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Comparison of Short and Long-term Effectiveness of Ixekizumab and Secukinumab in Real-World Practice

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ABSTRACT

Background: Although secukinumab and ixekizumab both act by inhibiting IL-17A, some scientific evidence suggests that there are differences in efficacy between the two agents.

Objective: The aim of this study was to compare the short- and long-term effectiveness of ixekizumab and secukinumab in clinical practice.

Methods: A retrospective study was conducted on a cohort of 245 psoriatic patients receiving secukinumab or ixekizumab during the period from September 2016 to December 2019. The proportion of patients achieving PASI75, PASI90 and PASI100 at weeks 12 and 24 was calculated. Additionally, we recorded the 12- and 24-month drug survival as a measure to assess long-term effectiveness.

Results: A higher proportion of patients in the secukinumab group achieved PASI75, 90 and 100 at 12 weeks. The Kaplan-Meier survival curve for any of the reasons of discontinuation showed no differences between the two groups. Instead, the multivariate analysis for ineffectiveness, adjusted for potential confounders, showed a lower drug survival rate in the secukinumab group, with an adjusted HR of 2.57 (95% CI 1.05-6.28, p 0.038).

Conclusion: This extensive real-life study demonstrated that ixekizumab and secukinumab are both highly effective in short and long-term treatment of psoriasis, even though few differences exist concerning speed of action and long-term effectiveness.

Keywords: psoriasis, real word, IL-17A, secukinumab, ixekizumab, drug survival

Article Highlights

- Although secukinumab and ixekizumab act by inhibiting the same inflammatory pathway, some evidence suggests that these agents might have different safety and effectiveness profiles in psoriatic patients. However, there is paucity of data regarding a direct comparison between these two anti IL17A agents in patients with psoriasis.
- This extensive real-life study showed a very similar efficacy profile of ixekizumab and secukinumab in the short- and long-term treatment of psoriasis.

- Particularly, we observed that secukinumab has a more rapid onset and ixekizumab a longer effectiveness.

1.0 INTRODUCTION

The first biological therapies available for moderate-to-severe psoriasis, which profoundly changed its therapeutic scenario, were the anti-tumour necrosis factor agents and the interleukin (IL)-12/23 inhibitor ustekinumab [1]. Further researchers have focused on the IL-17 pathway, which is a critical therapeutic target due to its pivotal role in psoriasis pathogenesis [2]. The first approved anti-IL17 drug was secukinumab, followed by ixekizumab. Afterwards, brodalumab, a human monoclonal antibody that targets the IL-17receptor A (IL-17RA) expressed on keratinocytes and immune cells, has enriched the therapeutic armamentarium of psoriasis, although data regarding its use in a real-life setting are still scarce, at least in Italy [2].

Several randomized clinical studies have demonstrated a higher clinical efficacy of both ixekizumab and secukinumab compared to previous biologic agents, such as etanercept and ustekinumab; these data have also been confirmed in various real-life studies [3,4,5]. Moreover, despite sharing common action on the same cytokine pathway, secukinumab and ixekizumab seem to differ slightly in terms of efficacy and safety in psoriatic patients [6]. This is probably due to their different molecular structures; in fact, secukinumab is a human IgG1/κ monoclonal antibody, while ixekizumab is an IgG4 monoclonal antibody [2]. To date, there is a scarcity of literature data concerning a direct comparison between the efficacy and safety profiles of these two anti-IL17A agents. Rather, some information is available from an indirect comparison performed through network meta-analysis [7].

The aim of this study was to compare retrospectively the short- and long-term effectiveness of ixekizumab and secukinumab in the clinical practice of two main Italian dermatological centres.

2.0 METHODS

A retrospective analysis was performed on a cohort of patients with chronic plaque psoriasis, with or without psoriatic arthritis. Patient started secukinumab or ixekizumab therapy during the period from September 2016 to December 2019. The study population was comprised of patients who referred to outpatient clinics of two main dermatologic Italian centres (Fondazione Policlinico Universitario A. Gemelli IRCCS, Rome, and Policlinico San Martino-IRCCS, Genova).

