When IL-17 inhibitors fail: real-life evidence to switch from secukinumab to adalimumab or ustekinumab.

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Abstract

Psoriasis is a chronic, systemic inflammatory disease that in the moderate to severe forms may benefit of biologics, namely TNF and IL-12/23 and IL-17 inhibitors. Loss of response, lack of response or discontinuation due to adverse events represent a concrete therapeutic challenge for dermatologists that have to switch patients to other treatments. Although some evidences already exist toward the switch from IL-12/23 and TNF inhibitors to IL-17 inhibitors, conversely nothing is present toward the switch from IL-17 inhibitors to IL-12/23 and TNF inhibitors. We performed a real-life study enrolling 50 patients randomly switched to adalimuamb, a TNF inhibitor, or ustekinumab, an IL-12/23 inhibitor. Our observational study suggests that switching from IL-17i to TNFi and IL-12/23i is a safe and effective therapeutic strategy.

Keywords: psoriasis, real-life, secukinumab, switching, adalimumab, ustekinumab, PASI, DLQI.

Introduction

Psoriasis is a chronic, systemic inflammatory disease affecting 0.5-11.4% of the population (Michalek, 2017). An increasing body of evidences seem to suggest that psoriasis-related comorbidities contributes to make challenging the choice of a systemic treatment, in particular dermatologists first should carefully screen relative and absolute contraindications (Santus, 2018; Strober, 2018; Fiore, 2018). Furthermore, dermatologists are currently driven by experience and contraindication in choosing a biological therapy due to the lack of information of the so called biological signature of the patients (Feldamn, 2014). About 25% psoriatic patients present moderate-to-severe psoriasis and deserve a biologic treatment, that actually includes IL17inhibitors(i) such as secukinumab, TNFi such as adalimumab and IL12/23i such as ustekinumab (Strober, 2018). Due to the novelty of IL-17i, scattering evidences exists towards the switch between different IL-17i and from TNFi to IL-17i (Georgakopoulos, 2018). Conversely, no evidence for switching from IL-17i to TNFi or to anti-IL12/23i. To this end, we aimed to describe real-life characteristics of patients switching from secukinumab to adalimumab or ustekinumab.

Material and Methods

This is a real-life multicenter prospective cohort study involved 4 primary referral dermatological centers in northern Italy. Adult patients (>18 years old) with moderate-to-severe plaque psoriasis, defined as a Psoriasis Area and Severity Index (PASI) score >10, who failed secukinumab were recruited from June 2016 to April 2018. Criteria for failure of secukinumab were a) adverse effect to secukinumab, b) no improvement after 16 weeks or worsening of PASI. The only exclusion criterion was psychiatric diagnosed diseases. The enrolled patients were assigned randomly to adalimumab or ustekinumab group. Adalimumab was administered, after induction, at 40 mg/2weeks as well as ustekinumab at 45 mg/12 weeks. Patients were followed bi-weekly for 52 weeks. Diagnosis and assessment of psoriasis was performed by two independent board-certified dermatologists with more than five years of experience in anti-psoriatic biologics management, and

if the PASI number was discordant a third dermatologist performed PASI. Results were the average value of the obtained PASIs. Data regarding demographic characteristics, psoriasis therapy, PASI and dermatology quality of life index (DLQI) were collected. Psoriatic arthritis (PsA) was not an exclusion criterion. The data were analyzed using R statistical software (Version 3.4.1).

Results

The enrolled cohort comprehended 50 patients, namely 28 males and 22 females with an average age of 43±12.4 years old and average disease duration of 18.7±8.6 years. Average BMI was 27.3±2.1. Prior to starting secukinumab, 34 patients were biologic naïve, 8 underwent adalimumab, 4 etanercept, 2 infliximab, 2 ustekinumab, 19 Narrow band (NB)-UVB, 3 psoralen UVA (PUVA), 21 cyclosporine, 21 methotrexate, 4 acitretin. After failing secukinumab 29 patients received adalimumab and 21 received ustekinumab (Figure 1). Patients had secukinumab average duration of 49,6±8,9 months and discontinue. Secukinumab was discontinued for lack of efficacy at 16 weeks in 15 cases, for loss of efficacy in 20 cases, infectious reasons (fungal +bacterial infections) in 7 cases and other causes in 8 cases. Our burden of comorbidities accounted 4 patients with arterial hypertension, 3 with PsA, 2 with diabetes mellitus and 1 with emphysema. Demographics of the entire cohort and specific demographics of adalimumab and ustekinumab groups are summarized in Table 1.

