Time to relapse after tildrakizumab withdrawal in patients with moderate-to-severe psoriasis who were responders at week 28: post hoc analysis through 64 weeks from reSURFACE 1 trial

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Abstract

Background As treatment interruptions occur during psoriasis management in clinical practice, it is important to know the duration of clinical response after treatment withdrawal.

Objectives To report time to and predictors of relapse in patients who were tildrakizumab 100 and 200 mg responders (≥ 75% improvement in Psoriasis Area and Severity Index, PASI 75) at week 28 re-randomized to placebo from reSURFACE 1 trial.

Methods Post hoc analysis of adult patients with moderate-to-severe plaque psoriasis from a 64-week phase 3 trial. Relapse was primarily defined as loss of PASI 75 response. Both relapses defined as loss of PASI 90 and loss of absolute PASI < 2 response were included as sensitivity analyses. PASI 75, PASI 90 and PASI < 2 responders re-randomized to placebo at week 28 and followed up until week 64 were included. The Kaplan–Meier (KM) estimates of the 64-week relapse rate were calculated. The log-rank test to compare KM curves from responders to tildrakizumab 100 and 200 mg was used. Independent predictors of relapse were explored.

Results Median time to loss of PASI 75/PASI 90/PASI < 2 response from week 28 was 142/111/112 days with tildrakizumab 100 mg and 172/140/113 days with tildrakizumab 200 mg, respectively (all not significant). Around 20% of patients did not relapse (either maintained a PASI 75 response or were lost to follow-up) during the 36-week period. Increase in body mass index (BMI) (hazard ratio, HR [95% confidence interval, CI] for loss of PASI 75 response: 1.0345 [1.0112 – 1.0582]) and increase in disease duration (HR [95% CI]: 1.0151 [1.0028 – 1.0275] for loss of PASI 75 response) were associated with an increased risk of relapse, regardless of the relapse definition.

Conclusions When treatment is interrupted, tildrakizumab provides durable maintenance of efficacy with a median time to loss of PASI 75 response of 5–6 months, irrespective of the dose. Interventions on modifiable risk factors for relapse, such as BMI, may improve personalized long-term psoriasis management.

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Conflicts of Interest

RBW reports non-financial support from Janssen, during the conduct of the study; grants and personal fees from AbbVie, Almirall, Amgen, Celgene, Lilly, Leo Pharma, Novartis and UCB; and personal fees from Boehringer Ingelheim and Sanofi, outside the submitted work. JMC reports personal fees from Almirall, AbbVie, Janssen, Novartis, Amgen, Leo Pharma, Sandoz and Lilly, outside the submitted work. EF is an employee of Almirall. AS reports personal fees from Trial Form Support (TFS), during the conduct of the study; and other from InnoUp

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Psoriasis is a chronic inflammatory skin disease affecting about 2% of the worldwide population. Tildrakizumab is a specific monoclonal antibody that targets the p19 subunit of interleukin (IL)-23, approved for the treatment of plaque psoriasis, and that has shown to be effective and safe in the long term. Despite the associated risk of relapse, the temporary or permanent interruption of psoriasis treatment may occur in clinical practice. As patients may discontinue therapy for several reasons, it is important for physicians to know the duration of clinical response after treatment withdrawal. In responder patients, the duration of effect varies depending on the biologic therapy, and thus, data on time to relapse are critical for physicians when choosing between therapies for psoriasis. Also, an understanding of factors predictive of relapse of disease is helpful to inform individualized treatments.

A randomized withdrawal phase as part of a randomized controlled trial allows evaluation of the maintenance of efficacy in a placebo-controlled manner. Reich et al. used a randomized treatment-withdrawal period in the reSURFACE 1 phase 3 trial of tildrakizumab in patients with moderate-to-severe plaque psoriasis. The main objective of this post hoc study was to report time to relapse in patients who were tildrakizumab responders (≥75% improvement in Psoriasis Area and Severity Index; PASI 75) at week 28 who were re-randomized to placebo from reSURFACE 1 trial.

