Wiley
Dermatologic Therapy
Volume 2025, Article ID 2605209, 10 pages
https://doi.org/10.1155/dth/2605209

WILEY

Research Article

Survivin as a Promising Biomarker for Patients Under IL17 RA Inhibitor Therapy: A Single-Center, Pilot Study

Eleftheria Tampouratzi,[1] **John Katsantonis**,[1] **Athanasios Chaniotis**,[2] **George Pesiridis**,[2] **Efthymios Stathatos**,[2] **Artemis Tsega**,[3] **Panagiotis Dikeakos**,[4] **Petros Karkalousos**,[5] **Konstantinos Asonitis**,[6] **Emmanouil Georgiadis**,[7] **and Konstantinos Sfaelos**[2]

[1]*Dermatological Department, Tzaneio General Hospital, Piraeus, Greece*
[2]*Dermatology, LEO Pharmaceutical Hellas S.A., Athens, Greece*
[3]*Private Practice, Athens, Greece*
[4]*A' Surgical Department, Tzaneio General Hospital, Zanni and Afentouli Avenue, Piraeus 18536, Greece*
[5]*Department of Biomedical Sciences, Lab Chemistry, Biochemistry and Cosmetic Science, University of West Attica, Athens, Greece*
[6]*Department of Internal Medicine, Réseau Hospitalier Neuchâtelois, Neuchâtel, Switzerland*
[7]*School of Social Sciences and Humanities, University of Suffolk, UC Suffolk, Ipswich, UK*

Correspondence should be addressed to Eleftheria Tampouratzi; elefteria_tab@yahoo.gr

Received 27 November 2024; Revised 6 June 2025; Accepted 6 October 2025

Academic Editor: Sebastian Yu

Background: Tissue and blood survivin overexpression has been associated with psoriasis.
Objectives: To evaluate the effect of brodalumab therapy on survivin expression in blood samples and tissue biopsies.
Methods: Peripheral blood samples and skin biopsies were obtained from 16 psoriatic patients and 16 healthy controls. Clinical scores (Psoriasis Area and Severity Index [PASI] and Dermatology Life Quality Index [DLQI]) were recorded at 0, 3, and 12 months. Serum and tissue survivin expression were examined using an enzyme-linked immunosorbent assay (ELISA) method.
Results: Brodalumab produced a remarkable clinical response at 3 and 12 months compared to baseline (median PASI score change: −10.6 [*Q*1–*Q*3: −11.4, −8.1], $p < 0.001$ and −12.3 [*Q*1–*Q*3: −14.8, −11.0], $p < 0.001$, respectively, and mean DLQI score reduction: 13.1 ± 3.1, $p < 0.001$ and 15.1 ± 2.5, $p < 0.001$, respectively). A significant reduction in tissue survivin was found in psoriatic skin at 12 months ($p = 0.046$). The median difference in tissue survivin between the two groups at baseline was also statistically significant ($p < 0.001$), showing higher levels in the psoriasis group. Similarly, the mean difference between tissue survivin levels at baseline and 12 months was statistically significant ($p < 0.001$, 95% CI of 0.034 [0.022, 0.047]). At 12 months, serum survivin decreased significantly compared to baseline, in the psoriasis group ($p = 0.004$, 95% CI 11.2 [4.2, 18.1]). A moderate to strong negative correlation was found between the change in serum survivin levels and the change in DLQI at 3 months ($p = 0.020$).
Conclusions: Our study provides the first evidence that serum and tissue survivin may serve as a potential biomarker in patients treated with brodalumab treatment.

Keywords: brodalumab; drug response; IL17 RA inhibitors; plaque psoriasis; survivin

1. Introduction

Psoriasis is a chronic, complex, autoimmune skin disease characterized by overproduction and decreased apoptosis of keratinocytes. It represents a significant global health issue, with prevalence rates ranging from 0.09% to 11.4%, affecting an estimated 100 million people worldwide [1]. Although the pathogenesis of this inflammatory disorder is not fully

understood, T helper 1 (Th1) and Th17 cells have been suggested to be key contributors of the interplay between immune cells and keratinocytes [2].

Survivin protein is the smallest member of the inhibitor of apoptosis protein (IAP) family and the only one exhibiting double action by inhibiting apoptosis and regulating cell division. Its peculiarity lies in its structure as a 16.5 kDa protein, encoded by the BRIC5 gene located on chromosome 17 [3]. Being a multifunctional protein that belongs to an apoptosis inhibitor family, survivin has significant effects on the immune system, such as dendritic and T-cells activation and immunomodulation [1]. There is evidence that survivin is overexpressed in 70%–80% of psoriatic plaques as compared to the apparently normal skin of psoriatic patients as well as normal individuals' skin [4, 5]. In psoriatic skin, this apoptosis-related protein is localized intracellularly, and there is an increase in its cytoplasmic and nuclear expression. Moreover, in normal skin, it is restricted in a few cells of the basal layer, while in psoriatic one is detected mainly in the upper layers [6, 7]. Survivin overexpression in psoriatic skin is probably directly related to the excessive proliferation of psoriatic plaque keratinocytes. Indeed, the forementioned relationship has been strongly suggested in both survivin tissue expression and blood levels, which were constantly decreased following anti-TNF psoriasis therapy [5, 6, 8, 9].

Taking these into consideration, we conducted a single-center, prospective, observational, case-control study to investigate possible associations between anti-IL17RA therapy (brodalumab) and survivin expression in psoriatic patients, as well as possible relationship with the clinical response to treatment. Hence, since survivin seems to precipitate initiation of cellular apoptosis, it is reasonable to speculate that survivin serum and/or tissue levels could possibly serve as an early indicator for disease activity or relapse.