In the adalimumab group at baseline, PASI was 15,5±3,3 and DLQI was 16±2,7 for patients who were biologic naïve prior to secukinumab (n=23), 11±4,0 and 22±3 respectively for those receiving TNFi previously (n=4) and PASI 15,5±2,12 and DLQI 21,5±2,1 for those on ustekinumab previously (n=2). At week 28 all the 4 patients, that underwent TNFi before failing secukinumab, lost response to adalimumab and were switched to ixekizumab (n=1) or ustekinumab (n=3). At week 52, PASI was 2,8±0,9 and DLQI 6±2,3 for biologic naïve patients prior to secukinumab, and 3,1±0,4 and 8±1,2 respectively for those who received ustekinumab prior to starting secukinumab.

In the ustekinumab group at baseline, PASI was 18,5±3,6 and DLQI was 14,3±2 for patients who were biologic naïve prior to secukinumab (n=11), 16±2,4 and 22±3,2 respectively for those receiving TNFi previously (n=10). At week 52, PASI was 2.6±0,3 and DLQI 4,1±3,7 for biologic naïve patients prior to secukinumab, and 3.8±0,2 and 10±2,1 respectively for those who received TNFi prior to starting secukinumab.

One non-responder in the biologic naïve prior to secukinumab group was switched to adalimumab, and the 2 non-responders who previously received TNFi were switched to ixekizumab. No adverse events were recorded.

Discussion

Nowadays, biologic drugs represent the standard treatment for moderate to severe psoriasis due to the high efficacy and promising safety (Georgakopoulos, 2018). These drugs are particularly effective in patients who do not respond to conventional treatments. Despite these advantages, 10–30% of patients treated with TNFi or IL12/23i agents are still partial or non-responders, or experience adverse effects, thus leading to treatment discontinuation (Warren, 2015; Umezawa, 2013). Therefore, these patients often switch to other biologics (Hu, 2018). The development of IL-17i agents has been met with great anticipation, and PASI 90 or even PASI 100 has been regarded as the new gold standard for satisfactory treatment response (Kerdel, 2015). Physicians' high expectation of secukinumab efficacy, especially in patients with concurrent PsA, could lead to an earlier switching to well-established PsA-approved agents, such as adalimumab, in case these predictions are not met (Kerdel, 2015). Furthermore, the high number of patients returning to their previous therapy upon failing on secukinumab could suggest that these were controlled with an acceptable but incomplete, skin clearance and consequently switched to secukinumab to obtain a lower PASI value (Piaserico, 2014). However, several studies have reported that patients previously treated with biologics dysplay a lower PASI 75 than those treated with non-biologics, suggesting that previously treated patients may fail on subsequent biologics as well (Georgakopoulos, 2018;

Fagerli 2013; Ritchlin, 2014). Whilst switching partial or non-responding patients to a different biologic agent is a relatively common practice, few studies have assessed the efficacy of a second-line biologic treatment in these patients (Honda, 2017). Therefore, we investigated these cases retrospectively by using patient records.

Our data indicate that patients non-responders to secukinumab, where secukinumab was the first biologic drug underwent, may achieve significant improvements in PASI and DLQI by switching to adalimumab or ustekinumab. Furthermore, if the patient had received TNFi prior to secukinumab and subsequent secukinumab failure, the switching to ustekinumab is preferable than attempting an another TNFi. Similarly, if a patient received ustekinumab prior to secukinumab failure, TNFi may be a valid alternative therapy. Although the limited number of patients enrolled in this real-life observational study, switching from IL-17i to TNFi and IL-12/23i seem a safe and effective therapeutic strategy. Further and larger studies are mandatory to confirm these results.

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Table 1. Demographic characteristics and therapeutic results.

