Psoriasis: Targets and Therapy

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ORIGINAL RESEARCH

Effectiveness and Drug Survival of Ixekizumab and Secukinumab in Patients with Moderate to Severe Plaque Psoriasis: Real-World Data from Bucharest, Romania

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Purpose: Multiple biological therapies have been developed for the treatment of inflammatory diseases, including moderate to severe plaque psoriasis. Choosing the optimal treatment for psoriasis can depend on several factors and is strongly influenced by a drug's efficacy and safety profile. Continuous treatment with biological therapies is recommended to achieve effective disease management in patients with psoriasis. However, in real-world, patients often discontinue biologic therapy within the first year of treatment. Therefore, in this study, we aimed to investigate the effectiveness and drug survival of two anti-interleukin 17 agents (ixekizumab and secukinumab) in a group of adult patients with moderate to severe psoriasis from Bucharest, Romania.

Patients and Methods: We designed an observational, non-interventional, retrospective study of 255 adult patients with moderate to severe psoriasis receiving ixekizumab and secukinumab. We performed descriptive statistics and inferential methods, such as z-test, median test and Kaplan Meier curve comparison, to characterize the groups with two biological treatments.

Results: Patients treated with ixekizumab had a longer drug survival compared to those treated with secukinumab with lower risks of non-persistence, discontinuation and switching therapy. Patients age-groups and psoriasis durations found to be significant factors in drug survival.

Conclusion: This study contributes to the understanding of the drug survival profile and the factors that may influence it in ixekizumab and secukinumab treatment in a real-world setting.

Keywords: anti-IL-17 effectiveness, anti-IL-17 drug survival, ixekizumab, secukinumab

Introduction

Psoriasis is a common chronic immunological disorder with an estimated prevalence ranging from 1.0% to 8.5% worldwide.[1,2] Disease-specific signs and symptoms have a significant impact on mental health, social relationships and professional activities, leading to a low quality of life.[3–5]

In recent years, multiple biological therapies with different mechanisms of action have been developed for the treatment of inflammatory diseases, including moderate to severe plaque psoriasis. Moderate to severe psoriasis is defined as body surface area (BSA) >10 or psoriasis area and severity index (PASI) >10 and dermatology life quality index (DLQI) >10.[6] Choosing the optimal treatment for psoriasis can depend on several factors and is strongly influenced by a drug's efficacy and safety profile. Continuous treatment with biological therapies is recommended to achieve

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effective disease management in patients with psoriasis. However, in real-world, approximately 18–46% of patients discontinue biologic therapy within the first year of treatment leading to the reappearance of signs and symptoms of the disease.[7,8]

Drug survival is the length of time until the patient continues the regimen or discontinues the therapy and it may be influenced by several factors, such as treatment-related factors such as effectiveness, safety profile and tolerability, health system factors and access to therapy, and factors related to patient choice. This is an important parameter related to long-term therapeutic performance in the real-world setting.[9] Biologic treatments for psoriasis are discontinued or switched in many patients for multiple reasons, primarily due to loss of effectiveness, but also to tolerability issues or other reasons, including patient choice.[10–12] Studies regarding real-world drug survival data of biological therapies show better performance for newly emerging biological agents.[13–16] In particular, targeting anti-interleukin (IL)-17 or IL-23 drugs has shown efficacy in clinical trials compared to previously developed biologic therapies targeting tumor necrosis factor-α (TNF-α).[17–19]

Therefore, in this study, we aimed to investigate the effectiveness and drug survival profile of secukiumab (SEC) and ixekizumab (IXE) in a group of patients with moderate to severe psoriasis from Bucharest, Romania. At the time of data collection, IXE and SEC were the only two available anti-IL-17 drugs in Romania. IXE is a humanized monoclonal antibody (IgG4) that selectively binds to IL-17A preventing its binding to the IL-17 receptor and attenuating the inflammatory response mediated by IL-17A.[20] SEC is a human IgG1 monoclonal antibody that specifically targets IL-17A and blocks its binding with IL-17R.[21] IXE has been approved in Romania for treatment of moderate to severe psoriasis not responding to conventional immunosuppressive therapy starting from 2017, while SEC has been approved starting from 2019.