All patients were ≥18 years old and naïve to anti IL-17 inhibitors. Patients with pustular or palmoplantar psoriasis or who had started treatment within a clinical trial were excluded. The administration of secukinumab and ixekizumab followed the indications included in the package leaflet. No change in dose or frequency or no concomitant therapies were allowed.

The decision to start treatment with ixekizumab or secukinumab was not based on specific criteria, but was the result of our clinical experience, always in accordance with local guidelines.

Demographic and clinical data were collected for each patient (age, sex, height, weight, body mass index [BMI], age of onset and duration of psoriasis, comorbidity and previous systemic or biological therapies) at the time of initiation of IL-17A therapy. The severity of the disease was estimated by PASI [8] (Psoriasis Area and Severity Index) at baseline and after 12 and 24 weeks; all data were available for each patient**.** Treatment duration was recorded, and reasons of drug withdrawal were categorized into ineffectiveness and adverse events. Interruptions with a maximum of 90 days were accepted and not considered as withdrawal. Patients who discontinued treatment for reasons related to psoriatic arthritis were excluded. Only cases with complete available data were considered.

Clinical effectiveness was assessed as the proportion of patients who achieved a PASI reduction ≥75% (PASI75), ≥90% (PASI90) and 100 % (PASI100) at weeks 12 and 24, compared with the

baseline. The examination of drug survival patterns was carried out using Kaplan-Meyer survival curves for (i) any of the reasons of discontinuation; (ii) ineffectiveness and (iii) adverse events. The 12- and 24-month drug survival for secukinumab and ixekizumab was considered as a measure of long-term effectiveness. This particular endpoint can be considered as a reliable overall marker of treatment success and adherence, since it reflects information on drug efficacy, drug safety, and patient satisfaction [9,10,11,12]. The entire study was conducted according to the principles of the Helsinki Declaration.

2.1 Statistical analysis

Demographic and clinical characteristics of the sample were described through absolute and relative frequencies (%), means and standard deviations, or medians and interquartile range (IR) where appropriate. T-test or Kruskal-Wallis test, and Chi-squared test were used to compare the quantitative and qualitative characteristics of the populations treated with the two different drugs. Univariate and multivariate logistic regression analyses were used to estimate differences in efficacy (PASI) between the two treatments and adjust for potential confounders (age, gender, BMI, previous biologic drug). These analyses were carried out using the "non-responder imputation" (NRI) method, an approach used to handle missing data in responder analysis and that imputes that individuals with missing data are non-responders. Differences in drug survival between the two drugs were examined using Kaplan-Meier survival analysis and tested using the logrank test. "Event" was defined as the discontinuation or switching of a biologic therapy and the "event date" was considered as the date of treatment discontinuation. Patients who had not discontinued treatment at the time of lost to follow-up were censored. Cox regression analyses with adjustment for covariates collected at entry into the study or before the start of a new therapy were used, whenever possible [13], to compare treatment discontinuation times. Adjusted hazard ratios (HRs), 95% confidence intervals (95% CIs) and corresponding p□values was calculated for each clinical

characteristic to compare treatment groups and a defined reference group. A p-value <0.05 was considered statistically significant. The statistical analysis was performed by using the software STATA 13 (StataCorp. College Station, TX: StataCorp LP.)

3.0 RESULTS

The study population included 245 patients treated with an antiIL-17A antibody. In detail, 123 patients received ixekizumab and 122 secukinumab. At week 12 and 24, 7 (2.72%) and 18 (7.0%) patients were imputed as non-responder, respectively. All patients were Caucasians. Clinical and demographic characteristics of patients in both treatment groups were comparable (Table 1). The PASI 75, 90 and 100 improvements were achieved at week 12 by 78 (63.41%), 65 (52.85%) and 61 (49.59%) patients in the ixekizumab group and in 102 (83.6%), 95 (77.9%) and 91 (74.6%) patients in the secukinumab group (figure 1). Secukinumab had a higher rate of PASI75, 90 and 100 responders at 12 weeks with crude ORs, all significant with a p<0.001, of: 2.95 (95% CI 1.61–5.38); 3.13 (95% CI 1.80-5.47); 2.98 (95% CI 1.74-5.12), respectively. Furthermore, the multivariate analysis showed a higher success of secukinumab for PASI75, 90 and 100 with adjusted ORs [all values were significant with a p<0.001, of: 3.20 (95% CI 1.71-5.95); 3.55 (95% CI 1.99-6.34); 3.36 (95% CI 1.92-5.91), respectively].

