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Time to relapse after treatment withdrawal for different biologics used to treat plaque psoriasis

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Psoriasis is a common chronic recurrent inflammatory disease. Plaque psoriasis accounts for more than 90% of psoriasis patients. Currently, no therapies are curative. Biologics have greatly improved the clinical efficacy and potentially provide a better long-term safety profile, with respect to toxicity to major organs, than conventional treatments; however, relapse after treatment withdrawal is still an important issue. Although maintenance treatment is recommended in most guidelines, treatment withdrawal occurs quite frequently in real-world clinical practice. Thus, the time to relapse is an important consideration when choosing among the different therapies.

We analyzed the available literature with respect to biologic-based strategies for psoriasis treatment and relapse time after withdrawal. The selected biologics, including their approval dates, standard regimen, and half-life time values are listed in Supplementary Table 1, http://links.lww.com/CM9/A387. Two head-to-head studies and fourteen individual studies with relapse data were included. The definition of "relapse" varied among the different studies, the most common being "loss of a 50% reduction in the Psoriasis Area and Severity Index (PASI 50) and a Physician's Global Assessment score (PGA) ≥ 3". The comparison of relapse time among different biologics with the same relapse definition is presented in Figure 1.

Tumor necrosis factor (TNF) inhibitors

Etanercept

Among 409 patients who were assigned to stop etanercept treatment at week 24, 347 relapsed (showing loss of PASI 50) within the 24-week period. The median time to relapse was 85 days (range: 70–91 days) in PASI 50 responders and 91 days (range: 85–112 days) in PASI 75 responders (252 patients).[1] Bellinato *et al*[2] reported that among 53 patients who were asked to discontinue etanercept after achieving a stable clinical remission (PASI 0/1 for at least 1 year), 33 (62%) of the patients relapsed (PASI score variation ≥ 5) within 6 months. The median time to relapse was 184 days.

Infliximab

Giunta *et al*[3] presented a retrospective infliximab withdrawal study. In 15 patients (13 reached PASI 75) who received infliximab for 22 weeks and then discontinued, the median relapse time to loss of PASI 50 was 182 days (range: 84–308 days).

Adalimumab

Among 285 patients who had achieved PGA 0/1 and then stopped adalimumab treatment for up to 40 weeks, 178 relapsed (PGA ≥ 3), with the median time of 141 days (interquartile range [IQR]: 93–202 days).[4]

Interleukin (IL)-12/IL-23 inhibitors

Ustekinumab

Griffiths *et al*[5] conducted the ACCEPT trial, which included 903 patients who were randomized to receive ustekinumab (45 mg or 90 mg) or etanercept (50 mg). At week 12, patients with PGA ≤ 2 stopped treatment until psoriasis relapsed (PGA ≥ 3). The median time to relapse was 14.4, 18.1, and 7.3 weeks in the three groups, respectively. An 8-year multicenter retrospective study included 202 patients who had responded to ustekinumab treatment and then withdrawn.[6] The duration of ustekinumab treatment prior to withdrawal was 16.7 ± 10.2 months. The cumulative probability of relapse free was 49.3%, 12.6%, 5.3%, 4.7%, and 1.6% after 6, 12, 18, 24,

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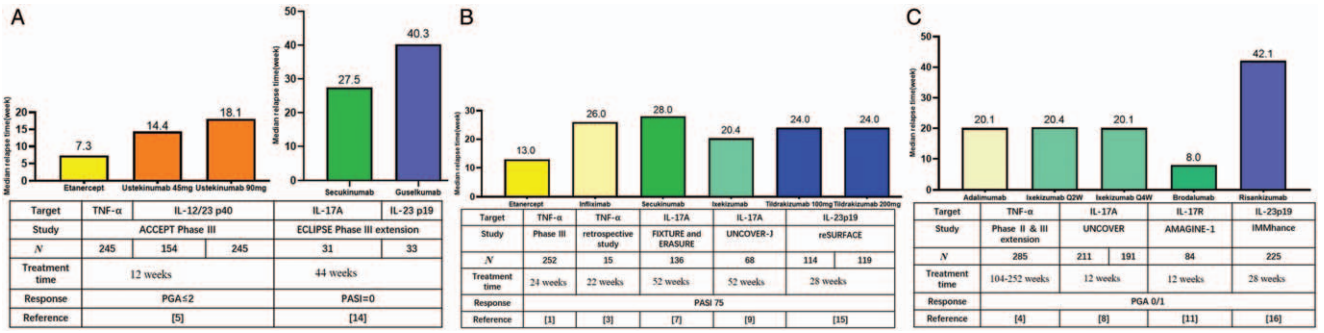

Target	TNF-α	IL-12/23 p40		IL-17A	IL-23 p19
Study	ACCEPT Phase III			ECLIPSE Phase III extension	
N	245	154	245	31	33
Treatment time	12 weeks			44 weeks	
Response	PGA≤2			PASI=0	
Reference	[5]			[14]	

Target	TNF-α	TNF-α	IL-17A	IL-17A	IL-23p19	
Study	Phase III	retrospective study	FIXTURE and ERASURE	UNCOVER-J	reSURFACE	
N	252	15	136	68	114	119
Treatment time	24 weeks	22 weeks	52 weeks	52 weeks	28 weeks	
Response	PASI 75					
Reference	[1]	[3]	[7]	[9]	[15]	

Target	TNF-α	IL-17A		IL-17R	IL-23p19
Study	Phase II & III extension	UNCOVER		AMAGINE-1	IMMhance
N	285	211	191	84	225
Treatment time	104-252 weeks	12 weeks		12 weeks	28 weeks
Response	PGA 0/1				
Reference	[4]	[8]		[11]	[16]