Materials and Methods

We designed an observational, non-interventional, retrospective study of patients with moderate to severe psoriasis receiving biologic treatment with IXE and SEC. For this study, we used data from patients from our department and from private clinics in Bucharest. The initial analyzed group included 311 patients with moderate-severe psoriasis who are currently on treatment or have had in the past biologic therapies with IXE and SEC. This group was drawn as randomly as possible from the National Registry of Dermato-Venereological Diseases in Romania. Data were collected using questionnaires completed by treated patients and dermatologists at regular office visits at 3-month intervals for the first 6 months of treatment and then every 6 months. The analyzed period was from January 2018 until December 2021.

Giving the fact that, in Romania, SEC therapy was approved much later than IXE, we selected from the initial sample of 311 patients, in accordance with the literature data, a subsample of patients who had biological therapy with IXE or SEC and discontinued therapy either for adverse reactions or for therapeutic ineffectiveness. Some of these patients were switched to another biological agent. To this group was added a subset of patients currently under biological therapy with IXE or SEC. Subsequently, we matched patients on IXE or SEC biologic therapy according to the onset of IXE or SEC therapy, with the aim of including patients with the longest duration of treatment in the sample. We performed a quasi-random selection of patients for this stage, in such a way that the following conditions are met: (1) for each group or subgroup of analyzed patients there are as many patients as possible; (2) on each initial arm, respectively IXE versus SEC, there must be at least 100 patients; (3) the difference in the rate of patients discontinued/at time t between arms (IXE versus SEC) to be statistically insignificant;[22] (4) there must be a minimum of 10 discontinuation/pause/switch events for each analysis arm.[23] Therefore, a subset of 255 patients was obtained. We retained the data, including the main characteristics related to sex, age, duration of disease, risk factors such as smoking, and family history, comorbidities and previous therapies. We report main descriptive indicators like mean, median, standard deviation and homogeneity coefficient. Furthermore, we performed the z-test to assess the differences between proportions, the median test and Fisher Exact Test to evaluate potential association between patient characteristics and persistence of treatment for main competitors, respectively IXE and SEC. We performed a comparative Kaplan–Meier survival analysis of drug survival. Statistical testing of the difference between curves was performed based on the Log-Rank (LR) test.[24] Patient data were entered in Microsoft Excel, and the subsequent analyses were performed in IBM SPSS and MedCalc.[25,26]

Results

In the analyzed sample, 110 female patients were included, representing 43.1% of the total sample and 145 male patients, representing 56.9% of the total sample. In the IXE arm, 17.1% of females were switched, while in the SEC arm 25.3% of females were switched. Fisher's Exact test rejected the association between gender and switch status for both IXE and SEC sub-groups.

It appeared that the main characteristics of the two groups were quasi-similar (Table 1). Patients were aged between 24 and 84 years in IXE group, and between 22 and 78 years in the SEC group. The mean age was 50.4 years for IXE and 51.2 for SEC, with a small standard deviation of 14.4 and 13.2, respectively.

No significant differences were found between the two groups regarding previous treatments.

The patients had a disease duration ranging from 0 to 45 years, with a 45 years range for SEC and 42 years range for IXE. For the IXE arm, the average duration of the disease was 14.1 years, the standard deviation was 11.1 and the median age was 12 years. In the SEC arm, the mean age was 14.8, the standard deviation was 10.4, and the median was 13. Thus, from the point of view of the duration of the disease, the patients in both groups were extremely heterogeneous, with a homogeneity coefficient that reached 78.7% for IXE and 66.9% for SEC.

Furthermore, 47% of the IXE arm and 44% of the SEC arm were bio-naïve. The z-test did not show a statistically significant difference between the two groups (p=0.61). Overall, we noticed that 20% of all switches occurred within the first 6 months after initiation of biological therapy, and only 15% of switches after 24 months. On the one hand, in the IXE group, the mean follow-up duration was 28.1 months, with a standard deviation of 12.1, and the median was 31.6 months. On the other hand, in the SEC group, the mean follow-up was 23.9 months, the standard deviation was 10.5 months and the median was 24.4 months. Regarding this heterogeneity of follow-up, the median test showed a significant

Table 1 Characteristics of Patients in the Two Groups, IXE versus SEC and Their Association with Switch Status

