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Commentary

Long-term follow-up of 22 psoriatic patients treated with ixekizumab after failure of secukinumab

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Abstract

Switching of biologic agents in treatment of plaque psoriasis is a common strategy. Only a few studies are available on switching between IL17A-blockers. In a retrospective study, we identified 22 psoriasis patients who, after failing secukinumab as a first IL17A-blocker received ixekizumab with an observation period of at least 24 weeks. At last observation 10/22 patients had a good response (PASI75 or PASI<3) using ixekizumab therapy. None of five patients with primary non-response to secukinumab reached a good, durable response to ixekizumab. In conclusion, ixekizumab appears to be a therapeutic option as a second IL17A-blocker in psoriasis patients who did not show a primary non-response to secukinumab.

Introduction

In the past years, the number of different biologics for treatment of plaque psoriasis has increased considerably. Drugs with new targets (IL17A, IL17RA, IL23) have been developed and several drugs with the same molecular target are available, for example ixekizumab and secukinumab, both blocking IL17A. When a biologic therapy fails, the question arises whether a biologic with the same target or with a different target should be given. Although there is data available on this issue for TNF-blockers [1, 2], only a few studies have addressed this question for IL17A-blockers [3-6]. Herein, we present a retrospective analysis of patients who were switched from secukinumab to ixekizumab with an observation of at least 24 weeks.

Case Synopses

Adult patients with plaque psoriasis treated in the dermatology departments of four German universities who received ixekizumab after prior treatment with secukinumab were identified. Only patients who started ixekizumab at least 24 weeks prior to data collection were included. Patient characteristics were extracted from their medical records. Additionally, treatment with secukinumab and ixekizumab with regard to dosage, concomitant treatment, treatment duration, cutaneous efficacy (PASI, primary non-response, secondary non-response), efficacy on psoriatic arthritis (PsA), adverse events (AEs), and reason for drug discontinuation were assessed. A good response was defined as reaching a PASI75 or a PASI value <3.0, partial response as reaching a PASI50, primary non-response as not reaching a PASI50, and secondary non-response as losing a PASI50 response. The study was performed according to the principles of the Declaration of Helsinki and approved by the ethics committees of all participating centers [7].

A total of 22 patients were identified whose baseline characteristics are shown in Table 1. Of these, 16 patients suffered from additional psoriatic arthritis.
(PsA) and patients had been pretreated with 4.9±2.6 systemic therapies before treatment with secukinumab, among those 2.4±2.0 biologics. Patients had a mean PASI value of 15.9±8.4 at the start of secukinumab therapy (Table 1). In 21 patients secukinumab was given in a dose as licensed for plaque psoriasis (with dose escalation in 6 patients receiving 300mg every three weeks) and in one patient as licensed for psoriasis arthritis. Treatment duration with secukinumab lasted on average 16.0±7.6 months. The most frequent reasons for treatment discontinuation were secondary (12/22) and primary non-response (5/22) of the skin. In three patients secukinumab was stopped owing to non-response of joints and in another two patients because of adverse events. Of these 22 patients, 16 were switched directly from secukinumab to ixekizumab whereas 6 patients received at least one other systemic therapy in between.

The mean PASI value at baseline of ixekizumab therapy (available in 21 patients) was 12.0±5.5. Ixekizumab was given in a dose licensed for plaque psoriasis in all cases. Three patients received additionally methotrexate, one leflunomide, and another patient oral prednisolone (for treatment of multiple sclerosis). At week 12, 11/21 patients (52.4%) with available data reached a good response (PASI 75 response or PASI<3). At week 24, eight of 19 patients (42.1%) had a good response (prior discontinuation (N=1) counting as non-response, three patients without data), (Table 1). At last observation, 16/22 patients were still on therapy with ixekizumab (Figure 1). Of these 16 patients, 10 patients (62.5%) showed a good response, two patients a PASI 50 response and four patients a secondary non-response at final observation. All these 12 patients showing a good or a partial response under ixekizumab therapy had experienced at least a partial primary response during secukinumab therapy (Figure 1). Among the six patients who discontinued ixekizumab, two had primary and four secondary non-response to ixekizumab. Table 1 gives additional information on the respective mean PASI values (as observed) at the indicated time points. Adverse events during

Table 1. Cohort characteristics, response to secukinumab, response to ixekizumab.