PASI 75, 90 and 100 responders at 24 weeks were 101 (82.11%), 89 (72.36%) and 86 (69.92%) in the ixekizumab group and 103 (84.4%), 99 (81.1%) and 95 (77.9%) in the secukinumab group (figure 1). Crude-ORs of PASI75, 90 and 100 between the two treatment groups showed higher but not significant superiority of secukinumab: 1.18 (95% CI 0.60-2.31, p=0.628) 1.64 (95% CI 0.90-3.00, p=0.105); 1.51 (95%CI 0.85-2.69, p=0.158).

At 12 months, 29 out of 234 (12.39%) uncensored patients had discontinued treatment; reasons for discontinuation were ineffectiveness in 18 patients (7.69%) and adverse events in 11 patients

(4.70%). At 24 months, 37 (23.27%) out of 159 uncensored patients had ceased treatment, 23 (14.47%) for ineffectiveness and 14 (8.8%) for adverse events. Precisely, at 12 months, 11 (8.94%) patients had discontinued ixekizumab (6 due to loss of effectiveness and 5 for adverse events) and 18 (14.75%) secukinumab administration (12 due to loss of effectiveness and 6 for adverse events, respectively).

At 24 months, the therapy for 14 patients (11.4%) in the ixekizumab group was discontinued (8 due to loss of effectiveness and 6 due to adverse events). Similarly, the therapy for 23 patients (20%) in the secukinumab group was discontinued (15 due to loss of effectiveness and 8 due to adverse effects). The Kaplan-Meier survival curve for any reason of discontinuation is shown in Figure 2 and the corresponding logrank test showed no significant differences (p=0.141). No significant results were found even by analysing data on ineffectiveness (p=0.113) and adverse events (p=0.731) (supplementary Figures).

A regression analysis was performed for ineffectiveness adjusting for the above-mentioned potential confounders, which showed a lower survival for secukinumab with an adjusted HR of 2.57 (95% CI 1.05-6.28, *p* 0.038).

Additionally, an analysis was conducted to assess the factors influencing treatment response **(Table 2, Table 3)**. We observed that in the ixekizumab group (adjusted for age, previous biologic drug use and BMI), males had a significant higher probability of achieving the PASI75, PASI90 and PASI100 at week 12 and 24. Moreover, a high BMI adversely influenced the PASI response (PASI75, PASI90 and PASI100) at week 24. Conversely, in the secukinumab group, males had a significant lower probability of achieving PASI 75 and PASI 90 at week 12 and 24. In addition, BMI had a negative impact on PASI response (PASI75, 90 and 100) at both time points; furthermore, a previous treatment with biologics reduced the probability of achieving a PASI100 at week 12.

Finally, a Cox regression analysis found that the male sex, a previous biologic therapy and BMI adversely affected the 24 months overall drug survival in the secukinumab [adjusted HR of 3.77 (95%CI 1.37-10.34, p=0.010), 9.8 (95%CI 2.19-44.08, p=0.003), 1.2 (95%CI 1.09-1.34, p<0.001), respectively)], but not in ixekizumab group. Age had no impact in either group.