	ADALIMUMAB COHORT (N=29)	**USTEKINUMAB COHORT (N=21)**	**OVERALL (N=50)**
Gender (M/F)	16/13	12/8	28/22
Age (years; mean±SD)	42 ± 9,7	44,5 ± 11,2	43 ± 12,4
Family history (N,(%))	8, (27,6)	11, (52,4)	19, (38)
Disease duration (years; mean±SD)	19,8 ± 9,2	17,2 ± 8,3	18,7 ± 8,6
BMI (kg/m^2; mean±SD)	28,1 ± 1,5	27 ± 3,3	27,3 ± 2,1
Previously failed:			
TNFi	4	10	14
. Adalimumab	0	8	8
. Etanercept	3	1	4
. Infliximab	1	1	2
IL-12/23i			
. Ustekinumab	2	0	2
Naïve	23	11	34
. NB-UVB	10	9	19
. PUVA	1	2	3
. Cyclosporine	10	11	21
. Methotrexate	7	14	21
. Acitretin	4	1	4
Reasons to discontinue			
Secukinumab	12	13	

. Lack of efficacy at 16 weeks	13	7	15
. Loss of efficacy after 16 weeks			20
. Recurrent mucosal fungal infections	2	3	5
. Headache and hypertension	3	2	5
. Erysipelas	2	0	2
. Dizziness and nausea	1	1	2
. Hypertrigliceridemia	0	1	1
Secukinumab duration (months; mean±SD)	45,8 ± 13,6	55,4 ± 3,7	49,6 ± 8,9
Comorbidities			
. Hypertension (N)	2	2	4
. Psoriatic arthritis (N)	2	1	3
. Diabetes mellitus (N)	1	1	2
. Emphysema (N)	0	1	1
Baseline			
PASI (mean±SD)	14,4 ± 4	16,8 ± 3,3	16,3 ± 3,7
DLQI (mean±SD)	18 ± 2,5	18,4 ± 1,2	18,4 ± 2,5
<u>Biologic naïve</u>			
PASI (mean±SD)	15,5 ± 3,3	18,5 ± 3,6	16,7 ± 3,3
DLQI (mean±SD)	16 ± 2,7	14,3 ± 2	15,2 ± 2
<u>Previous TNF inhibitor</u>			
PASI (mean±SD)	11 ±4,0	16 ± 2,4	14,1 ± 2,7
DLQI (mean±SD)	22 ±3	22 ± 3,2	22 ± 3
<u>Previous ustekinumab</u>			
PASI (mean±SD)	15,5 ± 2,12	-	15,5 ± 2,12
DLQI (mean±SD)	21,5 ± 2,1	-	21,5 ± 2,1
Week 52			
PASI (mean±SD)	3,0 ± 0,6	3,2 ± 0,3	3,1 ± 0,4
DLQI (mean±SD)	7 ±0,7	4,1 ± 3,7	5,5 ± 2,8

Biologic naïve	*	*	
PASI (mean±SD)	2,8 ± 0,9	2,6 ± 0,3	2,7 ± 0,5
DLQI (mean±SD)	6 ± 2,3	4 ± 2	5 ± 2,2
Previous TNF inhibitor	*		
PASI (mean±SD)	-	3,8 ± 0,2	3,8 ± 0,2
DLQI (mean±SD)	-	10 ± 2,1	10 ± 2,1
Previous ustekinumab			
PASI (mean±SD)	3,1 ± 0,4	-	3,1 ± 0,4
DLQI (mean±SD)	8 ± 1,2	-	8 ± 1,2

Legend: F: Female, i:inhibitor, M: Male, N: number, SD: Standard Deviation, IL: Interleukin, BMI: Body Mass Index, TNF: Tumor Necrosis Factor, PASI: Psoriasis Area Severity Index, DLQI: Dermatologic Quality of Life , PUVA: psorialen and ultraviolet-A, NB-UVB: narrowband ultraviolet-B.

Figure 1. Therapeutic results for switching from secukinumab to adalimumab or ustekinumab

Legend:

i:inhibitor, N: number, IL: Interleukin, TNF: Tumor Necrosis Factor, PASI: Psoriasis Area Severity Index.