<table>
<thead>
<tr>
<th>Baseline characteristics</th>
<th>Number, mean±SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender</td>
<td>male n=18, female n=4</td>
</tr>
<tr>
<td>Age (years)</td>
<td>47.4±8.3</td>
</tr>
<tr>
<td>BMI</td>
<td>32.8±5.0</td>
</tr>
<tr>
<td>Age at onset of disease (years)</td>
<td>23.8±10.0</td>
</tr>
<tr>
<td>Disease duration (years)</td>
<td>24.0±11.3</td>
</tr>
<tr>
<td>Psoriatic arthritis</td>
<td>16 pos, 6 neg</td>
</tr>
<tr>
<td>Comorbidities</td>
<td>obesity n=12 hypertension n=13 diabetes mellitus n=5 steatosis hepatitis n=6</td>
</tr>
<tr>
<td>Number of systemic pretreatments</td>
<td>4.9±2.6</td>
</tr>
<tr>
<td>Number of prior biologics</td>
<td>2.4±2.0</td>
</tr>
<tr>
<td><strong>PASI at baseline SECU</strong></td>
<td><strong>15.9±8.4</strong></td>
</tr>
<tr>
<td>Therapy duration of SECU</td>
<td>16.0±7.6 months</td>
</tr>
<tr>
<td>Cause of SECU discontinuation</td>
<td>5x prim nr skin 12x sec nr skin 3x nr joints 2x AEs**</td>
</tr>
<tr>
<td><strong>PASI at baseline IXE (21)</strong></td>
<td><strong>12.0±5.5</strong></td>
</tr>
<tr>
<td>PASI at weeks 12-16 (21)*</td>
<td>3.7±3.1</td>
</tr>
<tr>
<td>Response at weeks 12-16 (21)</td>
<td>11x PASI 75 7x PASI 50 3x prim nr 1x no data</td>
</tr>
<tr>
<td>PASI at weeks 24-26 (18)*</td>
<td>5.0±4.7</td>
</tr>
<tr>
<td>Response at weeks 24-26 (19)</td>
<td>8x PASI 75 3x PASI 50 5x sec nr 2x prim nr 1x IXE stopped 3x no data</td>
</tr>
<tr>
<td>Concomitant therapies</td>
<td>3x methotrexate 1x leflunomide 1x prednisolone</td>
</tr>
<tr>
<td>Therapy duration of IXE (all)</td>
<td>12.4±5.2 months</td>
</tr>
<tr>
<td>Therapy duration of patients who discontinued IXE</td>
<td>9.8±3.9 months</td>
</tr>
<tr>
<td>Cause of IXE discontinuation</td>
<td>2x prim nr skin 4x sec nr skin</td>
</tr>
</tbody>
</table>

AEs, adverse effects; BMI, Body Mass Index; IXE, ixekizumab; SECU, secukinumab; PASI, Psoriasis Area and Severity Index; prim nr, primary non-response; sec nr, secondary non-response; SD, standard deviation; *as observed. ** one patient with a lichenoid reaction and one patient with an urticarial rash.
Discussion

In our study at week 12, 52.4% of patients reached a good response to ixekizumab as second IL17A-blocker. This is less compared to three other retrospective studies in which patients receiving ixekizumab as second IL17A-blocker reached a PASI 75 response at week 12 in 71% [5], 81% [4], or even 100% [3]. In another retrospective study, 50% PASI 75 response at week 12 to ixekizumab as second IL17A-blocker was comparable to our study [8]. Until now, to our knowledge, only one study reported PASI 75 responses after 24 weeks of ixekizumab as second IL17A-blocker, which were reached by a higher proportion of patients (80%), compared to 42.1% in our study [4]. The reasons for the reported differences in PASI 75 response rates between the studies are not clear but may be manifold. Possibly, our patients suffered from a more recalcitrant disease. However, the number of previous systemic therapies including biologics as possible indicator of disease severity was similar in those studies [3, 5]. Analysis of response to secukinumab revealed that patients without a primary PASI 50 response to secukinumab did not achieve a good response to ixekizumab. This is in line with the results of a previous study with a 12-week observation of a second IL17A-blocker. The longer patients were treated with secukinumab (probably owing to better efficacy) the better patients later responded to ixekizumab [5].