4.0 DISCUSSION

The study evaluated the efficacy profiles of two biological drugs, both directed against the same target involved in psoriasis` pathogenesis, IL-17A. Both drugs have proven to be highly successful in the majority of treated patients, showing a rapid onset of action and a long-term effectiveness. However, few differences between the agents have been found in our study. We observed that secukinumab had a more rapid onset of action, with a significant higher percentage of patients achieving the outcomes of PASI75, PASI90 and PASI100 at week 12 compared with ixekizumab. On the other hand, at 24 weeks, these differences were no longer evident, and the clinical effectiveness became comparable. The more rapid onset of action in the secukinumab group was partially unexpected since several indirect comparison in phase III clinical trials have found a higher efficacy of ixekizumab after 12 weeks of treatment [14,15]. However, our finding is in line with another comparative study in real-world practice in which, at week 12, a higher percentage (even if not statistically significant) of patients achieved PASI75 and 90 response in the secukinumab group [16]. This difference confirms the need of real-world studies, which can sometimes provide different results from those of randomized clinical trials.

However, the purpose of this study was also to assess the differences between these two anti-IL17A agents in long-term effectiveness, by analysing their drug survival. This is defined as the time period in which a patient remains on a specific agent; it can be considered a comprehensive outcome encompassing effectiveness, safety and the preferences of both patients and physicians [17]. It is a suitable parameter for chronic diseases such as psoriasis, which requires long-term

management, and it reliably reflects therapeutic success in a real-life setting. This study showed no differences in drug-survival curves for any of the reasons of discontinuation, ineffectiveness and adverse events, after 24 months of therapy. However, the Kaplan-Meier survival curve for ineffectiveness, adjusted for potential confounders, showed a lower survival for secukinumab, suggesting that patients in the secukinumab group may more easily experience a loss of efficacy compared to the ixekizumab patients. The reasons of this difference in clinical effectiveness remain unclear, but diversity in the binding affinity to IL-17A may partially explain these findings. Also, immunogenicity may be another reason for the higher loss of efficacy in the secukinumab group, although a previous *in vitro* study showed significantly lower immunogenicity potential of secukinumab in a direct comparison with ixekizumab [18].

Our data are in line with previous real-world experiences. In fact, Ohata C. et al. (2020) did not find any difference in drug survival between these two anti-IL17 agents [19]. Moreover, Egeberg A. et al. (2019) compared the 12 month drug survival of secukinumab and ixekizumab in a nationwide cohort of psoriatic patients, finding that both drugs had a very high and similar drug survival rate (87% versus 84%) [6]. On the other hand, Blauvelt et al. (2020) observed that patients treated with ixekizumab had a higher persistence rate (54.8% vs. 45.1%) and lower discontinuation rate (37.8% vs. 47.5%) than secukinumab ones [20]. However, in this study the authors did not provide any detail about disease severity and clinical outcomes.

We also evaluated the impact of several clinical and demographic factors on treatment response. According to our results, BMI influences the effectiveness of both drugs and particularly the secukinumab short- and long-term effectiveness. In this regard, to date, contrasting data have been reported about the effects of BMI on the anti-IL17A agents´ effectiveness [4,21,22,23,24,25].

Furthermore, the long-term performance of secukinumab was worst in bio-experienced patients; conversely, having undergone previous biologic therapies did not adversely influence the

ixekizumab group. Most notably, this difference may depend on the fact that we did not consider the number of previous biologics, which is known to affect the drug effectiveness.

One previous study found that the number of previous biologic therapies significantly influenced the 3-year drug survival for secukinumab [4]. Galluzzo et al. (2018) observed that PASI90 and PASI100 were achieved very rapidly and more often in patients naïve to biologics [24]. As far as ixekizumab is concerned, no long term real-life studies have been published with a consistent number of patients; however, our findings are in agreeement with a real-life study by Chiricozzi et al. (2020) which found comparable outcomes at week 24 in bio-naïve and bio-experienced patients (significant difference only for the rate of PASI100 responders) [5].

Finally, the main differences between secukinumab and ixekizumab concern their effectiveness in relation to the gender. In fact, whilst ixekizumab provides significantly better results in males, secukinumab performs better in females. Although gender-related differences in the efficacy of the drugs are known to exist, to our knowledge, no similar findings have been previously published about antiIL-17A agents and they need further confirmation [26,27].

4.0 Conclusion

In conclusion, this wide real-life study has shown that ixekizumab and secukinumab are both very effective in the short- and long-term treatment of psoriasis. Despite their similar mechanism of action, we have noted few differences between these two drugs, which should be confirmed by further studies.

