

Effectiveness and Safety of Anti-interleukin-17 Therapies in Elderly Patients with Psoriasis

Céline PHAN¹, Nathalie BENETON², Juliette DELAUNAY³, Ziad REGUIAI⁴, Claire BOULARD⁵, Anne-Claire FOUGEROUSSE⁶, Elisa CINOTTI⁷, Marco ROMANELLI⁸, Laure MERY-BOSSARD⁹, Domitille THOMAS-BEAULIEU⁹, Josiane PARIER¹⁰, François MACCARI¹⁰, Jean-Luc PERROT¹¹, Mireille RUER-MULARD¹², Marie BASTIEN¹³, Edouard BEGON¹⁴, Mahtab SAMIMI¹⁵, Caroline JACOBZONE¹⁶, Nathalie QUILES-TSIMARATOS¹⁷, Vincent DESCAMPS¹⁸, Maud STEFF¹⁹, Paul BILAN¹⁹, Annie VERMERSCH-LANGLIN²⁰, Mathilde KEMULA²¹, Emmanuelle AMAZAN²², Ingrid KUPFER-BESSAGUET²³, Anne-Caroline COTTENCIN²⁴, Francesca PRIGNANO²⁵, Bulai LIVIDEANU²⁶, Jeremy GOTTLIEB²⁷, Alain BEAUCHET²⁸ and Emmanuel MAHÉ¹; for the Groupe d'Etudes Multicentriques (GEM) RESOPSO

Departments of Dermatology; ¹Hospital Victor Dupouy, Argenteuil, ²Hospital of Le Mans, Le Mans, ³University Medical center of Angers, Angers, ⁴Polyclinic of Courlancy, Reims, ⁵Hospital Jacques Monod, Le Havre, ⁶Hospital Begin, Saint Mandé, France, ⁷Department of medicine et neuroscience, University of Siene, Sien, ⁸University of Pise, Pise, Italy, ⁹Hospital Center of Poissy/Saint-Germain-en-Laye, Saint-Germain-en-Laye, France, ¹⁰University Hospital Center of Saint-Etienne, Saint-Etienne, ¹¹Hospital of Pontoise, Pontoise, ¹²University Hospital Center of Tours, ¹³Hospital Center of Lorient, Lorient, ¹⁴Hospital Saint-Joseph, Marseille, ¹⁵Hospital Bichat-Claude Bernard, Paris, ¹⁶Hospital Robert-Ballanger, Aulnay-sous-Bois, ¹⁷University Hospital Center of Martinique, Fort-de-France, Martinique, ¹⁸Hospital Center of Niort, Niort, France, ¹⁹Hospital of Firenze, Firenze, Italy and ²⁰Hospital Larrey, Toulouse, ²¹Private Office, La Varenne, ²²Private Office, Martigues, ²³Private Office, Joinville le Pont, France, ²⁴Department of Internal Medicine, University Hospital Center Bicêtre, Le Kremlin Bicêtre, and ²⁵Department of Public Health, University Hospital Center Ambroise Paré, Boulogne-Billancourt, France

Anti-interleukin-17 agents have recently been developed for the treatment of psoriasis. This study evaluated the tolerance and effectiveness of anti-interleukin-17 agents for psoriasis in elderly patients in daily practice. A multicentre, retrospective study was performed, involving psoriatic patients aged ≥ 65 years who had received an anti-interleukin-17 agent, including secukinumab, ixekizumab or brodalumab. A total of 114 patients were included: 72 received secukinumab, 35 ixekizumab, and 7 brodalumab. Treatment was stopped in 32 patients (28.9%), because of relapses in 14 patients (41.2%), primary failures in 11 patients (32.4%), or adverse events in 7 patients (20.6%). The 3 most frequently reported adverse events were injection site reactions ($n = 4$), oral candidiasis ($n = 3$), and influenza-like illness ($n = 3$). Regarding effectiveness, 80 patients (70%) reached a Physician Global Assessment score of 0/1, 6 months after treatment initiation. In conclusion, anti-interleukin-17 therapy appears to be an effective and safe therapeutic option for psoriasis treatment in patients aged ≥ 65 years.

Key words: psoriasis; anti-interleukin 17; elderly; safety; drug survival.