In summary, the overall response to ixekizumab as second IL17A-blocker is relatively good. Neutralizing anti-drug antibodies to secukinumab appear not to be relevant as a possible explanation for treatment failure to secukinumab [9]. The better effect of ixekizumab might be at least partly explained by the fact that ixekizumab has shown a 50–100 times...
higher in-vitro affinity to IL17A compared to secukinumab [10, 11]. However, data about use of IL17A-blockers in reverse order are needed to support this explanation. We observed only a few adverse events in patients undergoing treatment with ixekizumab, none leading to discontinuation.

Limitations of our study include the retrospective design and the comparably low number of included patients, particularly in subgroup analyses.

Conclusion
Our study results provide evidence that the use of ixekizumab as second IL17A-blocker is a reasonable therapeutic option in patients with at least a partial prior response to secukinumab. Further studies are needed to assess risk and benefit of employing a second IL17A-blocker after therapy failure of a first IL17A-blocker.

Potential conflicts of interest
This work was supported by a grant from Lilly. S.P. has received travel grants or honoraria, or has been a consultant member of advisory boards and speakers bureaus for one or more of the following: AbbVie Deutschland GmbH & Co. KG, Almirall Hermal GmbH, Amgen GmbH, Biogen Idec GmbH, BMS GmbH, Boehringer Ingelheim Pharma GmbH & Co. KG, Celgene GmbH, Charité Research Organisation GmbH, Dermira, Inc, Forward Pharma, GlaxoSmithKline GmbH & Co. KG., Janssen-Cilag GmbH, Leo Pharma GmbH, Lilly Deutschland GmbH, Maruho Europe Ltd., MSD Sharp & Dohme GmbH, Mundipharma, Novartis Pharma GmbH, Pfizer Deutschland GmbH, Sandoz Pharmaceuticals GmbH, VBL Therapeutics, and UCB Pharma. D. W. T. has been an advisor and/or received speakers’ honoraria or travel expense reimbursements and/or received grants and/or participated in clinical trials of the following companies Abbvie, Almirall, Amgen, Biogen, Boehringer Ingelheim Pharma, Celgene, Forward Pharma, GlaxoSmithKline, Janssen-Cilag, Leo, Lilly, Medac, Merck Sharp & Dohme Corp., Novartis, Pfizer, UCB Pharma, VBL. R. M. has been an advisor and/or received speakers’ honoraria and/or received grants and/or participated in clinical trials of the following companies: Abbott/Abbvie, Allmirall, Biogen IDEC GmbH, Böhhringer-Ingelheim, Celgene, Essex Pharma GmbH, Janssen-Cilag GmbH, Leo Pharma GmbH, Lilly, Merck Serono GmbH, MSD SHARP & DOHME GmbH, Novartis Pharma GmbH, Pfizer GmbH and UCB. S. G. has been an advisor and/or received speakers’ honoraria and/or received grants and/or participated in clinical trials of the following companies: Abbott/Abbvie, Affibody AB, Akari Therapeutics Plc, Almirall-Hermal, Amgen, Anaptyx Bio, Baxalta, Bayer Health Care, Biogen Idec, Bioskin, Boehringer-Ingelheim, Celgene, Centocor, Dermira, Eli Lilly, Foamix, Forward Pharma, Galderma, Hexal AG, Isotechnika, Janssen-Cilag, Johnson & Johnson, Leo Pharma, Medac, Merck Serono, Mitsubishi Tanabe, MSD, Novartis, Pfizer, Polichem SA, Regeneron Pharmaceutical, Sandoz Biopharmaceuticals, Sanofi-Aventis, Schering-Plough, Sienna Biopharmaceuticals, Takeda, Teva, UCB Pharma, VBL therapeutics, Wyeth Pharma. S. P. participated in clinical trials of the following companies Janssen-Cilag, Leo and Novartis. J. M. has participated in clinical trials of the following companies: Abbott/Abbvie, Biogen IDEC GmbH, Böhringer-Ingelheim, Celgene, Essex Pharma GmbH, Janssen-Cilag GmbH, Leo Pharma GmbH, Lilly, Merck Serono GmbH, Novartis Pharma GmbH, Pfizer GmbH and UCB. K. A. declares no conflicts of interest.

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