Dermatol Ther (Heidelb) (2023) 13:1377–1387
https://doi.org/10.1007/s13555-023-00931-1

BRIEF REPORT

InflammamiR-146a and -155 Plasma Levels are Associated with Clinical Efficacy of Risankizumab Treatment in Psoriatic Patients: Pilot Study

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Received: March 6, 2023 / Accepted: April 17, 2023 / Published online: May 17, 2023

ABSTRACT

Introduction: The key role of microRNAs (miRNAs) in the pathogenesis of psoriasis has been extensively discussed in the literature. Increasing evidence suggests that the analysis of miRNA levels may constitute an innovative approach for exploring the clinical efficacy of anti-inflammatory therapies in patients with psoriasis. However, so far there have been no published studies evaluating the effects of modulating circulating miRNAs and the efficacy of anti-interleukin-23 (anti-IL-23) therapy. The main objective of the present was to evaluate the diagnostic/prognostic relevance of the levels of five circulating candidate miRNAs (miR-21, miR-146a, miR-155, miR-210, miR-378) in psoriatic patients treated with the anti-IL-23 drug risankizumab.

Methods: A total of eight psoriatic participants were recruited consecutively from January 2021 to July 2021 at the Dermatology Clinic of Università Politecnica delle Marche (UNIVPM) "Ospedali Riuniti" of Marche. Data on anamnestic, clinical and miRNA evaluations before the initiation of risankizumab therapy and after 1 year (January 2021–July 2022) of risankizumab therapy were available for all patients.

Results: A significant reduction in the signs and symptoms in patients treated with risankizumab was observed after 1 year of treatment, suggesting that the drug is effective for treating psoriasis in a context of real-life clinical evaluation. Plasma levels of the two prototypical inflammamiRs, miR-146a and miR-155, were significantly reduced after 1 year of risankizumab therapy. Also, in patients before treatment, a significant positive correlation was found between circulating levels of miR-210 and miR-378 and disease severity scores.

Conclusions: Our results reinforce the notion that specific circulating miRNAs could have clinical relevance as diagnostic/prognostic

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biomarkers of psoriatic disease and suggest the potential relevance of these miRNAs as biomarkers of treatment response.

Keywords: Psoriasis; Psoriatic treatment; Risankizumab; miRNAs; miR-146a; miR-155

Key Summary Points
Why carry out this study?
The expression of several microRNAs (miRNAs) is deregulated in the psoriatic skin, with serum levels of four miRNAs having been found to differ between healthy subjects and untreated psoriatic patients.
Biological therapy with anti-interleukin - 23 (anti-IL-23) is effective for treating psoriasis.
What was learned from this study?
Plasma levels of two miRNAs associated with the modulation of inflammation, namely miR-146a and miR-155, were found to be reduced in psoriatic patients after anti-IL-23 therapy.
Circulating levels of miR-146a and miR-155 could be innovative markers of systemic anti-IL-23 therapy efficacy.
Plasma levels of two miRNAs, miR-210 and miR-378, correlated with psoriatic severity prior to treatment (baseline).

INTRODUCTION

MicroRNAs (miRNAs) are short, endogenous, non-coding RNA molecules that play important roles in modulating gene expression in human health and disease [1]. The key role of miRNAs in regulating hyper-proliferation, keratinocyte differentiation, apoptosis and dysregulated immune response in psoriasis has been extensively discussed in the literature [2–4]. Since psoriasis is an immune-mediated inflammatory disease supported by inflammatory pathways in which T helper 1 (Th1) lymphocytes play a fundamental role, miRNAs modulating the inflammatory response could be involved in the heterogeneity of psoriatic features and in clinical responses to treatment.

There are increasing efforts to identify psoriasis-associated miRNAs by applying "-omics" analyses, but conclusive results are lacking [5]. Interestingly, several studies have identified a number of circulating miRNAs whose levels were significantly modulated in psoriatic patients after anti-tumor necrosis factor alpha (TNF-α) therapy [6, 7]. Some of these miRNAs, for example, miR-146a, are typical inflammamiRs (i.e. miRs capable of regulating the inflammatory status) since they can modulate the inflammatory response [8]. MiR-146a plasma levels were previously found to be significantly correlated with anti-TNF-α clinical efficacy in patients affected by psoriasis [7].

