European Review for Medical and Pharmacological Sciences 2023; 27: 4060-4064

Long-term clinical efficacy and safety of ixekizumab for psoriatic patients: a single-center experience

M. BURLANDO, I. SALVI, R. CASTELLI, A. HERZUM, E. COZZANI, A. PARODI

Section of Dermatology, DISSAL, University of Genoa, Ospedale-Policlinico San Martino, IRCCS, Genoa, Italy

Abstract. – OBJECTIVE: While clinical trials provide invaluable evidence, real-world data can offer further insight on the efficacy and safety of biologic drugs. This report aims to analyze the long-term efficacy and safety of ixekizumab in real-world clinical practice in our facility.

PATIENTS AND METHODS: Patients with a diagnosis of psoriasis and who started treatment with ixekizumab were included in this retrospective study and followed for 156 weeks. The severity of cutaneous manifestations was evaluated using the PASI score at several time points and clinical efficacy was evaluated using PASI 75, -90 and -100 responses.

RESULTS: Not only PASI 75, but also PASI 90 and 100 responses showed a favorable outcome after treatment with ixekizumab. Responses at week 12 were sustained through the following three years in the majority of patients. No statistically significant difference was found between bio-naive and bio-switch patients and weight and disease duration had no impact on the efficacy of the drug. Ixekizumab had a favorable safety profile, as we observed no major adverse events. Two cases of eczema were observed and led to drug discontinuation.

CONCLUSIONS: This study confirms the efficacy and safety of ixekizumab in real-world clinical practice.

Key Words:
Psoriasis, Biologic therapy, Ixekizumab, Long-term, Safety.

Introduction

Ixekizumab is a recombinant, humanized IgG4 monoclonal antibody that selectively binds to interleukin (IL)-17A and neutralizes its bioactivity. In Italy, it was approved in 2016 for the treatment of moderate to severe psoriasis (PSO) and psoriatic arthritis (PsA)[1]. Its excellent efficacy compared to placebo or etanercept was demonstrated in clinical trials[1-3]. In psoriatic patients receiving 80 mg ixekizumab, Psoriasis Area and Severity Index (PASI) 75, -90 and -100 responses were achieved by 78.8%, 67.1% and 46.2% at week 12, respectively, and sustained up to week 264[4]. However, aside from clinical trials, ixekizumab has not yet been sufficiently assessed in daily clinical practice for psoriatic patients. In this report, we present a retrospective analysis of the long-term efficacy and safety of ixekizumab in real-world clinical practice in our facility.

Patients and Methods

Patients

Patients of both sexes aged 18 years or more with a diagnosis of psoriasis and who started treatment with ixekizumab between January 2017 and December 2021 at the Department of Dermatology, DISSAL, Policlinico San Martino Hospital, Genova, Italy, were included in this retrospective study and followed for 156 weeks. The diagnosis was based on medical records, clinical findings and, in if deemed necessary, histopathological findings. Informed consent was obtained from the patients.

Treatment

Ixekizumab was administered *via* s.c. injection. After a starting dose of 160 mg, 80 mg were administered every two weeks for the following 12 weeks as an initial loading regimen and every 4 weeks thereafter.

Assessment of Efficacy

The severity of cutaneous manifestations was evaluated using the PASI score at week 0, week 12 (range, 12-16), week 26 (range, 24-30), week 52 (range, 50-54), week 104 (range 100-106) and week 156 (range 152-158).

Clinical efficacy was evaluated using PASI 75, -90 and -100 responses at each time point.

Corresponding Author: Martina Burlando, MD; e-mail: martina.burlando@unige.it

Safety Assessments

Potential adverse events were assessed at each visit, and laboratory tests and vital signs were monitored regularly.

Statistical Analysis

Data were expressed as mean standard deviation. The comparison of the groups was performed by using Student's *t*-test or the Mann-Whitney U test for quantitative variables, and Fisher's exact test for qualitative variables. A supportive analysis was performed using the last observation carried forward (LOCF) approach to impute missing values. To evaluate changes of variables between the baseline and the designated time point, a two-tailed Wilcoxon signed rank test was used. The drug survival rate was analyzed by log-rank test. Statistical analysis was performed using IBM SPSS Statistics for Windows, Version 28.0 (IBM Corp., Armonk, NY, USA). $p<0.05$ was considered statistically significant.