2. Materials and Methods

2.1. Study Design. A single-center, prospective, observational, case-control study was conducted at the outpatient Dermatological Clinic in Tzaneio General Hospital in Greece from June 2021 to October 2023. A total of 16 patients with moderate to severe plaque psoriasis with no previous exposure to biological therapy (bionaive) or conventional systemic therapy (conventional treatment-naïve), who initiated treatment with brodalumab based on clinicians' decision, and 16 healthy individuals (control group), were prospectively enrolled in the present study, from 06/2021 to 10/2023. None of the patients presented with any signs or symptoms suggestive of joint involvement. Pregnant or postpartum women, patients with malignancy, or under other local, systemic, or biological therapy for the disease under investigation, were excluded. The study was carried out following local Ethic Committee's approval and conformed with the Code of Ethics of the World Medical Association (Declaration of Helsinki). Informed consent forms were obtained from all participants included in this study. The start of the study (baseline) was defined as the visit before the first brodalumab administration and the patients were followed-up for 1 year (48 weeks).

2.2. Clinical Evaluation. The Psoriasis Area and Severity Index (PASI), Body Surface Area (BSA), and Dermatology Life Quality Index (DLQI) in baseline, 12 and 48 weeks after treatment initiation, were used to assess psoriasis activity. Each patient was subjected to complete laboratory testing pretreatment (hematology, biochemistry), chest x-ray, Mantoux or Quantiferon where necessary, and virology testing. At the same time, serum survivin levels were measured at weeks 0, 12, and 48 in each subject. Biopsies were also taken from lesional (center of the lesion) as well as normal skin areas, simultaneously in the same patient, at Week 0 to confirm the disease activity and to detect survivin tissue expression. Moreover, skin specimens from the psoriatic plaque (center of the lesion) that had been tested at baseline were also examined at Week 48. Study controls included randomly selected healthy individuals; besides demographic and somatometric data (age, weight, height, BMI, smoking, comorbidities, and other medications taken outside of the disease), serum and tissue survivin levels were also measured for this group.

2.3. Measurement of Serum and Tissue BIRC-5 (Survivin) Levels. Whole blood samples were collected in serum separator tubes (SST), left to separate for about 2 h, then centrifuged for 15 min at approximately 1000 rpm to collect sera, and either proceeded immediately for testing or stored at −20°C until further analysis (storage up to 6 months). Serum and tissue survivin levels were measured using the Human Survivin/BIRC-5 ELISA, kit Catalog number KBB-06E6A2, BioSite, Sweden, according to the manufacturer's instructions. Briefly, the kit consists of a solid phase immunoassay specially designed to measure Human BIRC5 with a 96 well strip plate that is precoated with antibody specific for BIRC-5. The capture and the detection antibody are mouse monoclonal and goat polyclonal, respectively. Standard is composed of a recombinant human survivin protein of 34 kD molecular mass. Standard, controls, and samples are tested in duplicate as per the manufacturer's instructions, and the results are read on an ELISA reader at 450 nm. Sensitivity or minimum detectable dose (MDD) is the lower limit of target protein that can be detected by the kit and is < 2 pg/mL, and the range is 62.5–4000 pg/mL.

2.4. Statistical Analysis. Continuous variables are summarized using mean ± standard deviation (SD) or median with 1st–3rd quartiles ($Q1$–$Q3$) based on their distribution. Categorical variables are presented as absolute (n) and relative (%) frequencies. The association between two categorical variables was assessed using Fisher's Exact Test. Differences in continuous variables between two paired groups were assessed using the Wilcoxon Signed-Rank Test or paired t-Test, while differences between two independent groups were analyzed using the two-Sample t-test or the Mann–Whitney U test. Associations between two

continuous variables were assessed using Spearman's Rho. Statistical significance was set at 0.05, with all tests being two-tailed. Data analyses were performed using Stata 17.0.

3. Results

3.1. Participants' Characteristics at Baseline. A total of 32 participants were included in the study, i.e., 16 subjects in each study group. Participants' demographic and clinical characteristics are presented in Tables 1 and 2. Both groups had an equal distribution of sexes, with females representing 25% of each group. There were no statistically significant differences regarding sex, age, BMI, and the presence of comorbidities between the psoriasis and control group. However, a notably higher but not statistically significant proportion of obese individuals was observed in the psoriasis group (43.8% vs. 18.8% in the control group, $p = 0.301$). Similarly, 25% of the control group and 50% of the psoriasis group reported having at least one comorbidity ($p = 0.273$) (Table 1).

3.1.1. Two-Sample t Test With Unequal Variances. The psoriasis group included entirely patients diagnosed with plaque psoriasis (100%). The duration of psoriasis among participants varied widely, with a mean of 13.2 ± 10.6 years. The majority (56.3%) of patients reported a family history of psoriasis, and 37.5% of participants were receiving concomitant medications. Smoking was prevalent among the participants, with 62.5% identifying as smokers (Table 2).

3.2. PASI and DLQI Scores During Follow-Up in Psoriasis Group. The median PASI score decreased from 12.5 (11.8–14.8) at baseline to 0.0 (0.0–0.5) at 12 months, indicating a remarkable improvement in psoriasis severity. The median change in PASI score from baseline was −10.6 (−11.4–−8.1) at 3 months and −12.3 (−14.8–−11.0) at 12 months, with both time points showing statistical significance ($p < 0.001$) (Table 3, Figure 1).

Similarly, DLQI scores decreased from a mean of 15.2 (SD = 2.4) at baseline to 0.1 ± 0.3 at 12 months, highlighting significant improvements in life quality. The mean reduction in DLQI score was 13.1 ± 3.1 at 3 months and 15.1 ± 2.5 at 12 months, with both reductions proving statistical significance ($p < 0.001$) (Table 3, Figure 2).