However, the effect of anti-IL-23 therapy on plasma miRNAs has not been investigated to date. Risankizumab is a humanized monoclonal antibody that exclusively binds and inhibits IL-23, resulting in a reduction of the inflammatory cascade and decreased infiltration, keratinocyte proliferation and epidermal thickness [9]. Furthermore, thanks to its molecular characteristics, including its high affinity for IL-23, risankizumab appears to have a rapid effect in reducing the symptoms and signs of psoriasis, with an improvement in patients' quality of life, even in subjects not responding to other biological drugs [10–13].

The overall focus of the present study was to determine whether risankizumab affects plasma miRNA levels in psoriatic patients. To this end, we selected five miRNAs, namely miR-21, miR-146a, miR-155, miR-210 and miR-378, that have been identified as deregulated during psoriasis, either in the blood or in diseased tissue samples [14]. The primary target of this study was the evaluation of the association between miRNA expression levels and risankizumab clinical efficacy. Secondly, we aimed to explore eventual correlations between miRNA levels and the clinical features of psoriasis patients prior to treatment (baseline [T0]).

METHODS

Patients

A total of eight ($n = 8$) psoriatic participants were recruited consecutively from January 2021 to July 2021 at the Dermatology Clinic of Università Politecnica delle Marche (UNIVPM) "Ospedali Riuniti" of Marche. Plasma samples were collected from these eight patients before the initiation and 12 months after the initiation of risankizumab therapy (150 mg subcutaneously at week 0, after 4 weeks and then every 12 weeks) [8]. Selected patients underwent anamnestic and clinical evaluations before and after 1 year (from January 2021 and July 2022) of risankizumab therapy. The physical examination and assessment of the severity of the disease were carried out using the following parameters: PASI (Psoriasis Area Severity Index), BSA (body surface area), PGA (Physician Global Assessment) and DLQI (Dermatology Life Quality index).

Patients attended monthly follow-up appointments for clinical evaluation and reporting of any adverse events.

The inclusion criteria were: (1) patients aged > 18 years who had moderate to severe plaque psoriasis according to national and international guidelines [9]; (2) patients who had not received any local or systemic treatment with corticosteroids or immunosuppressive therapy 1 month before enrollment; and (3) patients eligible for biological therapy with anti-IL-23 agents.

The exclusion criteria were: (1) patients suffering from major cardiovascular, cerebrovascular, hepatic, renal and hematopoietic diseases; (2) female patients who were pregnant or lactating; and (3) non-compliant patients.

This study was performed in accordance with the Helsinki Declaration of 1964 and its later amendments. The ethics committee of UNIVPM approved the study protocol, and all enrolled participants provided written informed consent. The patients reported in this manuscript have provided written informed consent to the publication of their case details.

RNA Isolation and Mature MiRNA Expression by Quantitative Real-Time PCR

To evaluate the expression of circulating miRNAs, we first collected 5 ml of blood samples both at the beginning and at the end of the observational period. The blood samples were centrifuged within 2 h of collection at 1800 RPM for 10 min to separate out the plasma. The plasma was then aliquoted and frozen at − 80 °C. Total RNA was isolated from 100 µl of plasma using the Norgen Biotek Total RNA Purification Kit (catalog #37500; Norgen Biotek Corp., Thorold, ON, Canada), according to the manufacturer's instructions.

MiRNA expression was quantified by quantitative real-time PCR (RT-qPCR) using the TaqMan miRNA assay (catalog #4427012; Thermo Fisher Scientific, Waltham, MA, USA) according to the manufacturer's protocol. Data were analyzed using the Rotor Gene Q real-time PCR cycler (Qiagen, Hilden, Germany) with the automatic comparative threshold (Ct) setting for adapting the baseline. The plasma levels of circulating miRNAs were reported as relative expression normalized to the mean of spiked-in miRNA cel-miR-39. The $2^{-\Delta CT}$ method was used to determine miRNA expression.

Bioinformatic Analysis

The prediction of the Kyoto Encyclopedia of Genes and Genomes (KEGG) pathways was achieved with the DNA intelligent analysis (DIANA)-mirPath online software suite [14] in order to individualize the pathways potentially altered by the deregulated miRNAs.

Statistical Analysis

All data were analyzed using SPSS/Win statistical software (version 25.0; SPSS IBM Corp., Armonk, NY, USA). Variables were reported as the mean ± standard deviation (SD). Comparisons between variables were performed using the paired *t*-test. The Spearman's rho correlation test was used to estimate the correlations between miRNA expression levels and clinical

parameters. A p-value < 0.05 was considered to show statistical significance.