Based on the current psoriasis treatment standards, we also evaluate the phenomenon of off-treatment response by looking to high levels of response such as PASI 90, which is an increasingly common primary endpoint in clinical trials, and absolute PASI ≤ 2, which corresponds to PASI 90 response and is currently a relevant endpoint for treat-to-target approaches in psoriasis. Thus, two additional definitions of relapse are secondarily applied and time to relapse is also estimated among PASI 90 and PASI < 2 responders at week 28 who were randomized to placebo. Finally, we evaluate predictive factors for relapse.

**Materials and methods**

**Study design**

Post hoc analysis of adult patients with moderate-to-severe plaque psoriasis from a three-part, parallel-group, double-blinded, randomized, placebo-controlled 64-week phase 3 trial was performed. Detailed methodology and patient characteristics have been previously published. In Part 1 (week 0 to week 12), patients were randomized 2 : 1 to tildrakizumab 100 mg, tildrakizumab 200 mg or placebo. In Part 2 (week 12 to week 28), placebo patients were re-randomized 1 : 1 to tildrakizumab 100 mg or 200 mg. Tildrakizumab 100 and 200 mg doses were given at week 0, week 4 and every 12 weeks thereafter (i.e., during Part 2, tildrakizumab doses were only given at week 16). In Part 3 (week 28 to week 64), tildrakizumab responders (i.e. patients who achieved at least a 75% improvement from baseline PASI) were re-randomized 1 : 1 in a double-blinded manner to continue the same tildrakizumab dose or to receive placebo every four weeks (starting at week 28) until relapse (defined as a reduction in maximum PASI response by 50% in the study protocol). Once relapse occurred, patients were retreated with the same tildrakizumab dose, subsequent dosing occurring after four weeks of treatment reinitiation, and every 12 weeks thereafter through week 64. At week 64, patients who achieved at least a
PASI 50 response at the end of Part 3 entered an optional long-term extension epoch (Fig. 1).

**Patients**

Eligible patients were aged 18 years or older, had body surface area affected ≥10%, Physician’s Global Assessment score ≥3 and PASI ≥12, and were candidates for phototherapy or systemic therapy at baseline. The study protocol was approved by the local institutional review boards or ethics committees at each site. All patients provided written informed consent.

**Statistical analyses**

In this *post hoc* analysis, relapse was primarily defined as loss of PASI 75 response as this was the response criterium in the study protocol. Either relapse defined as loss of PASI 90 response or relapse defined as loss of PASI < 2 response was considered as sensitivity analyses.

The primary analysis included PASI 75 responders (i.e. patients with ≥75% improvement in PASI) re-randomized to placebo at week 28 and followed up until week 64 (i.e. 36-week follow-up period) (tildrakizumab 100 and 200 mg withdrawal groups), and PASI 75 responders re-randomized to continue the same tildrakizumab dose at week 28 (tildrakizumab 100 and 200 mg maintenance or control groups).

Sensitivity analyses were conducted among PASI 90 responders (i.e. patients with ≥90% improvement in PASI) and PASI < 2 responders (i.e. patients with an absolute PASI < 2), who were re-randomized to placebo at week 28 and followed up until week 64 (i.e. 28-week response was defined differently, and the relapse definition was adapted accordingly).

The Kaplan–Meier estimates of the 64-week relapse rate were calculated. The log-rank test to compare the Kaplan–Meier curves from responders to tildrakizumab 100 mg and responders to tildrakizumab 200 mg was used.

Both logistic and Cox regression models to find independent factors predictive of loss of PASI 75, PASI 90 and PASI < 2 responses were built. For the logistic and Cox models, the pooled data from both tildrakizumab 100 and 200 mg doses were used. Presented analysis is based on observed cases.