Results

Patient Results

A total of 108 patients were included in this study. Five patients were excluded, as they were lost to follow-up after the initial injection. The baseline demographics and background characteristics are shown in Table I. The male:female ratio was 1.9:1, reflecting the male predominance in the Italian psoriatic population, and the age range was 24-93 years, with a mean age of 57 (±15). Forty-one (38%) patients were bioswitched to ixekizumab from other biologics, in particular 5 (7.6%) from infliximab, 21 (31.8%) from adalimumab, 5 (7.6%) from etanercept, 8 (12.1%) from ustekinumab, 15 (22.7%) from secukinumab and 1 (1.5%) from brodalumab. The other 67 (62%) patients were bio-naive, including 45 (67%) patients who were switched from other systemic medications, in particular 18 (40%) from cyclosporin, 26 (58%) from methotrexate and 3 (7%) from acitretin.

Table I. Patients characteristics by study at baseline visit.

Demography	N=108 mean (SD) or n (%)
Male	71 (65.7%)
Female	37 (34.3%)
Age (years)	56.9 (±14.6)
Disease duration (years)	22.4 (±12.8)
BMI	26.5 (±4.7)
Arthritis	28 (25.9%)
Onychopathy	20 (18.5%)
Palmoplantar	8 (7.4%)
Scalp	28 (25.9%)
Genitals	12 (11.1%)

Efficacy

The PASI score at baseline (week 0) ranged 9-30, with a mean of 15.0 (±4.8). After administration of ixekizumab, the mean PASI score declined rapidly to 1.4 (±1.9) at week 4 ($p<0.001$), and by LOCF analysis, it was maintained at 1.0

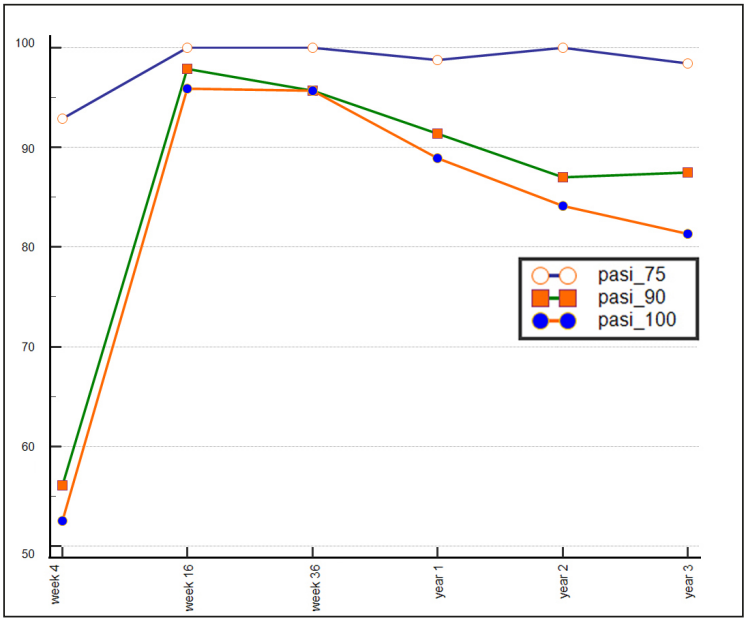

Figure 1. Time-course changes of PASI 75, -90 and -100 responses.