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Corr: Céline Phan, Department of Dermatology, Hôpital Victor Dupouy, 69 rue du Lieutenant-Colonel Prud'hon, FR-95100 Argenteuil, France. E-mail: celine.phan@ch-argenteuil.fr

Psoriasis is a chronic disease characterized by inflammation of the skin and joints (1). Onset can occur at any age, but 2 peaks in age of onset have been reported: the first at 15–25 years of age and the second at 50–60 years of age (1–3). Information about psoriasis in elderly patients is scarce, as older patients are often excluded from clinical trials and studies. However, comorbidities

SIGNIFICANCE

Anti-interleukin-17 agents are biologic therapies that have recently been developed for the treatment of psoriasis. However, data on their use for patients ≥ 65 years are limited. A total of 114 elderly psoriatic patients who had received an anti-interleukin-17 agent were included in this study. Treatment was stopped in 28.9% of patients, mostly because of relapses, primary failures and adverse events. The 3 most frequently adverse events ($n = 10$) were injection site reactions, oral mycosis, and influenza-like illness. Regarding effectiveness, the treatment was considered efficient in 70% of patients, 6 months after treatment initiation. Anti-interleukin-17 therapy appears to be an effective and safe therapeutic option for psoriasis patients aged ≥ 65 years.

and possible drug interactions make management of psoriasis in this population particularly problematic (4–8). As there are limited data about the clinical features and toxicities in this group (9), elderly patients with moderate-to-severe psoriasis, in particular those with multiple comorbidities, may be undertreated.

Anti-interleukin-17 (IL-17) biological agents have recently been licensed in France for the treatment of psoriasis. Secukinumab (Novartis Pharma, Rueil-Malmaison France) (Cosentyx[®]) and Ixekizumab (Lilly, Neuilly sur Seine, France) (Taltz[®]) are monoclonal antibodies that selectively inhibit IL-17A. They have shown significant efficacy in the treatment of moderate-to-severe psoriasis and psoriatic arthritis, demonstrating rapid onset of action and sustained responses with favourable safety profiles (10–17). Brodalumab (Léo Pharma, Voisins-Le-Bretonneux, France) (Kyntheum[®]) is a fully human anti-IL17 receptor A monoclonal antibody approved for the treatment of moderate-to-severe psoriasis in patients who have had an inadequate response to other systemic therapies (18, 19).

Few data are available on the use of biological agents in the elderly population. The aim of this study was to evaluate the tolerance and effectiveness of anti-IL-17 agents used in daily practice for the treatment of psoriasis in patients over 65 years of age.

METHODS

Study design and participants

This multicentre, retrospective study was performed using data from the medical records of patients receiving an anti-IL-17 agent for the treatment of psoriasis. Data were retrieved from February to June 2019 by French and Italian dermatologists who were members of the Groupe d'Etudes Multicentriques (GEM) RESOPSO.

Patients were included if they had received at least one injection of an anti-IL-17 agent (i.e. secukinumab, ixekizumab, or brodalumab) on or after the age of 65 years. Patients treated with these drugs as part of a clinical trial were excluded. Also excluded were patients who received one of the biological agents for psoriatic arthritis.

Data collection

Demographic data (including age, sex, body mass index (BMI), clinical characteristics, and comorbidities) were collected from patient medical records by the dermatologist. Details of the clinical type of psoriasis, and of current and previous systemic treatments for psoriasis, were also collected. Data on psoriasis severity (as assessed using the Physician Global Assessment (PGA) score) were collected at baseline, and 3–6 months after initiation of anti-IL-17 therapy. The study also collected the dates and causes of discontinuation of therapy with any of the biological agents, and details of any adverse events (AEs) and serious adverse events (SAEs).

Definitions of serious adverse events

SAEs included AEs that resulted in death; were life-threatening; required inpatient hospitalization or caused prolongation of existing hospitalization; resulted in persistent or significant disability or incapacity; or required intervention to prevent permanent impairment or damage.