3.3. Survivin Levels in Psoriasis Group and Comparisons Between Study Groups During Follow-Up. At baseline, the mean value of serum survivin levels was lower at the psoriasis group (24.3 ± 9.5) versus the control group (29.4 ± 18.1), though this difference did not reach statistical significance ($p = 0.329$). The observed reduction of the median serum survivin levels at 3 months in the psoriasis group was statistically nonsignificant compared to baseline levels in the control group ($p = 0.309$). However, at 12 months, the respective reduction reached the level of significance ($p = 0.007$) (Table 4, Figure 3).

At baseline, the upwards differentiated expression of tissue survivin in healthy skin biopsies taken from the psoriasis vs control group was statistically significant ($p = 0.001$). Accordingly, psoriatic skin tissue at baseline

Table 1: Participants characteristics in psoriasis and control groups.

	Control group $N = 16$	Psoriasis group $N = 16$	p^*
Sex, *n* (%)			
Females	4 (25.0%)	4 (25.0%)	0.657
Males	12 (75.0%)	12 (75.0%)	
Age, in years			
Mean (SD)	47.9 (8.4)	50.1 (12.3)	0.562[a]
BMI			
Median (Q1–Q3)	27.6 (25.6, 29.4)	29.3 (25.6, 32.3)	—
BMI, *n* (%)			
Underweight	0 (0%)	0 (0%)	0.301
Normal range	3 (18.8%)	3 (18.8%)	
Overweight	10 (62.5%)	6 (37.5%)	
Obese	3 (18.8%)	7 (43.8%)	
Comorbidities[1], *n* (%)			
At least one	4 (25.0%)	8 (50.0%)	0.273
Dyslipidemia	0 (0.0%)	2 (12.5%)	0.484
Hypertension	2 (12.5%)	5 (31.3%)	0.394
Diabetes	0 (0.0%)	3 (18.8%)	0.226
Arthritis	0 (0.0%)	1 (6.3%)	> 0.999
Renal failure	0 (0.0%)	1 (6.3%)	> 0.999
Thyroid disease	2 (12.5%)	0 (0.0%)	0.484
Asthma	1 (6.3%)	0 (0.0%)	> 0.999

[1]Each participant can have more than one comorbidity.
*Fisher's exact test except otherwise specified.
[a]Two-sample *t* test with unequal variances.

Table 2: Disease characteristics and smoking status at baseline in psoriasis group.

	Psoriasis group $N = 16$
Psoriasis type[1], *n* (%)	
Plaque	16 (100.0%)
Inverse	1 (6.3%)
Genitals	1 (6.3%)
Head	5 (31.3%)
Nails	1 (6.3%)
Psoriasis duration, years	
Mean (SD)	13.2 (10.6)
Family history of psoriasis, *n* (%)	
No	7 (43.8%)
Yes	9 (56.3%)
Comedication[2], *n* (%)	
No	10 (62.5%)
Yes	6 (37.5%)
Smoking, *n* (%)	
No	6 (37.5%)
Yes	10 (62.5%)

[1]Each participant can have more than one psoriasis type.
[2]Each participant can receive more than one comedications.

Table 3: PASI and DLQI scores during follow-up in psoriasis group.

Psoriasis group	Baseline	3 months	12 months
PASI			
Median (Q1–Q3)	12.5 (11.8, 14.8)	2.8 (1.1, 4.7)	0.0 (0.0, 0.5)
Change in PASI from baseline			
Median (Q1–Q3)		−10.6 (−11.4, −8.1)	−12.3 (−14.8, −11.0)
p-value*		**< 0.001**	**< 0.001**
DLQI			
Mean (SD)	15.2 (2.4)	2.1 (1.8)	0.1 (0.3)
Change in DLQI from baseline			
Mean (SD)		−13.1 (3.1)	−15.1 (2.5)
Mean (95% CI)		13.1 (11.5, 14.8)	15.1 (13.8, 16.5)
p value**		**< 0.001**	**< 0.001**

Note: *p* values that are highlighted with bold font indicate statistical significance.
*Wilcoxon signed-rank test.
**Paired *t* test with equal variances.

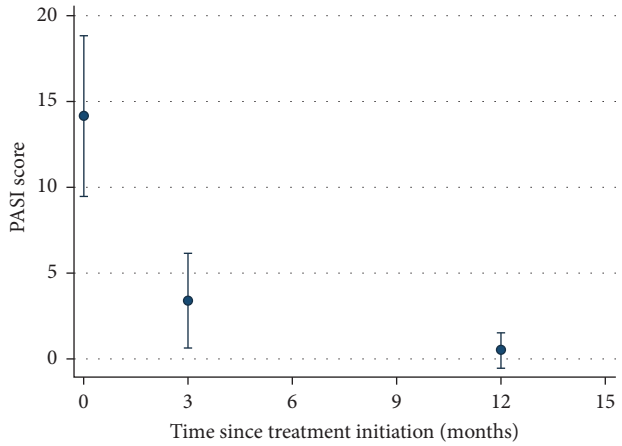

Figure 1: PASI score distribution during follow-up. *Note*: Standard error bar chart.

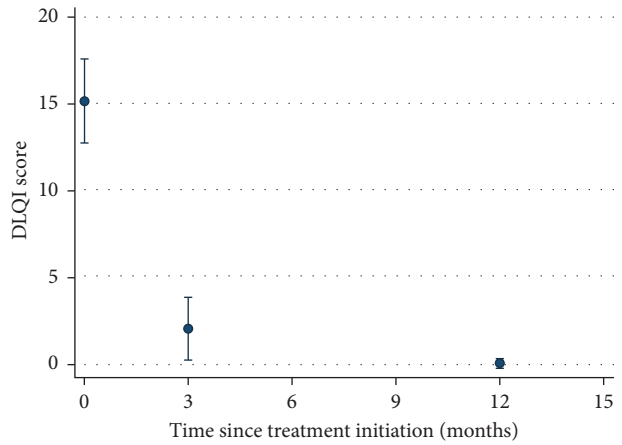

Figure 2: DLQI score distribution during follow-up. *Note*: Standard error bar chart.

exhibited significantly elevated survivin levels compared to healthy skin from the control group ($p < 0.001$). At 12 months, tissue survivin levels in psoriatic skin decreased significantly ($p = 0.046$), which, while showing a reduction to levels akin to healthy skin in the psoriatic group, still differed significantly from the baseline levels of healthy skin in the control group ($p = 0.001$) (Table 4, Figure 4).