Figure 1: Comparison of the median time to relapse among different biologics. (A) Head-to-head comparison of time to relapse (PGA ≥ 3) between etanercept and ustekinumab (left); head-to-head comparison of time to relapse (initiation of new systemic treatment) between secukinumab and guselkumab (right). (B) Time to relapse (loss of PASI 50) in individual studies. (C) Time to relapse (PGA ≥ 3) in individual studies. IL: Interleukin; PASI: Psoriasis Area and Severity Index; PGA: Physician's Global Assessment score; TNF: Tumor necrosis factor.

and 36 months, respectively. The relapse time was 6.7 ± 4.1 months (range: 3–30.8 months). The authors of the study also tried to identify predictors and found the following possible predictors for a longer time to relapse: biologic-naïve, higher PASI improvement, shorter time to achieve PASI 50, no family history of psoriasis, no chronic kidney disease, and immunosuppressant use while ustekinumab was withdrawn.

IL-17 inhibitors

Secukinumab

Blauvelt *et al*[7] presented relapse results after secukinumab withdrawal. Among 181 patients who completed treatment with secukinumab (300 mg) for 52 weeks and then randomized to treatment withdrawal, the median time to loss of PASI 50 was 28 weeks (95% CI: 24.14–32.00) and the mean PASI at recurrence was 15.6 (range: 4.5–65.1).

Ixekizumab

Blauvelt *et al*[8] analyzed data pooled from two clinical trials. After the induction period of 12 weeks, 402 ixekizumab responders (PGA = 0/1) were randomized to placebo simulation. The median time to relapse (PGA ≥ 3) was 20.4 weeks in the ixekizumab Q2W/placebo group and 20.1 weeks in the ixekizumab Q4W/placebo group. Umezawa *et al*[9] reported that 70 patients who reached PASI 75 after 52 weeks of treatment were assigned to stop until relapse (loss of PASI 50). After withdrawal, approximately half of the subjects relapsed within 5 months. The median time to relapse was 143 days.

Brodalumab

Regnault *et al*[10] published a retrospective multicenter cohort study on brodalumab withdrawal. At the time of withdrawal, the mean duration of treatment was 3.1 ± 1.5 years. In total, 67 (87%) patients had reached PASI 90, while 74 (96%) had reached PASI 75. The relapse was defined by the desire of the patient to start a new treatment (topical or systemic) for psoriasis. Within the 9-month follow-up period, all of the patients relapsed; the median recurrence time was 46 days (range: 7–224 days). Papp *et al*[11] reported that 84 patients who attained PGA 0/1 with brodalumab (210 mg Q2W) were randomized to placebo simulation at week 12. The median time to relapse was 56.0 days.

IL-23 inhibitors

Guselkumab

As reported by *Reich et al*,[12] among 182 patients who had achieved PASI 90 at week 28 and then randomized to placebo simulation, the median time to loss of PASI 90 response was 15.2 weeks (23 weeks after last guselkumab dose); Gordon *et al*[13] further showed that 30.6% of patients experienced loss of PASI 50 by week 52, 49.1% by week 60, and 67.6% by week 72; although 32.4% showed no loss in PASI 50 by week 72. It was found that the correlation of IL-23 signaling serum cytokines (IL-17A, IL-17F, and IL-22) increased with disease recurrence; however, these increases had poor predictive value for relapse as they lagged after increases in PASI scores. Rivera *et al*[14] reported the head-to-head comparison of guselkumab and secukinumab withdrawal in Spanish patients who participated in the ECLIPSE study. The median time from the last dose of biologics to the initiation of new systemic treatment (relapse) was 282 days (IQR: 180–333 days) for patients with guselkumab and 192.5 days (IQR: 107–308 days) for patients with secukinumab. The univariate regression models revealed statistically significant differences in factors of arthritis and the psoriasis duration. Relapse time was longer in patients without arthritis or with a more recent diagnosis of psoriasis. The authors stated that these results might suggest that there is a window of opportunity in the treatment of psoriasis during which the natural course of the disease could be altered. Multivariate linear regression model adjusted for different covariates confirmed the association between the study drug and relapse time.

Tildrakizumab

Kimball *et al*[15] published relapse results after 28 weeks of tildrakizumab treatment (placebo simulation thereafter). The median time to loss of PASI 50 was 24 weeks in the group treated with 100 mg tildrakizumab ($n = 114$) as well as the group treated with 200 mg of this biologic ($n = 119$). The proportions of patients who experienced relapse were

0.9% (4 weeks after withdrawal), 5.5% (12 weeks), 10.8% (24 weeks), and 11.8% (36 weeks) in the 100 mg treatment group and 0.8%, 3.5%, 14.1%, and 10.0% at each corresponding time point in the 200-mg group.

Risankizumab

Among 225 patients who stopped risankizumab treatment at week 28 (placebo simulation thereafter), PGA 0/1 could be maintained in 61.3% at week 52 and 7.1% at week 104. The median time to relapse (PGA ≥ 3) was 295 days (IQR: 211–428 days).[16]

Conclusion

Based on this review of published studies, we conclude that the time to relapse after psoriasis treatment withdrawal varies among different biologics, partly due to the differences in their mechanisms of action and pharmacokinetics of specific drugs. IL inhibitors, especially IL-23 inhibitors, generally sustained longer time to relapse after treatment withdrawal than TNF inhibitors. Possible clinical predictors for longer relapse time, as reported in the literature, are as follows: biologic-naive, shorter psoriasis duration, no arthritis or chronic kidney disease, no family history of psoriasis, and higher and more rapid response to treatment.

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Conflicts of interest

None.

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