5.0 LIMITATIONS

This analysis had a retrospective design, therefore it could suffer from the lack of a randomization process of patients. Our analysis was limited by bias in patients' enrollment, including the absence of a standardized clinical approach in the choice of secukinumab vs ixekizumab. Particularly, in the

early stage of this study, all patients recruited were treated with secukinumab, since it was the only anti IL-17A agent commercially available. Additionally, due to the lack of codified guidelines, which could help physicians in the choice of biological agents in psoriatic patients, our therapeutic decision was based mainly on our personal clinical experience.

Moreover, although patients assuming concomitant systemic therapies have been not enrolled in this study, we cannot rule out the possibility that some patients have applied some topical therapies during the treatment with the anti-17A agents. However, we do not believe that this could have occurred so frequently that our data is heavily affected.

In this study, an evaluation number of previous biologic therapies was lacking and it is known to be a factor affecting the drug efficacy in psoriatic patients. In fact, a decrease in efficacy is observed in relation to the number of previous biological therapies [28,29].

Finally, the retrospective design of the study may also have affected the reliability of the efficacy measures, although PASI values' collection was based on information recorded by physicians.

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Declaration of Interests

Giacomo Caldarola reports consulting fees or honorarium and payment for lectures from Lilly and Novartis, outside the submitted work. Clara De Simone reports consulting fees or honorarium from Abbvie, Amgen, Novartis, Celgene, Sanofi, UCB Pharma, Janssen, Lilly and payment for lectures from Abbvie, Lilly, Novartis, UCB Pharma, Celgene, outside the content of this manuscript. Ketty Peris reports Consulting fees or honorarium from Almirall, AbbVie, Biogen, Lilly, Celgene,

Galderma, Leo Pharma, Novartis, Pierre Fabre, Sanofi, Sandoz, Sun Pharma and Janssen, outside the submitted work. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

Authors' contributions

Giacomo Caldarola designed the content of the manuscript and wrote the manuscript; Marco Mariani carried out the statistical analysis; Federico Pirro, Laura Calabrese, Clara De Simone and Ketty Peris acquired data from the literature; Nicola Nicolotti, Martina Burlando and Aurora Parodi contributed to the writing of manuscript; Giacomo Caldarola, Federico Pirro and Laura Calabrese created figures and table and revised language the manuscript. All authors made substantial contributions to the concept and design of the study, revised the manuscript, and gave their approval to the final version of the manuscript.

Data availability:

The datasets generated during and/or analysed during the current study are available from the corresponding author on reasonable request.

Reviewer Disclosures

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www.DrScore.com, and a founder and part owner of Causa Research, a company dedicated to enhancing patients' adherence to treatment. Two additional peer reviewers on this manuscript have no relevant financial relationships or otherwise to disclose.

Table 1. Patients' demographic and clinical characteristics

	Total population (245 patients)	Ixekizumab group (123 patients, 50.20%)	Secukinumab group (122 patients, 49.80%)	*p-value*
Gender, n (%)				
Females	112 (45.71%)	57 (46.34%)	55 (45.08%)	0.843
Males	133 (54.29%)	66 (53.66%)	67 (54.92%)	
Age (years), mean (SD)	54.58 (14.07)	53.64 (12.44)	55.53 (14.05)	0.266
BMI (Kg/m2), mean (SD)	26.54 (3.82)	26.16 (4.14)	26.93 (3.44)	0.117
Duration of disease (years), median (IR)	17.00 (9.00-30.00)	15.00 (8.00-34.00)	17.50 (10.00-26.00)	0.507
Concomitant psoriatic arthritis, number (%)				
No	198 (80.82%)	104 (84.55%)	94 (77.05%)	0.136
Yes	47 (19.18%)	19 (15.45%)	28 (22.95%)	
Patients with previous biological therapy, n (%)				
No	110 (44.90%)	61 (49.59%)	49 (40.16%)	0.138
Yes	135 (55.10%)	62 (50.41%)	73 (59.84%)	
PASI at baseline, mean (SD)	15.01 (7.22)	15.34 (6.57)	14.68 (7.88)	0.264
Duration of anti IL-17A therapy (months), median (IR)	23.96 (14.80-27.80)	23.66 (16.63-26.58)	25.16 (13.92-35.64)	0.263