At 12 months, the decrease in serum survivin levels was significant compared to baseline, among psoriasis patients ($p = 0.004$, 95% CI 11.2 [4.2, 18.1]). The median difference in survivin levels between healthy and psoriatic skin at baseline was also statistically significant ($p < 0.001$), showing higher tissue survivin levels in psoriatic skin. However, the respective difference in survivin levels between healthy skin at baseline and psoriatic skin at 12 months was not statistically significant. On the contrary, the mean difference between survivin expression in psoriatic skin at baseline and psoriatic skin at 12 months was statistically significant ($p < 0.001$, 95% CI 0.034 [0.022, 0.047]) (Table 5).

From all the associations under investigation, only the change in serum survivin levels from baseline show a moderate to strong negative correlation with the change in DLQI at 3 months, indicating a statistically significant relationship ($p = 0.020$). However, at 12 months, while still negatively correlated, the relationship does not reach statistical significance ($p = 0.138$) (Supporting Table 1, Figure 5).

3.4. Psoriasis Duration Association With Survivin Levels, PASI and DLQI. There are no significant differences in baseline serum or tissue survivin levels, baseline PASI and DLQI scores, and their changes over 3 and 12 months between the two groups. However, notably, the change in PASI from baseline to 3 months (< 10 years with psoriasis: median −9.1; *Q*1, *Q*3: −10.6, −7.1 vs. ≥ 10 years with psoriasis: median −11.3; *Q*1, *Q*3: −11.8, −10.7) shows a statistically significant difference ($p = 0.046$), indicating that patients with a longer duration of psoriasis might experience more substantial improvements in PASI scores in the initial months of treatment (Supporting Table 2, Figure 6).

There are no significant differences in baseline serum or tissue survivin levels between patients with a family history of psoriasis and those without such history. Similarly, no association was identified regarding the change in serum

Table 4: Survivin levels in psoriasis group during follow-up and comparisons with the control group.

	Psoriasis group $N = 16$	Control group $N = 16$	p
Serum survivin at baseline			
Mean (SD)	24.3 (9.5)	29.4 (18.1)	
Mean difference (95% CI)	5.1 (−5.5, 14.7)	0.329[a]	
Serum survivin at 3 months			
Median (Q1, Q3)	19.9 (14.4, 31.0)		0.309[b^]
Serum survivin at 12 months			
Median (Q1, Q3)	12.9 (6.2, 16.8)		**0.007**[b^]
Tissue survivin from healthy skin at baseline			
Median (Q1, Q3)	0.042 (0.031, 0.046)	0.020 (0.015, 0.028)	**0.001**[b]
Tissue survivin from psoriatic skin at baseline			
Median (Q1, Q3)	0.071 (0.061, 0.081)		< **0.001**[b*]
Tissue survivin from psoriatic skin at 12 months	$N = 15$		
Median (Q1, Q3)	0.037 (0.030, 0.046)		< **0.001**[b*]

Note: p values that are highlighted with bold font indicate statistical significance.
^Compared to "Serum survivin at baseline" of control group.
*Compared to "Tissue survivin from healthy skin at baseline" of control group.
[a]Two-sample *t* test with unequal variances.
[b]Mann–Whitney *U* test.

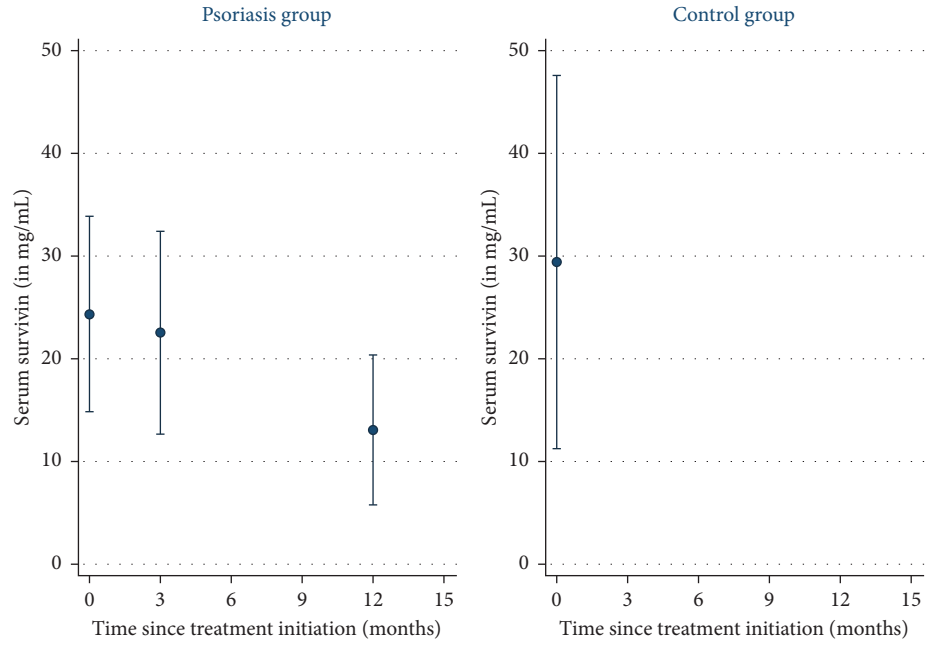

Figure 3: Serum survivin levels in psoriasis and control group during follow-up. *Note*: Standard error bar chart.

survivin or tissue survivin during the study follow-up (Supporting Table 3).