Variable	Values	IXE n1=102		Type I error, Fisher Exact (p-values)	SEC, n n2=153		Type I error, Fisher Exact (p-values)
		Persistent n=88	Switch n=14		Persistent n=111	Switch n=42	
Sex	Females	29 (82.9%)	6 (17.1%)	p=0.548	56 (74.7%)	19 (25.3%)	p=0.591
	Males	59 (88.1%)	8 (11.9%)	Fisher -Exact	55 (70.5%)	23 (29.5%)	
Age group (>50 ani)	No	46 (92.0%)	4 (8.0%)	p=0.150	46 (65.7%)	24 (34.3%)	p=0.102
	Yes	42 (80.8%)	10 (19.2%)		65 (78.3%)	18 (21.7%)	
Psoriasis duration (≥13 years)	No	50 (96.2%)	2 (3.8%)	p=0.004	58 (79.5%)	15 (20.5%)	p=0.101
	Yes	38 (76%)	12 (24%)		53 (67.1%)	26 (32.9%)	
Smoking	No	49 (83.1%)	10 (16.9%)	p=0.384	73 (72.3%)	28 (27.7%)	p=0.999
	Yes	39 (90.7%)	4 (9.3%)		38 (73.1%)	14 (26.9%)	
Family history of psoriasis	No	62 (82.7%)	26 (96.3%)	p=0.106	93 (70.5%)	39 (29.5%)	p=0.192
	Yes	13 (17.3%)	1 (3.7%)		18 (85.7%)	3 (14.3%)	
Psoriatic arthritis	No	73 (85.9%)	12 (14.1%)	p=0.999	88 (73.3%)	32 (26.7%)	p=0.666
	Yes	15 (88.2%)	2 (11.8%)		23 (69.7%)	10 (30.3%)	
Nail psoriasis	No	79 (85.9%)	13 (14.1%)	p=0.999	101 (72.1%)	39 (27.9%)	p=0.999
	Yes	9 (90%)	1 (10.0%)		10 (76.9%)	3 (23.1%)	
Psychological impairment	No	84 (86.6%)	13 (13.4%)	p=0.530	109 (74.1%)	38 (25.9%)	p=0.049
	Yes	4 (13.4%)	1 (20%)		2 (33.3%)	4 (66.7%)	
Bio-naïve	No	40 (74.1%)	14 (25.9%)	p<0.01	44 (51.2%)	42 (48.8%)	p<0.01
	Yes	48 (100%)	0 (0%)		67 (100%)	0 (0%)	
Methotrexate	No	3 (100%)	0 (0%)	p=0.999	4 (100%)	0 (0%)	p=0.999
	Yes	85 (91.4%)	8 (8.6%)		107 (79.9%)	27 (20.1%)	
UVB therapy	No	83 (86.5%)	13 (13.5%)	p=0.999	104 (72.2%)	40 (27.8%)	p=0.999
	Yes	5 (100%)	0 (0%)		7 (77.8%)	2 (22.2%)	
PUVA therapy	No	54 (83.1%)	11 (16.9)	p=0.129	80 (69.0%)	36 (31.0%)	p=0.093
	Yes	34 (94.4%)	2 (5.6%)		31 (83.8%)	6 (16.2%)	

Abbreviations: UVB, Ultraviolet B; PUVA, psoralen and Ultraviolet A.

difference between the two groups. Thus, patients from the SEC group had a significantly shorter follow-up time than the IXE group ($p<0.01$). For the 14 IXE and 42 SEC patients who switched therapy, the median time to switch was 8.9 months and 13.4 months, respectively. The median test showed no significantly difference between the two groups ($p=0.355$).

More precisely, 16.4% of patients treated with IXE and 27.5% of patients with SEC, respectively, switched therapy due to an adverse reaction or treatment ineffectiveness. There were 6 patients who switched from SEC to IXE and 4 patients from IXE to SEC. Switching from IXE therapy was done after a mean of 392 days, while switching from IXE to SEC was done after a mean of 537 days. Among other existing comorbidities, only psychological impairment was statistically associated with switching in the SEC arm ($p=0.046$). In the IXE arm, no association was found ($p=0.53$).