Patient with a 24 month follow-up, n (%)				0.565
No	123 (50.20%)	64 (52.03%)	59 (48.36%)	
Yes	122 (49.80)	59 (47.97%)	63 (51.64%)	

Abbreviations: BMI: body mass index; SD: standard deviation; IR: interquartile range

Ixekizumab	**Week 12**								
	PASI 75	**p-value**	**PASI 90**	**p-value**	**PASI 100**	**p-value**	**PASI 75**	**p-value**	**PASI 9**
	aOR (95%CI)		**aOR(95%CI)**		**aOR(95%CI)**		**aOR(95%CI)**		**aOR(95%**
Gender: male	**3.94 (1.75-8.84)**	**0.001**	**4.49 (2.03-9.94)**	**<0.001**	**3.80 (1.74-8.26)**	**0.001**	**3.41 (1.17-9.97)**	**0.025**	**4.32 (1.67-1**
BMI	1.06 (0.05-20.92)	0.823	0.95 (0.86-1.04)	0.266	0.95 (0.09-23.93)	0.290	**0.88 (0.78-0.98)**	**0.027**	**0.86 (0.77-0**
Previous biologic drug	0.78 (0.36-1.71 2)	0.552	0.76 (0.36-1.63)	0.480	0.89 (0.42-1.89)	0.767	0.845 (0.32-2.23)	0.741	0.74 (0.31-1
Age	1.00 (0.92-1.03)	0.800	1.01 (0.98-1.04)	0.566	1.00 (0.97-1.03)	0.782	1.02 (0.98-1.06)	0.297	1.02 (0.98-1
Secukinumab									
Gender: male	**0.21 (0.06-0.72)**	**0.013**	**0.22 (0.08-0.63)**	**0.005**	0.40 (0.16-1.02)	0.055	**0.25 (0.07-0.85)**	**0.026**	**0.31 (0.105-**
BMI	**0.82 (0.71-0.94)**	**0.005**	**0.82 (0.72-0.94)**	**0.005**	**0.85 (0.75-0.97)**	**0.015**	**0.83 (0.72-0.95)**	**0.007**	**0.81 (0.71-0**
Previous biologic drug	0.40 (0.11-1.33)	0.134	0.42 (0.14-1.21)	0.107	**0.30 (0.11-0.84)**	**0.022**	0.67 (0.21-2.13)	0.504	0.44 (0.14-1
Age	1.02 (0.98-1.06)	0.312	0.01 (0.97-1.04)	0.644	1.02 (0.98-1.05)	0.182	1.01 (0.07-0.84)	0.570	1.01 (0.98-1

Abbreviations: BMI: body mass index; aOR: adjusted Odds ratio; CI: Confidence Interval