4. Discussion

Over the last decade, significant advancements have been made in understanding the immunopathology and pathogenesis of psoriasis, leading to revolutionary progress in therapeutic approaches. Targeted biologic therapies have provided new hope for psoriasis patients, demonstrating effectiveness in modifying the disease and potentially offering a cure by preventing the accumulation of tissue-resident memory T cells in the skin. Nevertheless, many challenges in treating psoriasis remain unresolved, particularly the toxicity profiles of the novel medications as well as disease relapse after treatment cessation. Thus, a deeper understanding of the mechanisms underlying psoriasis pathophysiology that could lead to early interventions would be highly beneficial.

Several studies have explored the role of survivin in psoriasis. Indeed, this member of the IAP family has been associated with keratinocyte hyperplasia, immune pathogenesis, and other psoriasis-related processes, via several signaling pathways, such as (i) the promotion of the PI3K/AKT/mTOR signaling cascade [10–12], (ii) the nuclear factor kappa B (NF-κB) pathway [5, 13], and (iii) the Wnt/-

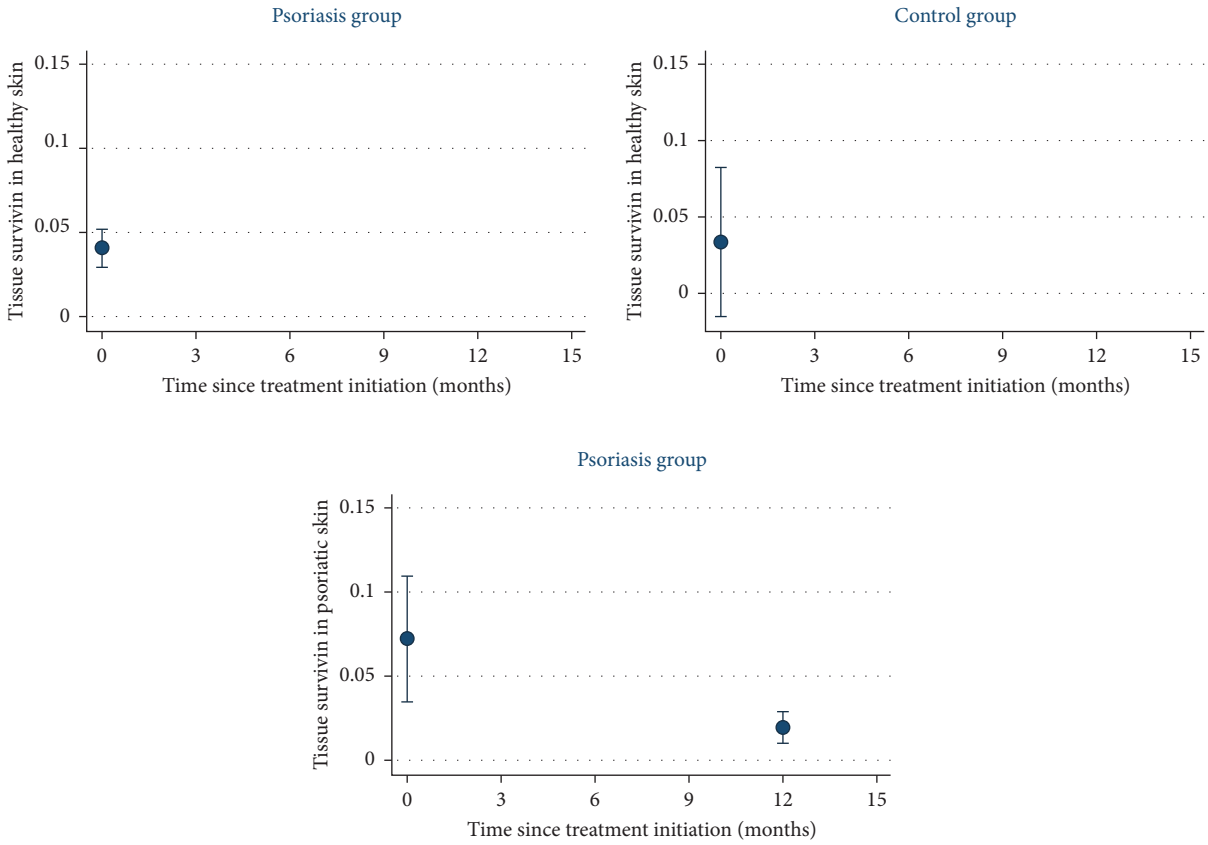

Figure 4: Tissue survivin levels in psoriasis and control group during follow-up. *Note*: Standard error bar chart.

Table 5: Survivin levels during follow-up in psoriasis group.

	Psoriasis group ***N*** **= 16**
Change in serum survivin from baseline to 3 months	
Median (*Q*1–*Q*3)	−3.900 (−7.000, 3.550)
p value	0.404*
Change in serum survivin from baseline to 12 months	
Mean (SD)	−11.194 (13.04)
Mean difference (95% CI)	11.2 (4.2, 18.1)
p value	< **0.004****
Difference in tissue survivin from healthy skin at baseline and psoriatic skin at baseline	
Median (*Q*1–*Q*3)	0.030 (0.020, 0.042)
p value	< **0.001***
Difference in tissue survivin from healthy skin at baseline and psoriatic skin at 12 months	*N* = 15
Median (*Q*1–*Q*3)	−0.001 (−0.015, 0.002)
p value	0.309*
Difference in tissue survivin from psoriatic skin at baseline and psoriatic skin at 12 months	*N* = 15
Mean (SD)	−0.034 (0.02)
Mean difference (95% CI)	0.034 (0.022, 0.047)
p value	< **0.001****

Note: p values that are highlighted with bold font indicate statistical significance.
*Wilcoxon signed-rank test.
**Paired *t* test with equal variances.