Analyzing the two Kaplan–Meier curves, it can be seen that two years after the initiation of biological therapy, 88% of the patients with IXE were still in treatment, while only 75% of the patients with SEC were still benefiting from this treatment (Figure 1). The 4-year analysis showed a similar result with 80% of patients who were still on IXE and 67% on SEC after 48 months. Overall, the mean drug survival for IXE was 43 months, while the one for SEC was 37 months. Thus, a statistically significant difference in favor of IXE was observed ($p<0.01$).

It should be noted that age seemed to be an important factor in the IXE group. More precisely, patients over 50 years of age tended to have a shorter drug survival compared to the younger group ($p=0.038$). It should be noted that the differences by age groups, as can be seen in Figure 2, happened quite quickly over time, generally after the first 10 months. In the SEC group, a significant difference could be observed between the two age groups analyzed only if we accept a $p=0.046$ risk. The difference between the sub-branches defined by age-groups appeared later than in the case of IXE. In general, one may see a greater difference after 20 months of treatment.

Patients with a more recent onset of disease (less than 13 years) had a longer drug survival with an average duration of treatment of 44.4 months. For patients with a disease duration longer than 13 years, the average period of treatment was 39.5 months. However, the difference recorded between the two groups was statistically significant for IXE therapy only if a $p=0.09$ risk was accepted. For SEC, the difference was not statistically significant because the assumed risk is $p=0.35$ (Figure 3).

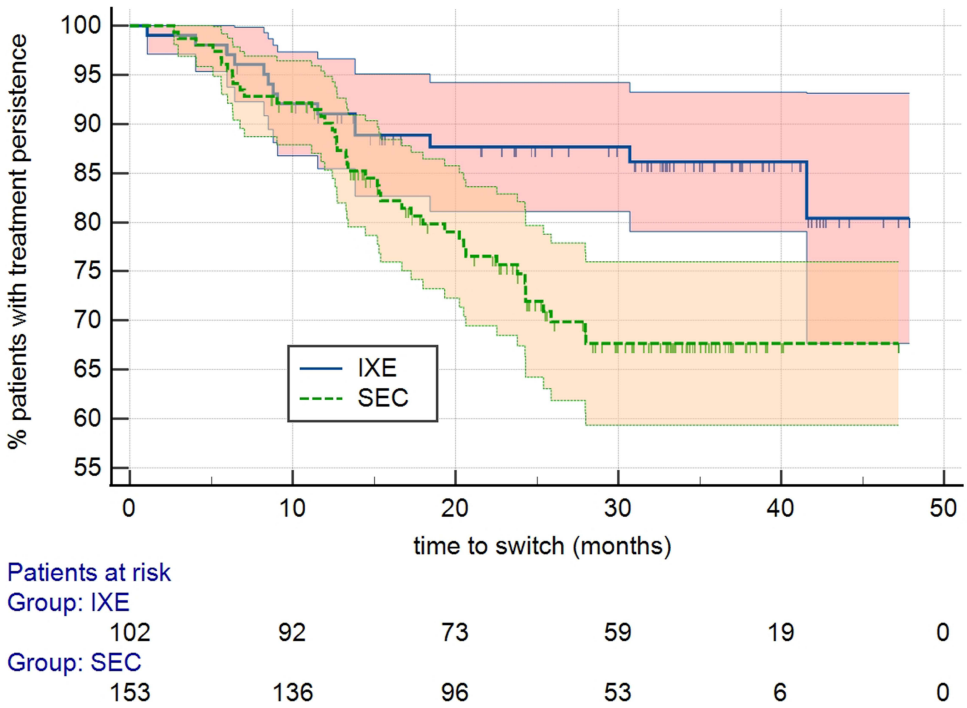

Figure 1 Drug survival profile of IXE and SEC.