RESULTS

Patient Characteristics

Among the patients who attended the Dermatological Clinic of UNIVPM—"Ospedali Riuniti" of Ancona between January 2021 and July 2021, we recruited eight individuals ($n = 8$) for risankizumab therapy. Plasma samples were available for all patients. The clinical characteristics and baseline demographics of these eight patients are shown in Table 1.

All observed patients had moderate to severe plaque psoriasis at baseline (T0); none had other variants of psoriasis (erythrodermal, suberitrodermal, pustular psoriasis etc.) and psoriatic arthritis.

At T0, the average (± SD) disease duration was 15.6 ± 14 (range 1–46) years. The average age at diagnosis was 29.3 years. Among the eight patients, one reported a positive family history of psoriasis; six exhibited involvement of special sites, of which two patients showed involvement of two special sites; one had lesions on the face; one had palmoplantar psoriasis; two had lesions on the scalp; and two had palmoplantar and scalp lesions.

In terms of previous treatments, all patients had used disease-modifying antirheumatic drugs (DMARDs) without success. Of the eight patients, four had used acitretin, six had used cyclosporine, three had used methotrexate and one has used apremilast.

Six patients were naïve to biologic therapy. Of the two patients who had previous experience with biologics, one had experienced failed combination therapy with one biological drug and one small molecule (adalimumab and apremilast) and one had experienced failed combination therapy with three biological drugs (adalimumab, certolizumab, etanercept).

At T0, the average (± SD) PASI score was 19.9 ± 14.8 (range 3–33.2). Five patients had PASI score between 10 and 20, while three patients had PASI score > 20. Average BSA was 27.8 ± 0.2% (range 3–75%), average PGA was 3.3 ± 0.5

Table 1 Patient baseline demographic and clinical characteristics

Variables	Values for $N = 8$ patients
Age (years)	44.9 ± 12.5
Gender (male)	5 (62.5%)
Weight (kg)	83.3 ± 16.6
BMI (kg/m^2)	27.3 (5.1)
Smokers	3 (37.5%)
Comorbidity, n (%)	
Dyslipidemia	1 (12.5%)
Hypertension	1 (12.5%)
Diabetes mellitus type 2	1(12.5%)
Atopy	1 (12.5%)
Anxiety-depressive disorders	1 (12.5%)
Thyroiditis	2 (25%)
Age of psoriasis onset (years)	29.3 ± 15.1 (range 10–64)
Duration of psoriasis (years)	15.6 ± 14 (range 1–46)
Family history of psoriasis	1 (12.5%)
Patients with special sites involvement	6 (75%)
Two special sites	2 (25%)
Facial lesions	1 (12.5%)
Palmoplantar lesions	3 (37.5%)
Scalp lesions	4 (50%)
Previous treatments with DMARDs	
Acitretin	4 (50%)
Cyclosporine	6 (75%)
Methotrexate	3 (37.5%)
Apremilast	1 (12.5%)
Previous treatment with biologics	
No	6 (75%)
Yes	2 (25%)
1 biologic	1 (12.5%)

Table 1 continued

Variables	Values for $N = 8$ patients
2 biologics	0
≥ 3 biologics	1 (12.5%)
PASI	19.9 ± 14.8 (range 3–33.2)
BSA	27.8 ± 0.2 (range 3–75)
PGA	3.3 ± 0.5 (range 3–4)
DLQI	7.1 ± 3.6 (range 2–15)

Values in table are presented as the mean ± standard deviation (SD), with or without the range in parentheses, or as the count (number of patients) with the percentage in parentheses

BMI Body mass index, *BSA* body surface area, *DLQI* Dermatology Quality of Life Impairment, DMARDs disease-modifying antirheumatic drugs, *PASI* Psoriasis Area Severity Index, *PGA* Physician Global Assessment

(range 3–4) and average DLQI was 7.1 ± 3.6 (range 2–15).

Changes in PASI, BSA, PGA, DLQI

After 1 year of treatment (T1), all of patients achieved PASI 50 and PASI 75 (50% and 75% reduction, respectively, in PASI), with seven patients achieving PASI 90 and six patients achieving PASI 100 (90% reduction and complete disease resolution, respectively). At T1, average (± SD) PASI score was 0.4 ± 0.8 (range 0–2; $p < 0.0007$), average BSA was 0.4 ± 0.01 (range 0–2; $p < 0.0018$), average PGA was 0.25 ± 0.5 (range 0–1; $p < 0.0001$); and average DLQI was 0.25 ± 0.5 (range 0–1; $p < 0.00008$). The results are reported in Table 2 and Fig. 1.

