted for in clinical trials. On the other hand, in the real-world, patients might be seen at other time-points than the scheduled times, registration is not as vigilant as in clinical trials, and missing values do not necessarily represent a non-responder. Non-responder imputation might therefore be too conservative, whereas imputation as observed does not take patients stopping treatment prior to evaluation into account. Both NRI and AO imputation have been used in real-world studies, but which approach is being used is not always clear (8, 13–19, 36). In the current study, the main outcome was based on a modified LOCF imputation as patients stopping treatment due to lack of effect were also considered and, by doing so, the highest possible number of patients could be included. In addition, this study presents all other responder imputation, which did not alter the results. In addition, the study used response criteria based on absolute PASI, as these are more suitable in real-world, considering the lack of wash-out of prior treatment (37). An absolute PASI ≤ 2 as response criterion appears to be optimal (38) and has been shown to correspond to PASI90 (37, 39). With a modified LOCF imputation, 56% of all patients with previous exposure to biologics regardless of mechanism of action achieved PASI ≤ 2 after 3 months of treatment with an IL-17A inhibitor, which is lower than the proportion of patients with previous biologic exposure who achieve PASI90 in phase III

trials (35). However, biologics with similar mechanism of action as the investigated biologics are often prohibited in clinical trials and patients in the real-world who are ineligible for clinical trials often have worse response than those who are eligible (40). A recent systematic review and meta-analysis showed that previous exposure to an IL-17 inhibitor did not necessarily predict failure to a subsequent IL-17 inhibitor (12). The meta-analysis could not assess whether the reason for discontinuation of the previous IL-17 inhibitor influenced response or if previous exposure to an IL-17 inhibitor was associated with worse response than exposure to another biologic with a different mechanism of action (12). In the current study, the cytokine target of previous biologics did not appear to influence the response. In addition, for patients with previous exposure to an IL-17A inhibitor, the reason for discontinuation of a previous IL-17A inhibitor did not affect the response. This indicates that there is no class effect regarding failure to respond to IL-17A inhibitors. However, after 3 months it appeared that more patients with previous secondary failure responded to an IL-17A inhibitor compared with patients with previous primary failure. Nevertheless, only a few patients with previous primary treatment switched to another IL-17 inhibitor, and the difference was not statistically significant.

Some limitations should be considered; due to limited data it was not possible to differentiate ixekizumab and secukinumab for some of the exposures. The lack of difference in response among patients with previous exposure to different cytokine targets could be due to the limited number of patients included. However, all patients in Denmark treated with an IL-17A inhibitor were included and any differences would be considered of little clinical relevance. Another limitation is the missing data on effect measures. Still, this study presents different approaches to analysing data and considers data to be missing at random between the groups. Finally, it is possible that factors other than previous treatment might have influenced the outcome; however, sensitivity analyses including multiple possible confounding variables were performed, which did not influence the results. The strengths of the study include the nationwide coverage of patients, the validated disease measures and response criteria, and the prospective collection of data.

In conclusion, when treating patients with IL-17A inhibitors the cytokine target of the previous biologic and the reason for discontinuation of a previous biologic do not appear to affect the response. However, additional studies assessing the individual IL-17A inhibitor are needed.

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The DERMBIO registry has entered into agreements with Abbvie, Eli Lilly, Bristol-Myers Squibb, UCB, Novartis, Janssen, and Leo Pharma. They receive post-marketing data and have no influence on the data collection, statistical analyses, manuscript preparation or decision to submit.

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