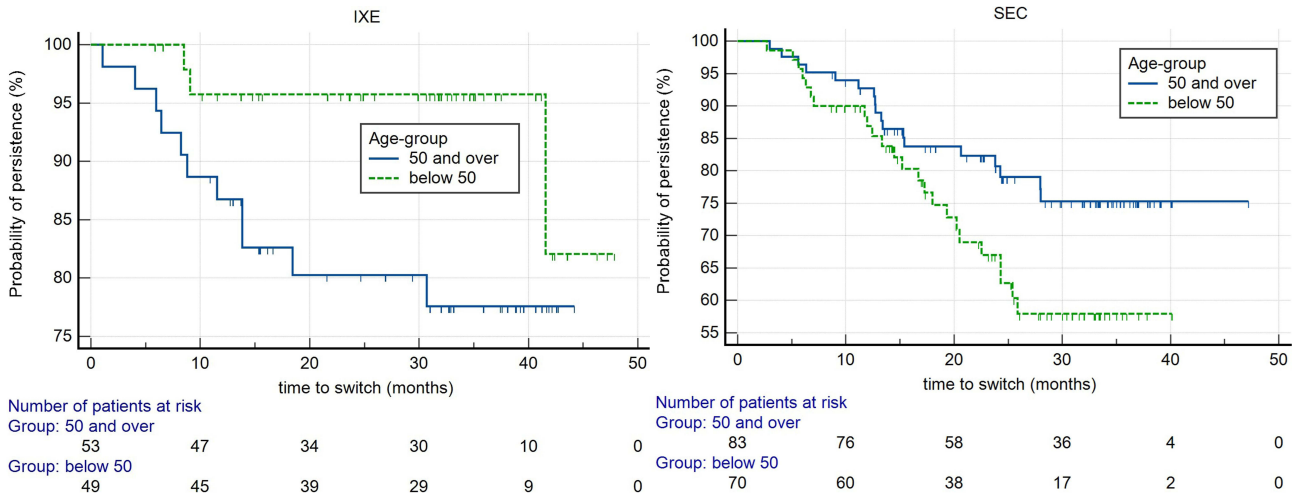

Figure 2 Drug survival according to the age group.

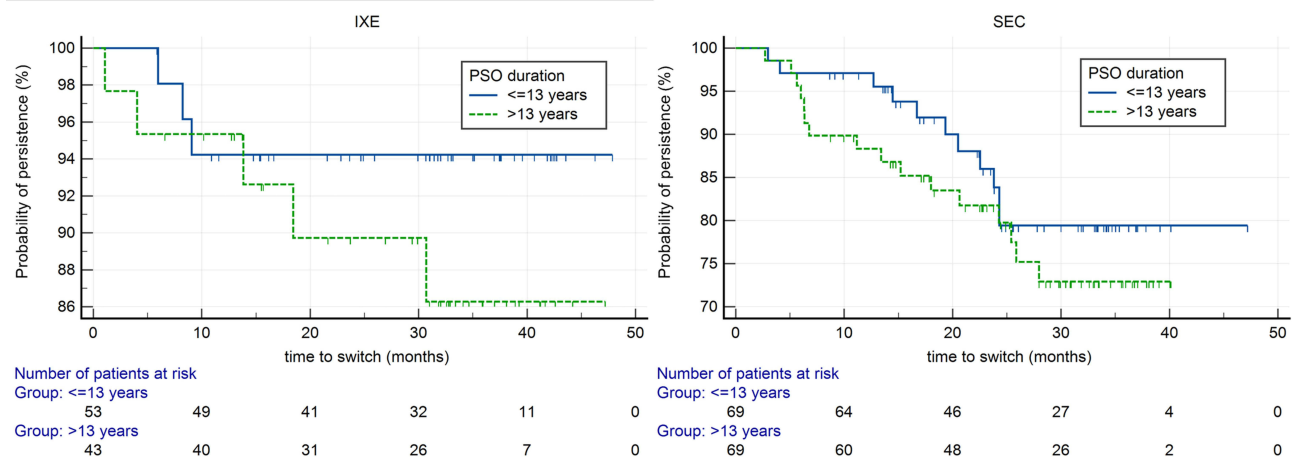

Figure 3 Drug survival according to the duration of disease.

To underline the effectiveness of IXE and thus the longer drug survival compared to SEC, the present study revealed that Psoriasis Area Severity Index (PASI) score values for patients on IXE decreased more in the first 6 months of treatment in comparison with SEC. At 6 months, the mean PASI score for patients with SEC was 3.8 and the median was 2.1. For patients with IXE the mean was 1.4, while the median was 0. However, it should be taken into account that both groups were characterized by high heterogeneity in PASI score. Consequently, testing the differences between medians, we found that the median PASI score at 6 months for the IXE group was significantly lower than for SEC ($p<0.001$). These results are consistent with data found in other studies, especially regarding PASI 75 and PASI 100 scores.[26]

Discussion

"Real-world" studies comparing treatment patterns of IXE versus SEC among patients with psoriasis are limited. In this retrospective observational study, we compared treatment patterns with IXE or SEC in adult patients with moderate to severe psoriasis. The results of our study showed that IXE had a longer drug survival in comparison with SEC. These results may be comparable to those of previously published studies from different countries, which also suggest a lower effectiveness of SEC in real-world practice than in clinical trials.[27–31] More specifically, 2 years after initiation of biologic therapy, 88% of patients treated with IXE were still on treatment, compared to only 75% of patients treated with SEC. After 4 years, 80% of patients were still on IXE, compared to 67% of patients on SEC.