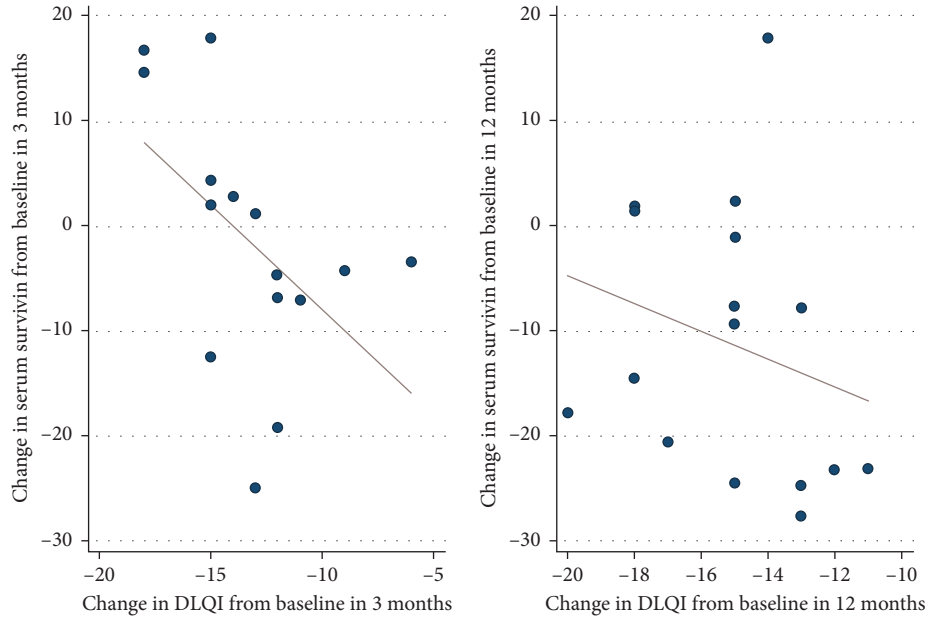

Figure 5: Change in serum survivin with change in DLQI from baseline to 3 months and 12 months.

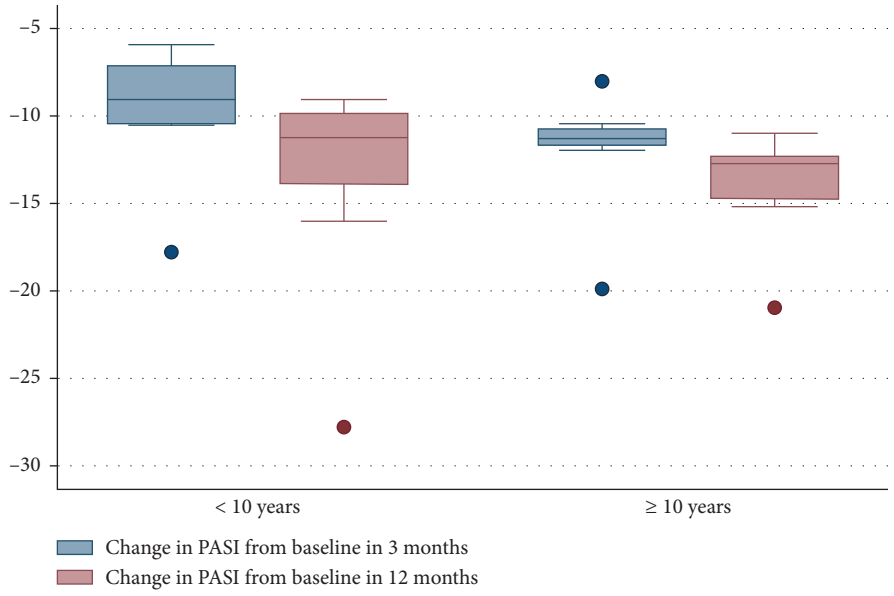

Figure 6: Change in PASI from baseline in 3 and 12 months stratified by psoriasis duration.

Catenin and Wnt5a/Ca^{2+} pathways [14]. However, very few studies have been conducted evaluating survivin expression simultaneously in peripheral blood and tissues of bionaïve psoriatic patients and investigating the effect of a biological treatment, compared to healthy controls. To be more specific, during our bibliographic research, only one study was identified, carried out by Markham et al. [6]. In this work, the authors investigated and reported the effect of infliximab (an anti-TNF-alpha agent) on survivin levels in psoriatic tissues before and after 3 months of treatment. Having said that, to the best of our knowledge, this is the first study that explores the expression of survivin protein in both skin and serum samples derived from bio- and conventional treatment-naïve, psoriatic patients, before and after a 12-month treatment with an anti-IL17RA inhibitor, as compared to a control group (healthy volunteers).

Despite that the abundant survivin levels in the peripheral blood of psoriatic patients have already been investigated and reported [2, 15], our results showed lower levels of suvivin in the psoriasis group, without however reaching statistical significance. On the other hand, our study results are in line with previous findings supporting that survivin is present in higher concentrations in the skin biopsies of psoriatic patients compared to healthy individuals [6, 7]. Furthermore, we also discovered that the levels of survivin in the skin are significantly reduced after

treatment with brodalumab, although they do not reach those of healthy individuals. This may suggest that survivin could serve as a valuable biomarker for monitoring patients' response to anti-IL17RA treatment. Furthermore, the present study found that not only serum pretreatment survivin levels were significantly decreased after 1 year of brodalumab therapy but also they were even lower when compared to those of the control group.

The precise mechanisms by which brodalumab-induced cell apoptosis is mediated are subject to further investigation. However, the potential effect of brodalumab in the IAP family protein survivin could be summarized as follows: IL-6 has been known to induce tyrosine phosphorylation of Stat3 protein by Janus kinase, which in turn promotes survivin gene expression, thus conferring resistance to apoptosis [16, 17]. On this basis, we could hypothesize that Il-17 RA inhibitors suppress survivin expression and therefore induce apoptosis and autophagic cell death via the inhibition of the IL-17-triggered release of IL-6 and the consequent inactivation of the STAT3 and NF-κB pathways. Nevertheless, this theoretical assumption requires more experimental and/or clinical evidence to be valid.