**Results**

**Primary analysis population**

At week 28, 114 and 119 patients who were PASI 75 responders to tildrakizumab 100 and 200 mg, respectively, were re-randomized to placebo (tildrakizumab 100 and 200 mg withdrawal groups), and 116 and 119 patients who were PASI 75 responders to tildrakizumab 100 and 200 mg continued the same tildrakizumab dose (tildrakizumab 100 and 200 mg maintenance groups) (Fig. 2). At week 64, 87.5% and 93.9% of patients in the tildrakizumab 100 and 200 mg maintenance groups, respectively, maintained a PASI 75 response. Baseline demographics and disease characteristics in the tildrakizumab withdrawal groups were comparable to those in the tildrakizumab maintenance groups (Table 1).
Among the patients in the tildrakizumab withdrawal groups, the median time to loss of PASI 75 response from week 28 was 142 days with tildrakizumab 100 and 172 days with tildrakizumab 200 mg (p = 0.2191) (Fig. 3). The Kaplan–Meier curves for tildrakizumab maintenance groups were included as control arms (Fig. 3). A total of 20.2% and 24.4% of patients who initially received tildrakizumab 100 mg or tildrakizumab 200 mg and were re-randomized to placebo did not relapse during the 36-week period (Table 2); either maintained a PASI 75 response (91.3% and 89.7% in the tildrakizumab 100 and 200 mg withdrawal groups, respectively) or were lost to follow-up (8.7% and 10.3% in the tildrakizumab 100 and 200 mg withdrawal groups, respectively).
Table 1 Patient’s baseline characteristics according to relapse status (relapse defined as loss of PASI 75 response) among tildrakizumab withdrawal and tildrakizumab maintenance groups

| Relapse (loss of PASI 75 response) | Tildrakizumab withdrawal (n = 114) | Tildrakizumab maintenance (n = 116) | Tildrakizumab withdrawal (n = 119) | Tildrakizumab maintenance (n = 119) |
|-----------------------------------|----------------------------------|----------------------------------|----------------------------------|----------------------------------|
| Male, n (%) | No (73.9) Yes (26.1) | No (61.5) Yes (38.5) | No (66.7) Yes (33.3) | No (77.8) Yes (22.2) |
| Age (years), mean (SD) | 43.7 (12.8) 46.4 (12.4) | 47.8 (14.9) 44.2 (12.1) | 46.1 (11.9) 45.9 (12.4) | 45.0 (13.6) 52.5 (11.1) |
| Weight (kg), mean (SD) | 83.2 (22.1) 91.1 (23.5) | 87.3 (23.6) 90.5 (22.2) | 83.0 (13.1) 87.8 (23.8) | 88.9 (24.0) 82.4 (14.1) |
| BMI (kg/m²), mean (SD) | 28.0 (6.3) 31.5 (7.6) | 30.2 (7.5) 30.1 (6.7) | 27.8 (5.8) 29.7 (7.2) | 30.7 (7.7) 29.9 (6.3) |
| Cigarette smoking, n (%) | Current or ex-smoker | 11 (47.8) 69 (75.8) | 59 (67.1) 15 (55.6) | 19 (65.5) 53 (60.2) |
| Non-smoker | 12 (52.2) 22 (24.2) | 29 (33.0) 12 (44.4) | 10 (34.5) 35 (39.8) | 33 (33.0) 7 (36.8) |
| BSA (%), mean (SD) | 26.2 (14.6) 28.6 (18.8) | 28.6 (15.7) 31.3 (17.5) | 28.1 (11.7) 30.4 (18.6) | 29.0 (16.5) 36.6 (20.7) |
| PASI score, mean (SD) | 18.6 (5.8) 19.7 (8.7) | 19.7 (7.3) 19.8 (6.3) | 19.7 (5.2) 20.6 (8.9) | 20.1 (8.0) 20.5 (8.4) |
| PGA category, n (%) | ≤3 | 16 (69.6) 61 (67.0) | 58 (65.2) 19 (70.4) | 22 (75.9) 58 (64.4) |
| ≥4 | 7 (30.4) 30 (33.0) | 31 (34.8) 8 (29.6) | 7 (24.1) 32 (35.6) | 31 (31.0) 5 (26.3) |
| Disease duration (years), mean (SD) | 11.8 (8.8) 16.5 (14.0) | 17.8 (14.3) 19.2 (10.7) | 12.3 (9.5) 15.9 (11.1) | 16.7 (12.6) 15.1 (10.8) |
| Psoriatic arthritis (yes), n (%) | 5 (21.7) 17 (18.7) | 13 (14.6) 3 (11.1) | 4 (13.8) 14 (15.6) | 17 (17.0) 3 (15.8) |
| Previously treated with biologics (yes), n (%) | 3 (13.0) 18 (19.8) | 14 (15.7) 10 (37.0) | 4 (13.8) 22 (24.4) | 23 (23.0) 6 (31.6) |
| Weeks sustaining a PASI 75 response between week 4 and week 28, mean (SD) | 19.5 (5.5) 17.5 (6.1) | 18.3 (6.3) 13.1 (6.9) | 20.0 (3.6) 16.5 (6.7) | 18.1 (5.2) 13.2 (7.3) |
| Weeks sustaining a PASI 90 response between week 4 and week 28, mean (SD) | 14.1 (7.8) 10.1 (8.1) | 12.6 (7.6) 4.0 (6.1) | 15.2 (6.1) 10.4 (8.2) | 11.6 (6.9) 4.5 (7.2) |