Prior biologic treatment is a well-known risk factor for discontinuation of therapy,[9] and the rate of discontinuation appears to increase as patients receive more types of therapy.[14] In our study, patients treated with SEC had fewer prior biological treatments than patients treated with IXE. Also, bio-naïve patients with IXE or SEC had a longer mean treatment duration than biologic-experienced ones, confirming the risk of treatment discontinuation after previous exposure to biologics. These results are supported by the literature, for example, a 2015 study showed a higher number of bio-naïve patients who remained on biological treatment,[9] and also in a recent analysis of the British registry, the previous treatment status strongly influenced the drug survival profile.[12] Therefore, it is very likely that the relatively lower survival rate for SEC was also due to the high percentage of biologic-experienced patients.

In the present study, the main reasons for switching biologic therapy for patients who were on IXE or SEC therapies were treatment ineffectiveness and adverse reactions. The ineffectiveness of the treatment was found in 95.2% of the cases that had treatment with SEC and in 90.5% of the cases with IXE. Regarding adverse reactions, the percentage is slightly higher among IXE treatment, this analysis being limited by the very small volume of subgroups, but consistent with the literature.[32,33]

The IXE group had lower discontinuation and switching rates of biologic therapy (15.5 months) compared to the SEC group (13.8 months).

Regarding age, there are very little data in the literature to reveal a correlation between it and the drug survival profile of IXE and SEC. The present study showed that patients with SEC older than 50 years tended to have longer drug survival compared to the younger ones. On the other hand, patients older than 50 years on IXE tended to have a shorter drug survival compared to the younger group. It seems that the duration of disease was a determining factor on the probability of switching in the case of IXE therapy. Patients who had a more recent onset (less than 13 years) of the condition tended to be more persistent on IXE.

Limitation

This study was limited by the relatively small number of patients and a short follow-up period. The small number of patients may limit the interpretation of whether the differences in performance between the two therapies were significant and clinically relevant. The study is observational and has a convenient sample on its basis. Over time, as larger groups with longer follow-up are created, it may allow such analysis.

Conclusion

The drug survival profile of biologic therapies is strongly related to effectiveness and safety in real-world practice and is a useful benchmark for clinical practice. This study contributes to the understanding of the drug survival profile of IXE and SEC in psoriasis and the factors that may influence it.

The results provide a real-world analysis of outcome and drug survival of these agents in a population-based cohort of 255 adult patients with moderate to severe psoriasis. The most important finding of the study was that IXE showed a longer drug survival than SEC in moderate to severe psoriasis.

It seems that previous exposure to other biologic therapies is an important factor in determining drug survival, and this fact can help both patients and clinicians in making treatment decisions. It might be relevant for physicians to choose a particular biological treatment based on the prognostic factors that are present in a particular patient, in a specific epidemiological and geographical context. It should be noted that a direct causal relationship between these prognostic factors and persistence of therapies cannot be estimated from such observational studies and this should be an important topic for future etiological research. Although we have presented multi-year data on both therapies, it remains unclear whether the performance and persistence of these biologic therapies will continue in a linear trend beyond the data presented in this study. Therefore, future drug survival studies should include data over longer periods of time to provide an accurate picture of current treatments.

Approaching the patient holistically and placing him at the center of our concerns should be an appropriate approach in order to reduce the burden of psoriatic disease.

Institutional Review Board Statement

The study was conducted in accordance with the Declaration of Helsinki and approved by the Ethics Committee of Colentina Clinical Hospital no. 3122/04.02.2022 for studies involving humans.

Informed Consent Statement

Informed consent was obtained from all subjects involved in the study.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Disclosure

The authors report no conflicts of interest in this work.

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