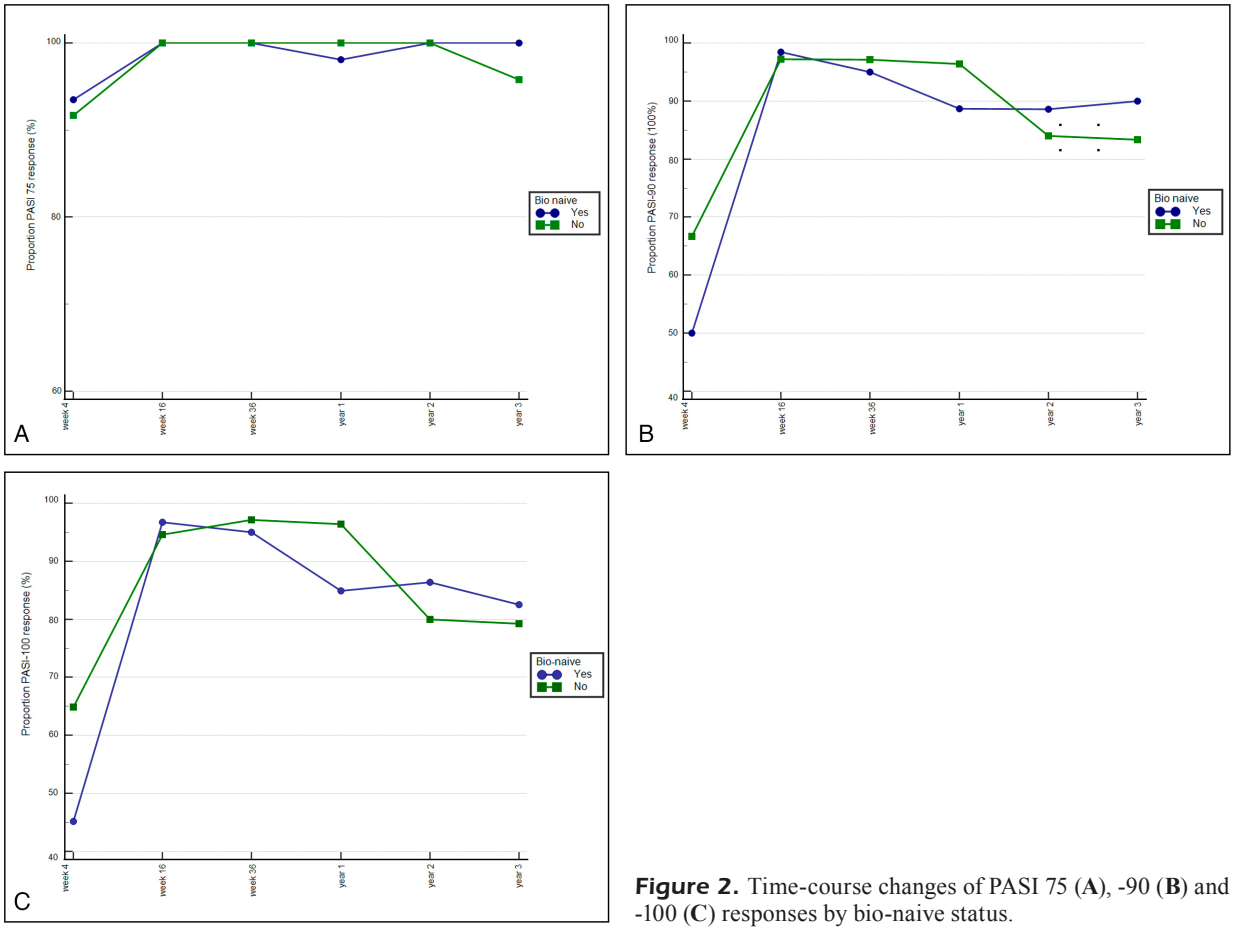

Figure 2. Time-course changes of PASI 75 (**A**), -90 (**B**) and -100 (**C**) responses by bio-naive status.

(±4.0) at week 16 (p<0.001), 1.0 (±4.0) at week 36 (p<0.001), 1.1 (±4.0) at year 1 (p<0.001), 1.2 (±4.0) at year 2 (p<0.001) and 1.3 (±4.2) at year 3 (p<0.001). The actual observed numbers were 103 at week 0, 99 at week 4, 98 at week 16, 94 at week 36, 81 at year 1, 69 at year 2 and 64 at year 3. Time-course changes of PASI 75, -90 and -100 responses are shown in Figure 1. After 4 weeks, 91 (92.9%) patients had PASI 75, 55 (56.1%) PASI 90, 52 (52.5%) PASI 100. After 16 weeks, 97 (100%) patients had PASI 75, 95 (97.9%) PASI 90, 94 (95.9%) PASI 100. After 36 weeks, 94 (100%) patients had PASI 75, 90 (95.7%) PASI 90 and PASI 100. After 52 weeks, 80 (98.8%) patients had PASI 75, 74 (68.5%) PASI 90 and 72 (88.9%) PASI 100. After 104 weeks, 69 (100%) patients had PASI 75, 60 (87.0%) PASI 90 and 58 (84.1%) PASI 100. After 208 weeks, 63 (98.4%) patients had PASI 75, 56 (87.5%) PASI 90 and 52 (81.3%) PASI 100. The baseline PASI score of bio-naive patients was not significantly different compared to that of bio-switched patients [15.5 (±5.2) *vs.* 14.3 (±4.2) p=0.23]. No significant differences in PASI 75 and -90 responses were found between the two groups after treatment at all visits. There was no correlation between the PASI improvement rate and body mass index or disease duration by multivariate data analysis (data not shown).