BMI, body mass index; BSA, body surface area; PASI, Psoriasis Area Severity Index; PGA, Physician’s Global Assessment; SD, standard deviation.

Figure 3 Time to relapse, defined as loss of PASI 75 response (date of first placebo dose during part 3 [week 28] to date of relapse [maximum of 260 days]) by treatment group. The y-axis displays the proportion of patients who relapsed (loss of PASI 75 response). PASI, Psoriasis Area Severity Index.
CI, confidence interval; PASI, Psoriasis Area Severity Index.

Predictive factors for loss of PASI 75 response
Since the Kaplan–Meier analysis did not show statistically significant differences between responders to tildrakizumab 100 and 200 mg, the pooled data from both doses were used for the logistic and Cox models to gain power. Regarding factors predictive of relapse, logistic regression model showed that patients who smoke had a twofold greater odds of loss of PASI 75 response than non-smokers. In addition, the odds of loss of PASI 75 response was 7% higher for every 1-unit increase in BMI, 3% higher for every 1-year increase in disease duration, respectively (Table 3).

Study population for sensitivity analyses
At week 28, 71 and 86 patients who were PASI 90 responders to tildrakizumab 100 and 200 mg, respectively, and 75 and 87 patients who were PASI < 2 responders to tildrakizumab 100 and 200 mg, respectively, were re-randomized to placebo.

Time to loss and factors predictive of PASI 90 response
The median time to loss of PASI 90 response was 111 days among the tildrakizumab 100 mg withdrawal group and 140 days among the tildrakizumab 200 mg withdrawal group (P = 0.2794). A total of 12.7% and 16.3% of patients who initially received tildrakizumab 100 or 200 mg and were re-randomized to placebo did not relapse (either maintained a PASI 90 response or were lost to follow-up) during the 36-week epoch (Table 2).

In relation to predictive factors for relapse, defined as loss of PASI 90 response, Cox regression analysis showed that increase in BMI, smokers, increase in disease duration and female sex were associated with an increased risk of relapse (Table 4).

Time to loss and factors predictive of PASI < 2 response
The median time to loss of PASI < 2 response was around 110 days either among the tildrakizumab 100 mg withdrawal group or tildrakizumab 200 mg withdrawal group (P = 0.4721). A total of 13.3% and 16.1% of patients who initially received tildrakizumab 100 or 200 mg and were re-randomized to placebo did not relapse (either maintained a PASI < 2 response or were lost to follow-up) during the 36-week period (Table 2).

With regard to factors predictive of relapse, defined as loss of PASI < 2 response, Cox regression analysis indicated that both increase in BMI and increase in disease duration were associated with an increased risk of relapse (Table 5).