Table I. Demographic and clinical characteristics of the total population and in patients stratified by age at treatment initiation

Characteristics	All <i>n</i> = 114	Age at initiation of anti-interleukin-17			<i>p</i> -value
		65–74 years <i>n</i> = 88	75–84 years <i>n</i> = 21	≥ 85 years <i>n</i> = 5	
Sex, male, <i>n</i> (%)	60 (52.6)	48 (54.5)	11 (52.4)	1 (20.0)	0.32
Age, years, mean ± SD	72.9 ± 6.0	70.3 ± 2.9	79.8 ± 3.9	89.2 ± 3.3	< 0.001
Psoriasis characteristics					
Age of onset, years, mean ± SD	48.5 ± 16.4	47.3 ± 15.2	49.2 ± 17.3	66.2 ± 25.6	0.04
Plaque psoriasis (missing data: 2), <i>n</i> (%)	99 (88.4)	77 (88.5)	17 (85.0)	5 (100.0)	0.49
Psoriatic arthritis, <i>n</i> (%)	34 (29.8)	23 (26.1)	10 (47.6)	1 (20.0)	0.13
Comorbidities					
BMI (missing data: 19), mean ± SD	29.5 ± 5.4	29.4 ± 5.4	30.4 ± 5.5	26.0 ± 1.8	0.40
Obesity, <i>n</i> (%)	40 (35.1)	32 (40)	8 (38.0)	0 (0)	0.43
Diabetes, <i>n</i> (%)	29 (25.4)	23 (26.1)	6 (28.6)	0 (0)	0.39
Dyslipidaemia, <i>n</i> (%)	54 (47.4)	38 (43.2)	14 (66.7)	2 (40)	0.14
Hypertension, <i>n</i> (%)	72 (63.2)	55 (63.2)	14 (66.7)	3 (60)	0.94
Tobacco, <i>n</i> (%)	25 (21.9)	22 (25.0)	2 (9.5)	1 (20)	0.30
Major adverse cardiac events, <i>n</i> (%)	24 (21.1)	18 (20.5)	6 (28.6)	0 (0)	0.35
WHO Classification (missing data: 27), <i>n</i>					0.73
0	71	57	12	2	
1	12	10	2	0	
2	2	2	0	0	
3	1	1	0	0	
4	1	0	0	1	

SD: standard deviation; BMI: body mass index

Study outcomes

The primary objective was analysis of treatment discontinuation and the occurrence of AEs and SAEs, together with identification of any risk factors associated with these events.

The secondary objective was to determine the effectiveness of anti-IL-17 therapy by evaluating the number of patients who obtained a PGA score of 0/1 (clear or almost clear) between 3 and 6 months after starting treatment. The rate of treatment continuation was also assessed over the year following the start of treatment. Outcomes were evaluated for the population as a whole, and compared between groups stratified by age at anti-IL-17 treatment initiation: 65–74, 75–84 and ≥ 85 years of age.

Statistical analysis

Quantitative data were expressed as mean ± standard deviation, and qualitative data as frequency and percentages. Comparisons of means were performed using the Student's *t*-test or by analysis of variance (ANOVA), as appropriate. Comparisons of frequencies were performed using χ^2 test or Fisher's exact test, as appropriate. Continuation rates were calculated using the Kaplan–Meier method. Curves for patients stratified by age were compared using the log-rank test. A *p*-value below 0.05 was considered statistically significant. Statistical analyses were performed using R software, version 3.4.3 (<http://www.r-project.org/>, Vienna, Austria).

RESULTS

In total, 114 patients were included: 72 patients received secukinumab, 35 ixekizumab, and 7 brodalumab. The characteristics of the whole population and the 3 subgroups stratified by age at treatment initiation are shown in **Table I**. Common comorbidities included hypertension (63.2%), dyslipidaemia (47.4%) and obesity (35.1%).

Among patients who discontinued treatment, the mean treatment duration was 12 months. Causes of anti-IL-17 discontinuation are reported in **Table II**. Treatment was stopped in 28.9% of patients, with relapses being the leading cause of discontinuation (41.2% of patients), followed by primary failures (32.4%) and AEs (20.6%).

Fifteen patients reported AEs, including injection site reactions (*n*=4), oral candidiasis (*n*=3) and influenza-like illness (*n*=3). Two patients reported SAEs: intracerebral haematoma (*n*=1) and palmoplantar pustulosis (*n*=1). There was no significant association between the frequency of AEs and age (*p*=0.34).