No patient reported adverse events during the follow-up period. No modification of any biological parameter was found in the treated patients.

Table 2 Psoriasis Area Severity Index, body surface area, Physician Global Assessment and Dermatology Life Quality index for patients pre-risankizumb treatment and at 1 year after initiation of risankizumab treatment

Parameters	T0	T1	*p*
PASI	19.9 ± 14.8 (3–33.2)	0.4 ± 0.8 (range 0–2)	0.0007*
BSA	27.8 ± 0.2 (3–75)	0.4 ± 0.01 (0–2)	0.0018*
PGA	3.3 ± 0.5 (3–4)	0.25 ± 0.5 (0–1)	0.0001*
DLQI	7.1 ± 3.6 (2–15)	0.25 ± 0.5 (0–1)	0.00008*

Values in table are presented as the mean ± SD with the range in parentheses

*Statistical significant difference between T0 and T1 at $p < 0.05$

T0 Baseline (pre-risankizumb treatment), *T1* 1 year after initiation of risankizumb treatment

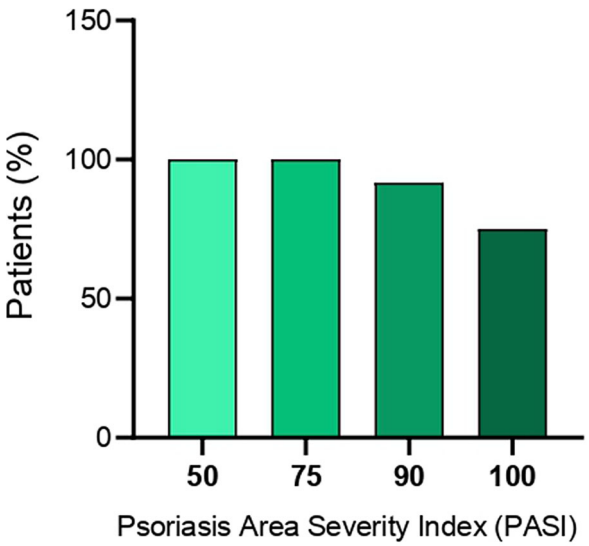

Fig. 1 Percentage of patients with psoriasis achieving PASI 50, PASI 75, PASI 90, PASI 100 at 1 year after treatment initiation with risankizumab. *PASI 50, PASI 75, PASI 90, PASI 100* represent the 50%, 75%, 90%, 100% (complete resolution) improvement from baseline (T0) PASI score

Table 3 Expression levels of microRNAs in plasma samples collected from patients at pre-treatment (baseline) and at 1 year after initiation of risankizumab therapy (n = 8 patients)

MicroRNAs	T0	T1	p
miR-21	0.0498 (± 0.035)	0.02851 (± 0.014)	0.83
miR-146a	0.0038 (± 0.003)	0.0021 (± 0.002)	**0.019***
miR-155	0.000147 (± 0.00007)	0.000083 (± 0.00002)	**0.041***
miR-210	0.000152 (± 0.00009)	0.000110 (± 0.00004)	0.26
miR-378	0.000038 (± 0.000025)	0.000020 (± 0.000010)	0.11

Values in table are presented as the mean ± SD
*Statistical significant difference between T0 and T1 at $p < 0.05$

Variations in Circulating miRNA Levels After Risankizumab Therapy

The circulating levels of miR-21, miR-146a, miR-155, miR-210 and miR-378 were quantified. The relative expression levels of each of these five miRNAs in the plasma samples collected from each patient were compared between the pre-treatment (T0) levels and 1-year post-risankizumab therapy (T1) levels.

We observed that miRNA levels in samples collected at pre-treatment (T0) were lower than those in samples collected after 1 year of treatment with risankizumab (T1). This reduction was statistically significant for miR-155 (p = 0.041) and miR-146a (p = 0.019) (Table 3; Fig. 2).

To identify the most relevant pathways enriched in genes targeted by miR-155 and miR-146a, we used the DIANA miRPath tool [15]. Figure 3 shows the heatmap based on the significance of the interaction between these two miRNAs and the target pathways as determined by Fisher's exact test. Interestingly, the signaling of nuclear factor kappa-light-chain-enhancer of activated B cells (NF-kB) is the only significant target pathway in common between miR-155 and miR-146a.

The correlation between the plasma levels of the five selected miRNAs at T0 and the PGA at T0 was also examined. As shown in Fig. 4, the levels of miR-210 and miR-378 exhibited a positive and statistically significant correlation with the PGA value in pre-treatment patients (r = 0.756; p = 0.030 for both).