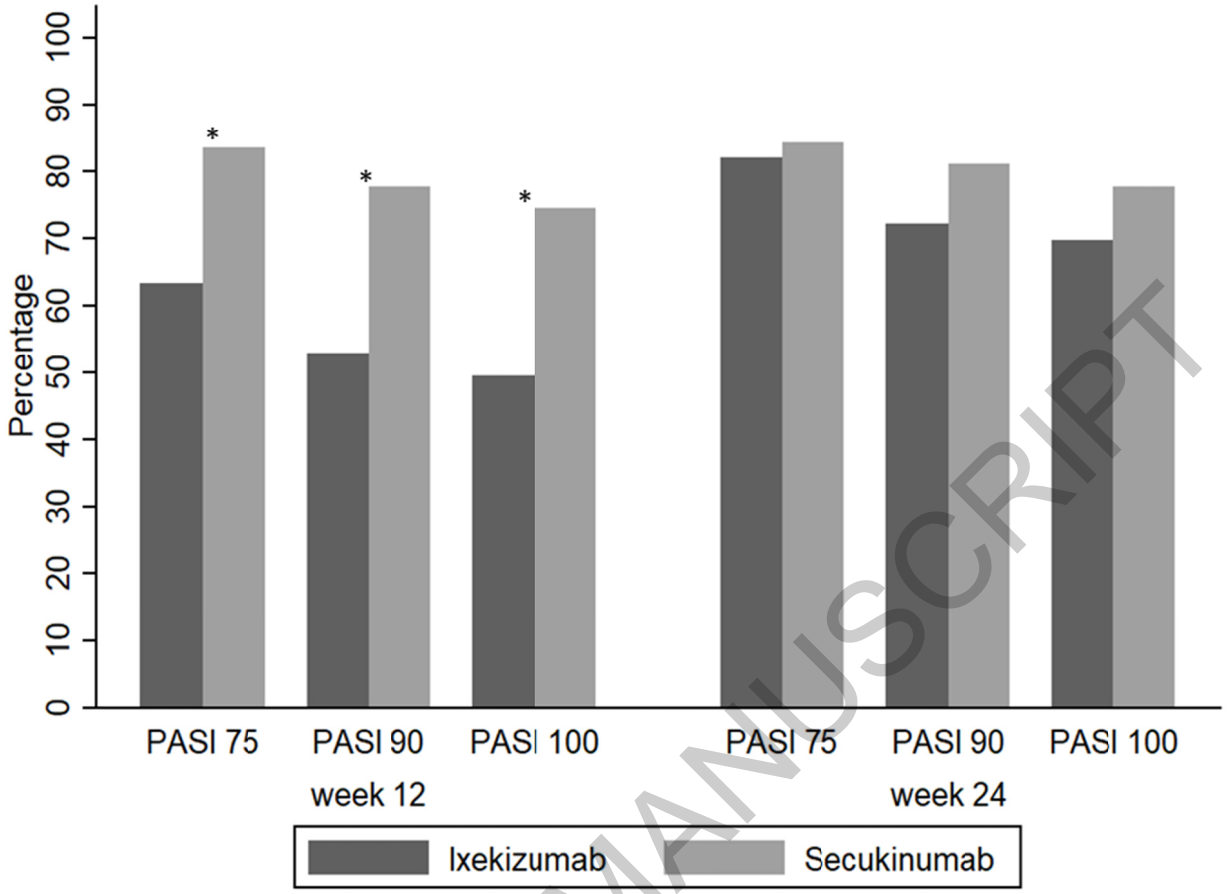
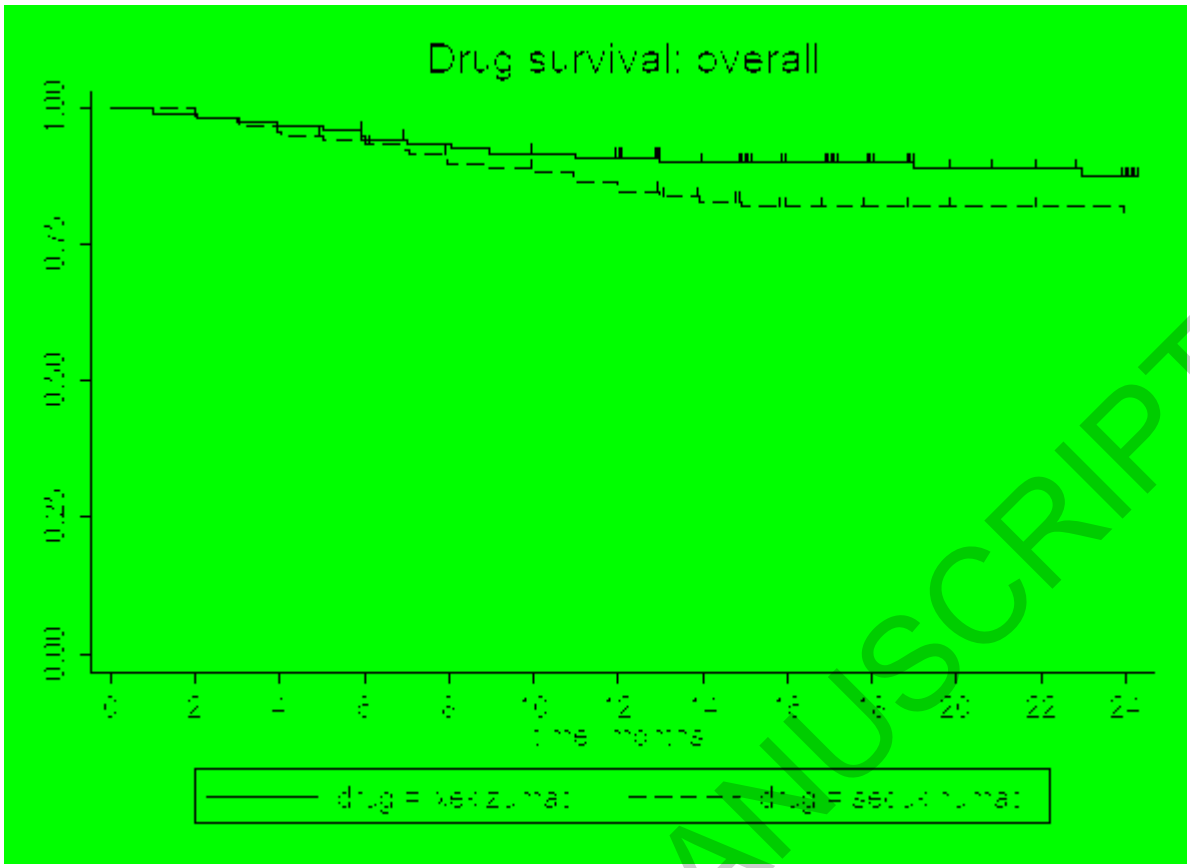