Clinical Course Assessments and Safety

There were no new or unexpected safety findings throughout the observation period. None of the 108 enrolled subjects developed candida, inflammatory bowel disease or tuberculosis. Four patients (3.7%) discontinued treatment with ixekizumab by week 52, namely 2 patients (week 12-24) and 2 patients (after week 24). Discontinuation of the drug was associated to no improvement or exacerbation of cutaneous manifestations (2/108, 1.9%) or eczema (2/108, 1.9%). As shown in Figure 2, there was a gradual time-dependent decline of the drug survival rate in PsO patients. After 1 year of treatment, the rate of patients with PASI 100 was 89% and it shows a mean-year decrease of 4.5%. The mean-year decrease of PASI 90 rate was 2.2%. PASI 75 rate was approximate-

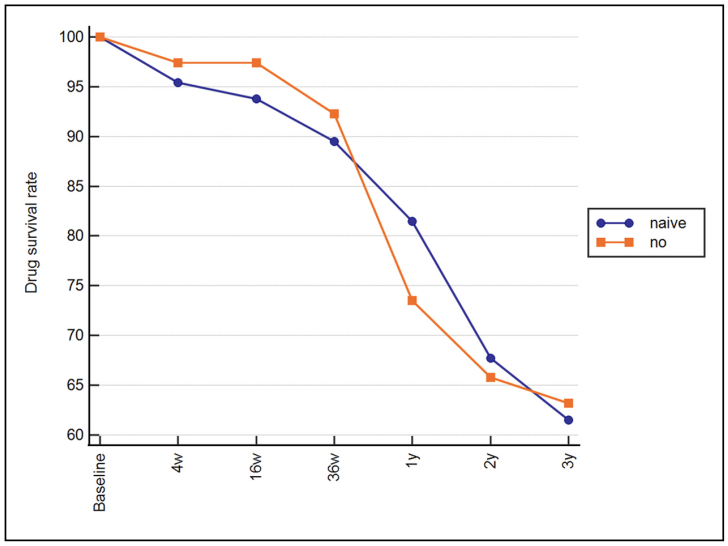

Figure 3. Comparison of the drug survival rate between the bio-naive group and bio-switched group.

ly constant over the three years of treatment. As shown in Figure 3, comparison of the drug survival rate between the bio-naive group and bio-switched group showed no significant difference.

Discussion

Biologic therapies for psoriasis are flourishing. The literature is brimming with clinical trials and relative sub-analyses that investigate drug performances. Notably, the results of clinical trials differ from those of real-life studies, and for this reason it has become increasingly important to publish personal experiences. In this study, not only PASI 75, but also the more stringent goals of PASI 90 and 100 responses showed a favorable outcome after treatment with ixekizumab, superior to those achieved in UNCOVER clinical trials[4,5]. In particular, responses at week 12 were sustained through the following three years in the majority of patients. Sixty-seven out of 108 (62%) were bio-naive patients while, usually, in real life new molecules are reserved for difficult-to-treat patients. This may explain the better results than in UNCOVER studies. However, no statistically significant difference was found in our population between bio-naive and bio-switch patients in achieving PASI 75/90/100, in both short and long term. Sixteen patients who had previously failed an anti-IL-17 molecule achieved and maintained clinical remission, which is consistent with the literature and reassures the physician who primarily selected an anti-IL-17 to continue with a similar drug, without changing mechanism of action[6]. Weight and longer disease duration, two aspects that often negatively influence the efficacy of biologics, seemed to have no effect on ixekizumab, contrarily to our findings on treatment with secukinumab over a long period[7,8].

Ixekizumab had a favorable safety profile, a finding that is consistent with previous trials[1-3]. The oldest patient in our center was a 93-year-old-man who was successfully on treatment for three years, demonstrating the safety of ixekizumab in this very fragile category. Our patient is the oldest reported in the literature and he confirms how multiple comorbidities and old age do not contraindicate anti IL-17 drugs[9]. Since IL-17A plays a key role in mucocutaneous defense against extracellular fungi and bacteria, non-serious skin/mucosal candidiasis are reported to occur dose-dependently[10]. No mucosal candidiasis or inflammatory bowel disease reactivations were observed in our study. This highlights how we have learned to profile the patient, avoiding this molecule in those with a history of fungal infection or bowel diseases. We observed two cases of eczema, which also led to drug discontinuation. This cutaneous side effects were not previously reported in pivotal clinical trials[4,5], but the use of anti-IL-17A agents in wide populations led to the publication of similar events and deserves further investigation, in order to gain experience on targeting the right biologic to the right patient.

Conclusions

To conclude, this study demonstrates the high efficacy and safety of ixekizumab over a period

of 3 years in psoriatic patients in daily clinical practice. Although the sample size was small if compared to multi-center experiences, and the study design was retrospective and observational, the present study confirms the usefulness of ixekizumab in real-world clinical practice and provides input on the topic of patient profiling.

Ethics Approval

The present study was conducted in accordance with the Helsinki Declaration of 1975, as revised in 2013, on Ethical Principles for Medical Research Involving Human Subjects, and approved by the San Martino Ethical Committee, with the number 193.