Parallel to the notable reduction in serum and tissue survivin expression, our research showed that brodalumab therapy led to a remarkable improvement in disease severity, as reflected by PASI and DLQI scores, both after 3 and 12 months from the initiation of treatment. However, our study failed to significantly correlate survivin protein levels with PASI at 3 and 12 months, as opposed to Markham et al. results, according to which survivin expression before and after 3 months of infliximab treatment were significantly associated with PASI and BSA scores [6]. This may be attributed to the small study population, and therefore we suggest that further larger scale research is needed, in order to draw more reliable conclusions. Nevertheless, despite our results did not reach statistical significance at 12 months, they do reveal a statistically significant negative correlation between the change in DLQI at 3 months and serum survivin levels. This indicates that patients may experience more substantial improvements in quality of life during the initial course of brodalumab treatment. In line with this, our results demonstrate a positive correlation between the change in PASI after 3 months of treatment, suggesting that patients with a longer personal history of psoriasis might experience more substantial improvements in PASI scores during the initial months of treatment.

As already mentioned, this is the first prospective, case-control study to investigate serum and tissue survivin levels in psoriatic patients under brodalumab therapy. Besides including a well-defined population—in terms of preceding therapies—by including only bio- and conventional treatment-naive patients, another strength of our work is associated with the longitudinal follow-up period, which extended to 12 months. The latest offers a significant advantage in observing the mid-term efficacy and tolerability of brodalumab, as well as the durability of its effects on psoriasis over a period of 12 months.

However, there are several important limitations in our study, mainly inherent to its pilot, case-control nature, and thus careful interpretation of our findings is proposed. First of all, larger-scale studies should be conducted in order to enhance the generalizability and validity of our findings. The current work aims to provide initial insights that will trigger the conduct of future, larger-scale studies to examine further the robustness of the observed outcomes. Other limitations include (i) the lack of randomization, conferring a risk for selection bias, (ii) the potentially unequal distribution of confounding factors between the study arms, and (iii) causal inference limitations. To mitigate the risk of selection bias, we implemented strict inclusion and exclusion criteria to ensure that our participant groups were homogeneous in terms of baseline characteristics (i.e., patients with moderate to severe plaque psoriasis with no prior exposure to biologics), in order to create a more balanced comparison with the healthy control group. Additionally, we collected baseline demographic and clinical data to identify any discrepancies between the groups. We should also reckon that in the absence of an active comparator or a placebo group, specific effects of brodalumab versus psoriasis' natural progression or versus placebo effects are challenging to be differentiated. Moreover, this is a single-center study, and thus the patient population may not fully represent the broader psoriasis community. Future research should focus on multicenter designs with larger sample sizes, ideally incorporating strategies to randomly assign participants to treatment and control groups. Furthermore, another point to be addressed relates to potential sex hormonal influences on psoriasis activity or treatment response, while equal distribution over the arms for female and male subjects was implemented in order to ensure that our participant groups were homogeneous, further investigation in larger cohorts could offer valuable input regarding hormonal differences and disease burden amongst psoriasis patients. Finally, our findings on survivin levels correspond to medium term responses to brodalumab treatment, since this pilot study employed a 12-month follow-up period; longer follow-up would provide important information regarding the sustainability and long-term efficacy of survivin as a biomarker for psoriasis.

In conclusion, our study provides the first evidence that serum and tissue survivin expression may serve as a potential biomarker in patients treated with anti-IL17 RA medications, towards the biomarker-guided individualization of psoriasis therapy. Larger-scale research should be conducted to validate our findings.

Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Ethics Statement

This study was reviewed and approved by the scientific committee of Tzaneio General Hospital with approval protocol number 10557/24.07.2020.

The patients in this manuscript have given written informed consent to the publication of their case details.

Conflicts of Interest

Eleftheria Tampouratzi reports personal fees and/or grants from AbbVie, LEO Pharma, Janssen, Sanofi, Genesis Pharma, UCB, Mylan, and Novartis. Athanasios Chaniotis is an employee of Leo Pharma Hellas. George Pesiridis is an employee of Leo Pharma Hellas. Efthymios Stathatos is an employee of Leo Pharma Hellas. Konstantinos Sfaelos is an employee of Leo Pharma Hellas. The other authors declare no conflicts of interest.

Author Contributions

Eleftheria Tampouratzi: writing–original draft (lead).

John Katsantonis: writing–review and editing (equal).

Athanasios Chaniotis: funding acquisition (equal) and project administration (equal).

George Pesiridis: funding acquisition (equal), project administration (equal), and resources (equal).

Efthymios Stathatos: funding acquisition (equal) and project administration (equal).

Artemis Tsega: data curation (equal).

Panagiotis Dikeakos: conceptualization (equal).

Petros Karkalousos: software (equal).

Konstantinos Asonitis: data curation (equal).

Emmanouil Georgiadis: software (equal).

Konstantinos Sfaelos: funding acquisition (equal), methodology (equal), project administration (equal), supervision (equal), and validation (equal).

Funding

This study was funded by LEO Pharmaceutical Hellas S.A.

Acknowledgments

This study was funded by LEO Pharmaceutical Hellas S.A.

Supporting Information

Additional supporting information can be found online in the Supporting Information section. *(Supporting Information)*

The manuscript includes the following Supporting Information: Supporting Table 1 titled: Correlations of change in survivin with several factors in psoriasis group, Supporting Table 2 titled: Effect of psoriasis duration in survivin levels, PASI and DLQI in psoriasis group, and Supporting Table 3 titled: Effect of family history of psoriasis in survivin levels in psoriasis group.