Fig 1

Ixekizumab	Week 12								W
	PASI 75 OR (95%CI)	p-value	PASI 90 OR(95%CI)	p-value	PASI 100 OR(95%CI)	p-value	PASI 75 OR(95%CI)	p-value	PASI 9 OR(95%
Gender: male	**3.72 (1.73 – 8.01)**	**0.001**	**3.84 (1.84 – 8.02)**	**<0.001**	**3.39 (1.64 – 7.02)**	**0.001**	2.26 (0.83-6.19)	0.112	**2.70 (1.17-6**
BMI	1.02 (0.93 – 1.13)	0.544	0.98 (0.91-1.07)	0.881	0.98 (0.91 – 1.08)	0.798	0.94 (0.84-1.04)	0.223	0.92 (0.83-1
Previous biologic drug	0.85 (0.41 – 1.77)	0.671	0.82 (0.41-1.65)	0.583	0.94 (0.47-1.88)	0.855	1.17 (0.44 – 3.11)	0.747	0.95 (0.43-2
Age	0.99 (0.97-1.02)	0.735	0.99 (0.97-1.03)	0.806	0.99 (0.97-1.03	0.650	1.02 (0.97-1.05)	0.566	1.01 (0.97-1
Secukinumab									
Gender: male	**0.19 (0.05 – 0.71)**	**0.013**	**0.23 (0.08-0.67)**	**0.007**	0.46 (0.18-1.09)	0.078	**0.18 (0.04-0.85)**	**0.030**	**0.34 (0.11-1**
BMI	**0.79 (0.62-0.91)**	**0.001**	**0.81 (0.72-0.92)**	**0.001**	**0.84 (0.74-0.94)**	**0.003**	**0.88 (0.77-1.01)**	**0.060**	**0.87 (0.76-0**
Previous biologic drug	0.36 (0.11-1.15)	0.084	0.39 (0.14-1.04)	0.060	**0.30 (0.11-0.80)**	**0.016**	0.83 (0.26-2.65)	0.757	0.60 (0.20-1
Age	1.01 (0.98-1.05)	0.433	1.00 (0.97-1.03)	0.941	1.01 (0.98-1.04)	0.540	1.02 (0.98-1.07)	0.235	1.02 (0.98-1

Abbreviations: BMI: body mass index; OR: Odds ratio; CI: Confidence Interval

Supplementry Fig1



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