Discussion
The post hoc analyses from the reSURFACE 1 trial presented here explored time to relapse in the randomized withdrawal

Table 3 Factors predictive of loss of PASI 75 response

| Logistic regression model predictors                  | Odds ratio | 95% CI       | P-value |
|------------------------------------------------------|------------|--------------|---------|
| Body mass index (kg/m²)                              | 1.073      | 1.016–1.132  | 0.0115  |
| Cigarette smoking (smoker vs. non-smoker)            | 2.039      | 1.020–4.073  | 0.0437  |
| Disease duration (years)                             | 1.033      | 1.001–1.067  | 0.0458  |
| Time sustaining a PASI 90 response between week 4 and week 28 (days) | 0.989      | 0.983–0.996  | 0.0008  |

| Cox regression model predictors                     | Hazard ratio | 95% CI       | P-value |
|-----------------------------------------------------|--------------|--------------|---------|
| Body mass index (kg/m²)                              | 1.0345       | 1.0112–1.0582| 0.0034  |
| Disease duration (years)                             | 1.0151       | 1.0028–1.0275| 0.0155  |

CI, confidence interval; PASI, Psoriasis Area Severity Index.
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period in PASI 75, PASI 90 and PASI < 2 responders to both tildrakizumab 100 mg and tildrakizumab 200 mg doses. Patients had only received three doses before they were withdrawn from tildrakizumab at week 28, and were followed up until week 64, thus 48 weeks without active treatment. Knowing time to relapse after treatment withdrawal is important in a real clinical setting where patients may need to stop therapy for different reasons (e.g. unexpected medical reason, surgery).

The median time to relapse (defined as time to loss of PASI 75 response) was 20 weeks with tildrakizumab 100 and 25 weeks with tildrakizumab 200 mg (i.e. 32–37 weeks after the last tildrakizumab dose). Kimball et al. had previously reported a median time to relapse of 24 weeks either with tildrakizumab 100 or 200 mg but defining relapse as a reduction in maximum PASI response by 50% following withdrawal of tildrakizumab treatment. Among those patients who relapsed and were retreated for at least 12 weeks, 86% and 83% of patients with tildrakizumab 100 mg and tildrakizumab 200 mg, respectively, achieved a PASI 75 response. No rebound of disease was observed by them after tildrakizumab withdrawal.

There are few published data on the time to relapse after treatment withdrawal in patients who have successfully been treated with an IL-23p19 blocker. The study conducted by Reich et al. assessed the time to loss of PASI 90 response in psoriasis patients treated with guselkumab and found a median time to relapse of 15 weeks for withdrawal patients (23 weeks after the last guselkumab dose). Remarkably, our study shows that the median time to loss of PASI 90 response after tildrakizumab withdrawal seems to be longer than after guselkumab withdrawal, being 16 weeks with tildrakizumab 100 mg (28 weeks after the last tildrakizumab dose) and 20 weeks with tildrakizumab 200 mg (32 weeks after the last tildrakizumab dose). As PASI < 2 is consistent with PASI 90 response, we expected a similar time to loss of PASI < 2 response than time to loss of PASI 90 response among tildrakizumab 100 and 200 mg withdrawal groups. Although the median time to loss of PASI < 2 response was 16 weeks either among the tildrakizumab 100 or 200 mg withdrawal group (28 weeks after the last tildrakizumab dose), there were no significant differences between tildrakizumab 100 and 200 mg Kaplan–Meier curves neither for loss of PASI 90 response nor for loss of PASI < 2 response relapse definitions. Thus, there was a high consistency between PASI 90 and PASI < 2 data as previously reported by Mahil et al. Recently, Blauvelt et al. have described a median time to loss of PASI 90 of 30 weeks (42 weeks after the last dose) in psoriasis patients treated with risankizumab, highlighting the durability of response with an IL-23 inhibitor.