Conflict of Interest

M. Burlando and A. Parodi have served as speakers for AbbVie, Amge, Almirall, Eli Lilly, Janssen, Novartis, UCB. The remaining authors declare no conflict of interest.

Informed Consent

All patients signed an informed consent for the publication of clinical data.

Funding

This research received no external funding.

Authors' Contributions

Study conception and design: MB; collection and interpretation of data: MB, RC, AH; manuscript editing: MB, IS, EC, AP; approval to submit: all authors.

Data Availability

Data are not available due to privacy restrictions.

References

1) Griffiths CE, Reich K, Lebwohl M, van de Kerkhof P, Paul C, Menter A, Cameron GS, Erickson J, Zhang L, Secrest RJ, Ball S, Braun DK, Osuntokun OO, Heffernan MP, Nickoloff BJ, Papp K; UNCOVER-2 and UNCOVER-3 investigators. Comparison of ixekizumab with etanercept or placebo in moderate-to-severe psoriasis (UNCOVER-2 and UNCOVER-3): results from two phase 3 randomized trials. Lancet 2015; 386: 541-551.
2) Gordon KB, Blauvelt A, Papp KA, Langley RG, Luger T, Ohtsuki M, Reich K, Amato D, Ball SG, Braun DK, Cameron GS, Erickson J, Konrad RJ, Muram TM, Nickoloff BJ, Osuntokun OO, Secrest RJ, Zhao F, Mallbris L, Leonardi CL; UNCOVER-1 Study Group; UNCOVER-2 Study Group; UNCOVER-3 Study Group. Phase 3 Trials of Ixekizumab in Moderate-to-Severe Plaque Psoriasis. N Engl J Med 2016; 375: 345-356.
3) Blauvelt A, Papp KA, Griffiths CEM, Puig L, Weisman J, Dutronc Y, Kerr LF, Ilo D, Mallbris L, Augustin M. Efficacy and Safety of Switching to Ixekizumab in Etanercept Non-Responders: A Subanalysis from Two Phase III Randomized Clinical Trials in Moderate-to-Severe Plaque Psoriasis (UNCOVER-2 and -3). Am J Clin Dermatol 2017; 18: 273-280.
4) Blauvelt A, Lebwohl MG, Mabuchi T, Leung A, Garrelts A, Crane H, ElMaraghy H, Patel H, Ridenour T, See K, Gallo G, Paul C. Long-term efficacy and safety of ixekizumab: A 5-year analysis of the UNCOVER-3 randomized controlled trial. J Am Acad Dermatol 2021; 85: 360-368.
5) Lebwohl MG, Gordon KB, Gallo G, Zhang L, Paul C. Ixekizumab sustains high level of efficacy and favourable safety profile over 4 years in patients with moderate psoriasis: results from UNCOVER-3 study. J Eur Acad Dermatol Venereol 2020; 34: 301-309.
6) Chiricozzi A, Burlando M, Caldarola G, Conti A, Damiani G, De Simone C, Dini V, Malagoli P, Peccerillo F, Potenza C, Scala E, Skroza N, Balato A. Ixekizumab Effectiveness and Safety in the Treatment of Moderate-to-Severe Plaque Psoriasis: A Multicenter, Retrospective Observational Study. Am J Clin Dermatol 2020; 21: 441-447.
7) Pirro F, Caldarola G, Chiricozzi A, Burlando M, Mariani M, Parodi A, Peris K, De Simone C. Impact of Body Mass Index on the Efficacy of Biological Therapies in Patients with Psoriasis: A Real-World Study. Clin Drug Investig 2021; 41: 917-925.
8) Reich K, Puig L, Mallbris L, Zhang L, Osuntokun O, Leonardi C. The effect of bodyweight on the efficacy and safety of ixekizumab: results from an integrated database of three randomised, controlled Phase 3 studies of patients with moderate-to-severe plaque psoriasis. J Eur Acad Dermatol Venereol 2017; 31: 1196-1207.
9) Körber A, Papavassilis C, Bhosekar V, Reinhardt M. Efficacy and Safety of Secukinumab in Elderly Subjects with Moderate to Severe Plaque Psoriasis: A Pooled Analysis of Phase III Studies. Drugs Aging 2018; 35: 135-144.
10) Saunte DM, Mrowietz U, Puig L, Zachariae C. Candida infections in patients with psoriasis and psoriatic arthritis treated with interleukin-17 inhibitors and their practical management. Br J Dermatol 2017; 177: 47-62.
11) Burlando M, Cozzani E, Russo R, Parodi A. Atopic-like dermatitis after secukinumab injection: A case report. Dermatol Ther 2019; 32: e12751.