Regarding effectiveness, the mean PGA score at initiation was 3.5, decreasing to 0.9 after 3 months of treatment. Eighty patients (70%) had reached a PGA score of 0/1 within 3–6 months of treatment initiation. There was no significant difference in drug survival between the 3 treatments (**Fig. 1**, *p*=0.42), and the

Table II. Treatment status and causes of discontinuation

Treatment	All n = 114	Age at initiation of anti-interleukin-17			p-value
		65–74 years n = 88	75–84 years n = 21	≥85 years n = 5	
Stopped, n (%)	33 (28.9)	25 (28.4)	6 (28.6)	2 (0.4)	0.85
If stopped, duration, mean±SD	12±11.8	13±13.2	9.0±4.3	26±3.5	0.07
If continued, duration, mean±SD	16.0±12.0	15.7±12.9	15.2±11.4	9.1±12.6	0.18
PGA at initiation, mean±SD	3.5±1.5	3.6±1.6	2.9±0.9	3.6±0.9	0.16
PGA after 3–6 months, mean±SD	0.9±1.3	0.9±1.4	0.6±0.8	0.3±0.5	0.37
Causes of treatment discontinuation					
	n = 34 ^a	n = 26 ^a	n = 6	n = 2	
Relapse, n (%)	14 (41.2)	10 (38.5)	0	1 (50.0)	0.17
Primary failures, n (%)	11 (32.4)	8 (30.8)	3 (50.0)	0	0.39
Adverse event, n (%)	7 (20.6)	6 (23.1)	3 (50.0)	1 (50.0)	0.34
Patient's choice, n (%)	0 (0)	0 (0)	0	0	ND
Remission, n (%)	0 (0)	0 (0)	0	0	ND
Other, n (%)	2 (5.9)	2 (7.7)	0	0	ND

^aPatients provided more than one reason for discontinuation. SD: standard deviation; PGA: Physician Global Assessment; ND: Not determined

survival rate for the 3 treatments did not seem to differ by age (as shown for secukinumab in **Fig. 2**).

DISCUSSION

This study provides real-life data on the effectiveness and safety of anti-IL-17 agents for the treatment of cutaneous psoriasis in a large population of patients over 65 years of age. Our findings show that the anti-IL-17 agents were an effective treatment for psoriasis in elderly patients, with 70% of patients in the total population (68% for secukinumab, 74% for ixekizumab and 71% for brodalumab) achieving a PGA score of 0/1 between 3 and 6 months after initiation of treatment.

These results for secukinumab are in concordance with those reported in the literature. A *post hoc* analysis of 3 phase III trials (ERASURE: <https://clinicaltrials.gov/ct2/show/NCT01365455>, FIXTURE: <https://clinicaltrials.gov/ct2/show/NCT01358578> and CLEAR: <https://clinicaltrials.gov/ct2/show/NCT02074982>) evaluating the efficacy and safety of secukinumab at the recommended dose (300 mg) in elderly subjects (≥65 years of age), showed that the efficacy of secukinumab in elderly

psoriasis patients over 52 weeks of treatment was similar to that in younger cohorts (6, 9). Similar rates of PASI 75 and DLQI 0/1 response were also observed in the 2 age groups.

Less information is available on the use of ixekizumab and brodalumab in elderly patients, as licensing of these agents for the treatment of moderate-to-severe psoriasis was obtained more recently. For the phase III trials of ixekizumab (UNCOVER-1, -2 and -3), the only age eligibility criterion was that patients were 18 years or older (17). A total of 301 patients, out of the 4,204 patients exposed to the drug

in the clinical trials, were aged 65 years or over and 36 patients were aged 75 years or older. Pharmacokinetic analysis showed that clearance in the elderly patients was similar that in the younger patients, although the population studied was limited. Concerning brodalumab, eligibility for inclusion in the phase III studies (AMAGINE-1, -2 and -3) was limited to adult subjects up to 75 years of age (18, 19): out of a total population of 4,271 patients, 259 were aged between 65 and 74 years and 14 were aged ≥75 years (6).