### Table 4 Factors predictive of loss of PASI 90 response

| Logistic regression model predictors | Odds ratio | 95% CI     | P-value |
|-------------------------------------|------------|------------|---------|
| Sex (female vs. male)               | 4.181      | 1.060–16.494 | 0.0411  |
| Cigarette smoking (smoker vs. non-smoker) | 2.944      | 1.097–7.899  | 0.0320  |
| Disease duration (years)            | 1.076      | 1.009–1.146  | 0.0245  |
| Time sustaining a PASI 75 response between week 4 and week 28 (days) | 0.977      | 0.957–0.998  | 0.0284  |

### Cox regression model predictors

| Hazard ratio | 95% CI     | P-value |
|--------------|------------|---------|
| Body mass index (kg/m²) | 1.0373      | 1.010–1.0645 | 0.0057  |
| Cigarette smoking (smoker vs. non-smoker) | 1.6519      | 1.114–2.4494 | 0.0125  |
| Disease duration (years) | 1.0213      | 1.005–1.0370  | 0.0068  |
| Sex (female vs. male) | 1.5175      | 1.043–2.2060  | 0.0289  |

CI, confidence interval; PASI, Psoriasis Area Severity Index.

### Table 5 Factors predictive of loss of PASI < 2 response

| Logistic regression model predictors | Odds ratio | 95% CI     | P-value |
|-------------------------------------|------------|------------|---------|
| Sex (female vs. male)               | 4.418      | 1.197–16.314 | 0.0258  |
| Disease duration (years)            | 1.068      | 1.011–1.128  | 0.0181  |
| Time sustaining a PASI 75 response between week 4 and week 28 (days) | 0.976      | 0.956–0.995  | 0.0154  |

### Cox regression model predictors

| Hazard ratio | 95% CI     | P-value |
|--------------|------------|---------|
| Body mass index (kg/m²) | 1.0301      | 1.003–1.0570 | 0.0242  |
| Disease duration (years) | 1.0228      | 1.008–1.0376  | 0.0022  |

CI, confidence interval; PASI, Psoriasis Area Severity Index.
Regarding patients successfully treated with an IL-12/23 inhibitor, Leonardi et al.\textsuperscript{10} had reported a median time to loss of PASI 75 and PASI 50 in patients withdrawn from ustekinumab treatment of 15 and 22 weeks, respectively. Also, Chiu et al.\textsuperscript{11} who included 202 patients who had responded to ustekinumab (PASI 50 for at least 3 months) and had withdrawn treatment, showed that after stopping ustekinumab, the median time to relapse (defined as loss of PASI 50) was 24 weeks.

The long time to relapse of psoriasis after withdrawal of an IL-23p19 blocker can be explained by the pharmacodynamics effect of IL-23 inhibitors as potential disease modifiers. IL-23 is a cytokine that is produced upstream of other inflammatory cytokines involved in psoriasis such as IL-17. Thus, inhibiting IL-23p19 may have a broader impact on these cytokines, which could influence on durability of response.\textsuperscript{12} Moreover, blocking IL-23 may play a role in changing the natural history of disease by altering epidermal T cells. Analyses conducted by Cheuk et al.\textsuperscript{13} suggested an epidermal population of tissue-resident memory T cells after years of biologic treatment at sites of former psoriasis lesions and a potential retention of IL-17 and IL-22 production in these cells. Regarding IL-17 inhibitors, an early relapse of psoriasis after brodalumab discontinuation was described by Masson Regnault et al.\textsuperscript{14} who reported a median time to relapse (defined as the desire of the patient to start a new topical or systemic treatment for psoriasis) of 46 days with some patients experiencing a rebound. However, among patients who were withdrawn from ixekizumab therapy, median time to relapse (defined either as static PGA $\geq 3$ or loss of PASI 50\textsuperscript{15}) was 20 weeks. The difference between brodalumab and ixekizumab on the time to relapse after withdrawal could be explained by different criteria of relapse.

Finally, regarding tumour necrosis factor (TNF)-alpha inhibitors, the median time to relapse (defined as loss of PASI 50) after withdrawal ranged from 12.1 weeks for patients who were successfully treated with etanercept to 19.5 weeks for patients who were treated with infliximab.\textsuperscript{5,17,18} Stinco et al.\textsuperscript{19} confirmed etanercept as the anti-TNF-alpha agent having the shortest clinical response after treatment withdrawal.