References

[1] World Health Organisation, "Global Report on Psoriasis," (2016), https://www.who.int/publications/i/item/global-report-on-psoriasis.

[2] U. Akpinar, G. Gur Aksoy, Y. Hayran, E. Firat Oguz, and B. Yalcın, "Serum Levels of Survivin in Patients With Psoriasis and Their Relation to Disease Characteristics," *Journal of Cosmetic Dermatology* 21, no. 4 (2022): 1721–1726, https://doi.org/10.1111/jocd.14318.

[3] G. Ambrosini, C. Adida, and D. C. Altieri, "A Novel Anti-Apoptosis Gene, Survivin, Expressed in Cancer and Lymphoma," *Nature Medicine* 3, no. 8 (1997): 917–921, https://doi.org/10.1038/nm0897-917.

[4] A. R. Bowen, A. N. Hanks, K. J. Murphy, S. R. Florell, and D. Grossman, "Proliferation, Apoptosis, and Survivin Expression in Keratinocytic Neoplasms and Hyperplasias," *The American Journal of Dermatopathology* 26, no. 3 (2004): 177–181, https://doi.org/10.1097/00000372-200406000-00001.

[5] A. G. Abdou and H. M. Hanout, "Evaluation of Survivin and NF-κB in Psoriasis, an Immunohistochemical Study," *Journal of Cutaneous Pathology* 35, no. 5 (2008): 445–451, https://doi.org/10.1111/j.1600-0560.2007.00841.x.

[6] T. Markham, C. Mathews, S. Rogers, et al., "Downregulation of the Inhibitor of Apoptosis Protein Survivin in Keratinocytes and Endothelial Cells in Psoriasis Skin Following Infliximab Therapy," *British Journal of Dermatology* 155, no. 6 (2006): 1191–1196, https://doi.org/10.1111/j.1365-2133.2006.07522.x.

[7] O. Simonetti, G. Lucarini, A. Campanati, et al., "VEGF, Survivin and NOS Overexpression in Psoriatic Skin: Critical Role of Nitric Oxide Synthases," *Journal of Dermatological Science* 54, no. 3 (2009): 205–208, https://doi.org/10.1016/j.jdermsci.2008.12.012.

[8] N. A. Nagui, R. M. Abdel Hay, and L. A. Rashed, "Effect of Narrow Band Ultraviolet B on Survivin in Psoriatic Skin Lesions," *European Journal of Dermatology* 21, no. 6 (2011): 866–869, https://doi.org/10.1684/ejd.2011.1496.

[9] K. Gunduz, P. Temiz, G. Gencoglan, I. Inanir, and A. Catalkaya, "Expression of Nuclear Factor Kappa B and Survivin in Psoriasis," *ISRN Dermatology* 2012 (2012): 1–4, https://doi.org/10.5402/2012/257059.

[10] H. Wang, L. W. Ran, K. Hui, X. Y. Wang, and Y. Zheng, "[Expressions of Survivin, PI3K and AKT in Keratinocytes in Skin Lesions and Their Pathogenic Role in Psoriasis Vulgaris]," *Nan Fang Yi Ke Da Xue Xue Bao* 37, no. 11 (2017): 1512–1516, https://doi.org/10.3969/j.issn.1673-4254.2017.11.14.

[11] L. Mercurio, C. Albanesi, and S. Madonna, "Recent Updates on the Involvement of PI3K/AKT/mTOR Molecular Cascade in the Pathogenesis of Hyperproliferative Skin Disorders," *Frontiers of Medicine* 8 (April 2021): 665647, https://doi.org/10.3389/fmed.2021.665647.

[12] J. C. Chamcheu, M. I. Chaves-Rodriquez, V. M. Adhami, et al., "Upregulation of PI3K/AKT/mTOR, FABP5 and PPARβ/δ in Human Psoriasis and Imiquimod-Induced Murine Psoriasiform Dermatitis Model," *Acta Dermato-Venereologica* 96, no. 6 (2016): 854–856, https://doi.org/10.2340/00015555-2359.

[13] M. Tsubaki, N. Ogawa, T. Takeda, et al., "Dimethyl Fumarate Induces Apoptosis of Hematopoietic Tumor Cells via Inhibition of NF-κb Nuclear Translocation and Down-Regulation of Bcl-xL and XIAP," *Biomedicine & Pharmacotherapy* 68, no. 8 (2014): 999–1005, https://doi.org/10.1016/j.biopha.2014.09.009.

[14] Y. Zhang, C. Tu, D. Zhang, et al., "Wnt/β-Catenin and Wnt5a/Ca^{2+} Pathways Regulate Proliferation and Apoptosis of Keratinocytes in Psoriasis Lesions," *Cellular Physiology and Biochemistry* 36, no. 5 (2015): 1890–1902, https://doi.org/10.1159/000430158.

[15] H. Hassan, A. State, S. Esmail, and A. S. Hasan, "Serum Level of Survivin in Patients With Psoriasis Vulgaris and Its Relation to Disease Severity," *The Egyptian Journal of Hospital Medicine* 90, no. 2 (2023): 2363–2369, https://doi.org/10.21608/ejhm.2023.286011.

[16] T. Gritsko, A. Williams, J. Turkson, et al., "Persistent Activation of stat3 Signaling Induces Survivin Gene Expression and Confers Resistance to Apoptosis in Human Breast Cancer Cells," *Clinical Cancer Research* 12, no. 1 (2006): 11–19, https://doi.org/10.1158/1078-0432.ccr-04-1752.

[17] X. W. Chen and S. F. Zhou, "Inflammation, Cytokines, the IL-17/IL-6/STAT3/NF-κB Axis, and Tumorigenesis," *Drug Design, Development and Therapy* 9 (2015): 2941–2946, https://doi.org/10.2147/dddt.s86396.