In the current study, anti-IL-17 therapy was discontinued in 28.9% of patients. The main reasons for discontinuation in this elderly population were relapses (41.2%), primary failures (32.4%) and AEs (20.6%). More precisely in secukinumab group (n=72), the treatment was discontinued in 32% of patients: 37.5% of relapses and primary failures and 22% of AEs; in ixekizumab group (n=35), treatment was discontinued in 23% of patients: 62.5% of relapses, 25% of primary failures and 12.5% of AEs; in brodalumab group (n=7), treatment was discontinued for 2 patients: one because of AEs and another for other reasons. In a recent systematic review,

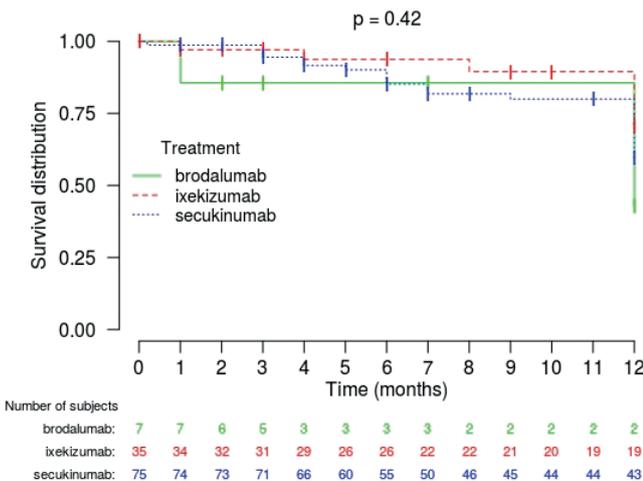


Fig. 1. Anti-interleukin-17 one-year continuation rates.

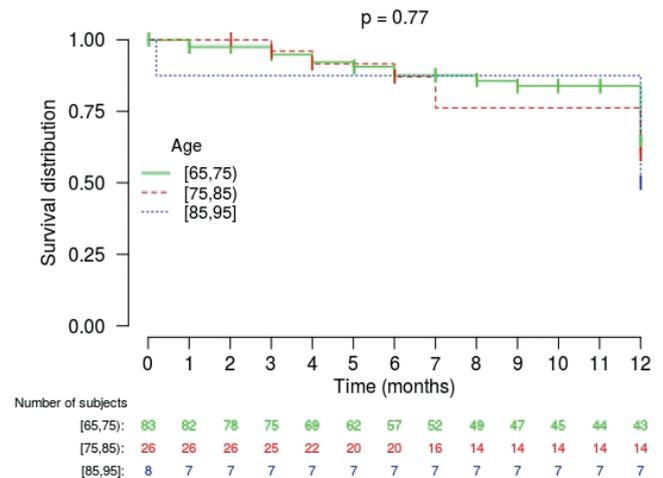


Fig. 2. Secukinumab one-year continuation rates in patients stratified by age at treatment initiation.

Sandhu et al. (20) reported that patients aged ≥ 65 years were more likely than younger patients to discontinue secukinumab over the 52-week treatment duration, with 5 elderly patients (7.5%) vs 15 younger patients (1.8%) discontinuing treatment.

The most frequent AEs reported in our study were injection site reactions ($n=4$), oral candidiasis ($n=3$) and influenza-like illness ($n=3$). These AEs do not seem to differ from those reported in younger populations. In the study of Sandhu et al. (20) and the phase III trials reported by Körber et al. (9), the total rate of AEs reported in association with secukinumab use was similar between elderly and younger subjects. However, in keeping with reports in the literature concerning the use of anti-tumour necrosis factor- α agents, the total rate of SAEs was higher in elderly subjects than in younger subjects (14.9% vs 8.2%), although the sample size for elderly patients included in the original studies was small (9, 20).

The strengths of the current study include the real-life design, the large sample size and the detailed assessments of the patient's characteristics.

Nevertheless, the presence of reporting bias generated by the use of patient reported characteristics cannot be ruled out. There are difficulties about reporting the exact chronology between the treatment and the adverse event, grading the severity of AEs or excessive reporting of mild AEs. Moreover, the number of patients is limited for 2 of the drugs evaluated (ixekizumab and brodalumab). Finally, the transversal design does not allow any conclusions to be drawn about the causality of the observed associations.

In conclusion, anti-IL-17 agents appear to be an effective and safe therapeutic option for the treatment of psoriasis in patients aged ≥ 65 years. The main AEs reported in elderly patients do not seem to differ from those reported previously in younger populations, despite the greater frequency of comorbidities in the elderly population (5).

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