Factors predictive of relapse were also explored in this post hoc analysis, and increase in BMI or increase in disease duration was clearly associated with an increased risk of relapse, regardless of the relapse definition. These results are consistent with previous data regarding biologic agents, where obesity is associated with lower efficacy to anti-TNF-alpha agents or IL-12/23 inhibitors.\textsuperscript{20} Additional independent predictors of relapse were smoking status or gender. Women had more risk of relapse than men. However, men accounted for around 70% of the overall population and the smaller numbers of women may have contributed to this outcome.

To the best of our knowledge, only two studies have investigated the predictors of time to relapse in psoriasis patients after responding to a biologic treatment. The study conducted by Gordon et al.\textsuperscript{21} in responders to guselkumab showed that loss of response (<PASI 75) following withdrawal was associated with increased serum protein levels of IL-17A, IL-17F and IL-22. Additionally, the study conducted by Chiu et al.\textsuperscript{11} showed that biologics naive, the maximum PASI improvement on ustekinumab, time to achieve PASI 50 after initiation of ustekinumab, family history of psoriasis, chronic kidney disease and immunosuppressant use while off ustekinumab were significant predictors of time to relapse following ustekinumab withdrawal. Overall, none of these predictors of relapse described previously might be changed by patients; i.e., all were non-modifiable. On the other hand, among the predictive factors described in this study, BMI and smoking are both modifiable independent risk factors, and thus, their effects could be reduced by making lifestyle changes, such as losing weight or smoking cessation.

This study supports a growing evidence on the potential impact of IL-23 inhibitors in the psoriasis pathogenesis. However, both duration of tildrakizumab effect and factors predictive of relapse need to be further explored to understand the benefits of tildrakizumab in the clinical setting and improve individualized treatments.

An important limitation of these analyses is that there is no consensus about definition of relapse. Different definitions of relapse have been used by different authors making head-to-head comparison difficult. However, findings of our sensitivity analyses were consistent with those from the primary analysis, supporting its robustness. In addition, this study was not intended to evaluate safety. A favourable long-term safety profile with both tildrakizumab 100 and 200 mg has been reported previously.\textsuperscript{3}

In summary, tildrakizumab provided durable maintenance of efficacy when treatment was interrupted, with a median time to loss of PASI 75 response of 5–6 months, not showing dose-dependent response. One out of five patients who had withdrawn from tildrakizumab had not relapsed after 36 weeks. BMI and disease duration were good predictors of relapse. The knowledge of modifiable risk factors for relapse, such as BMI, will facilitate appropriate personalized interventions, which could yield significant benefits for the long-term management of psoriasis and prevent future relapses.

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References

1. Boehncke W-H, Schön MP. Psoriasis. Lancet 2015; 386: 983–994.
2. Reich K, Papp KA, Blauvelt A et al. Tildrakizumab versus placebo or etanercept for chronic plaque psoriasis (reSURFACE 1 and reSURFACE 2): results from two randomised controlled, phase 3 trials. Lancet 2017; 390: 276–288.
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3 Reich K, Warren RB, Iversen L et al. Long-term efficacy and safety of tildrakizumab for moderate-to-severe psoriasis: pooled analyses of two randomized phase III clinical trials (resSURFACE 1 and resSURFACE 2) through 148 weeks. Br J Dermatol 2020; 182: 605–617.

4 Kamaria M, Liao W, Koo JY. How long does the benefit of biologics last? An update on time to relapse and potential for rebound of biologic agents for psoriasis. Psoriasis Forum 2010; 16: 36–42.

5 Sinclair R, Turner GA, Jones DAR, Luo S. Clinical studies in dermatology require a post-treatment observation phase to define the impact of the intervention on the natural history of the complaint. Arch Dermatol Res 2016; 308: 379–387.

6 Mahil SK, Wilson N, Dand N et al. Psoriasis treat to target: defining outcomes in psoriasis using data from a real-world, population-based cohort study (the British Association of Dermatologists Biologics and Immunomodulators Register, BADBIR). Br J Dermatol 2020; 182: 1158–1166.

7 Kimball AB, Papp KA, Reich K et al. Efficacy and safety of tildrakizumab for plaque psoriasis with continuous dosing, treatment interruption, dose adjustments, and switching from etanercept: results from phase 3 studies. Br J Dermatol 2019; 182: 1359–1368.

8 Reich K, Armstrong AW, Foley P et al. Efficacy and safety of guselkumab, an anti-interleukin-23 monoclonal antibody, compared with adalimumab for the treatment of patients with moderate to severe psoriasis with randomized withdrawal and retreatment: Results from the phase III, double-blind, placebo- and active comparator-controlled VOYAGE 2 trial. J Am Acad Dermatol 2017; 76: 418–431.

9 Blauvelt A, Leonardi CL, Gooderham M et al. Efficacy and safety of continuous risankizumab therapy vs treatment withdrawal in patients with moderate to severe plaque psoriasis: a phase 3 randomized clinical trial. JAMA Dermatol 2020; 156: 1–11.

10 Leonardi CL, Kimball AB, Papp KA et al. Efficacy and safety of ustekinumab, a human interleukin-12/23 monoclonal antibody, in patients with psoriasis: 76-week results from a randomised, double-blind, placebo-controlled trial (PHOENIX 1). Lancet 2008; 371: 1665–1674.

11 Chiu H-Y, Hui RC-Y, Tsai T-F et al. Predictors of time to relapse following ustekinumab withdrawal in patients with psoriasis who had responded to therapy: an eight-year multicenter study. J Am Acad Dermatol 2019; 80:90–962(19): 30142–30152.

12 Reich K, Armstrong AW, Langley RG et al. Guselkumab versus secukinumab for the treatment of moderate-to-severe psoriasis (ECLIPSE): results from a phase 3, randomised controlled trial. Lancet 2019; 394: 831–839.

13 Cheuk S, Wikén M, Blomqvist L et al. Epidermal Th22 and Tc17 cells form a localized disease memory in clinically healed psoriasis. J Immunol 2014; 192: 3111–3120.

14 Masson Regnault M, Konstantinou M-P, Khemis A et al. Early relapse of psoriasis after stopping brodalumab: a retrospective cohort study in 77 patients. J Eur Acad Dermatol Venereol 2017; 31: 1491–1496.

15 Blauvelt A, Papp KA, Sofen H et al. Continuous dosing versus interrupted therapy with ixekizumab: an integrated analysis of two phase 3 trials in psoriasis. J Eur Acad Dermatol Venereol. 2017; 31: 1004–1013.

16 Umezawa Y, Torisu-Itakura H, Morisaki Y et al. Long-term efficacy and safety results from an open-label phase III study (UNCOVER-J) in Japanese plaque psoriasis patients: impact of treatment withdrawal and retreatment of ixekizumab. J Eur Acad Dermatol Venereol 2019; 33: 568–576.

17 Gordon KB, Gottlieb AB, Leonardi CL et al. Clinical response in psoriasis patients discontinued from and then reinitiated on etanercept therapy. J Dermatol Treat 2006; 17: 9–17.

18 Gottlieb AB, Evans R, Li S et al. Infliximab induction therapy for patients with severe plaque-type psoriasis: a randomized, double-blind, placebo-controlled trial. J Am Acad Dermatol 2004; 51: 534–542.

19 Stinco G, Balato N, Buligan C et al. A multicenter retrospective case-control study on Suspension of TNF-inhibitors and Outcomes in Psoriatic patients (STOP study). G Ital Dermatol Venereol 2019; 154: 392–399.

20 Paroutoglou K, Papadavos E, Christodoulou G, Dalamaga M. Deciphering the association between psoriasis and obesity: current evidence and treatment considerations. Curr Obes Rep 2020; 9: 165–178.

21 Gordon KB, Armstrong AW, Foley P et al. Guselkumab efficacy after withdrawal is associated with suppression of serum IL-23-regulated IL-17 and IL-22 in psoriasis: VOYAGE 2 study. J Invest Dermatol 2019; 139: 2437–2446.