Taken together, these results suggest that the plasma levels of miR-210 and miR-378 could be correlated with disease activity.

DISCUSSION

Psoriasis is an immune-mediated inflammatory disease caused by a dysregulation of the immune system supported by an overexpression of multiple cytokines, characterized by an accelerated keratinocyte turnover [11]. Risankizumab is a high-affinity humanized monoclonal antibody specific for the p19 subunit of interleukin-23 (IL-23p19). IL-23 is hyper-produced by dendritic cells and keratinocytes in psoriatic patients [9]. In the present study, we observed a significant reduction in the signs and symptoms of psoriasis in patients treated with risankizumab, as evaluated by PASI, after 1 year of treatment, suggesting that the drug is effective for treating psoriasis in the context of a real-life clinical evaluation. The improvement in the patients' quality of life was also relevant, with a reduction in average DLQI score from 7.1 at T0 to 0.25 at T1. An absolute post-treatment DLQI score < 5, which is considered to be the cutoff value for patients' quality of life, was reached in all patients [16]. Furthermore, no patients reported adverse reactions during the first year of treatment, confirming the safety profile of risankizumab in psoriasis.

Many attempts have been made to identify circulating biomarkers potentially associated with the clinical response to antibody-based

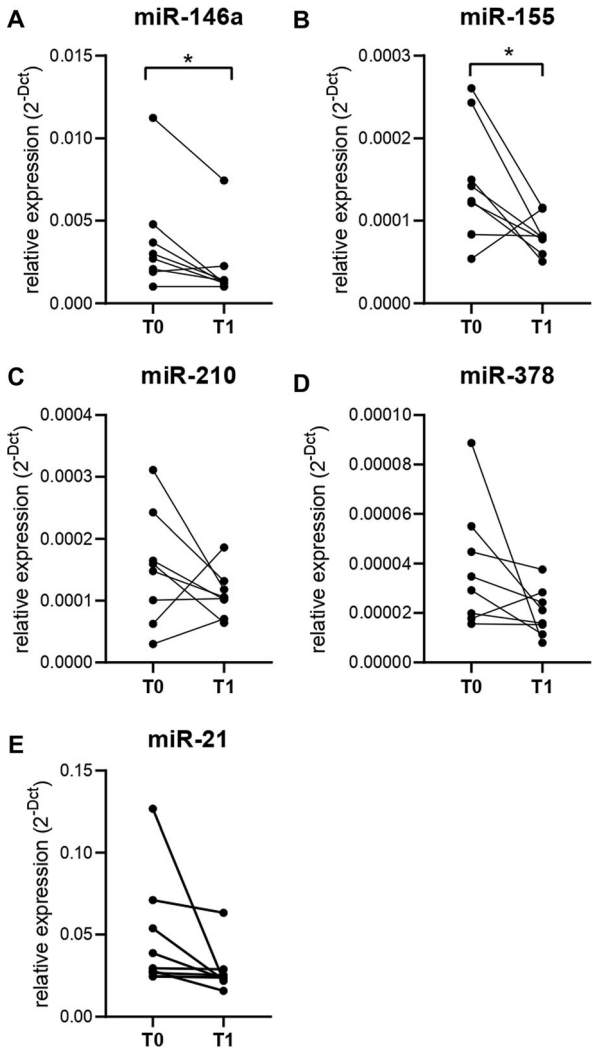

Fig. 2 Quantitative real time PCR expression level of the microRNAs miR-146a (**a**), miR-155 (**b**), miR-210 (**c**), miR-378 (**d**) and miR-21 (**e**) in blood samples collected from patients at pre-treatment (*T0*) and at 1 year after treatment initiation with risankizumab (*T1*). Asterisk indicates a significant difference between sampling time point at $p < 0.05$

therapies, which are characterized by high costs [1].

Recent studies have reported increasing evidence showing that plasma miRNA levels can be useful biomarkers for the diagnosis, prognosis and evaluation of treatment response, as well as potential biopharmaceuticals in various diseases [17–19]. Cheleschi et al. reported circulating mir-140 and serum leptin as possible new biomarkers that could help to discriminate psoriatic arthritis from rheumatoid arthritis, confirming the value of research in this field [20]. For the present study, we selected five miRNAs previously reported to be associated with psoriasis and observed that the circulating levels of two of these, miR-146a and miR-155, were significantly reduced in samples collected from patients after 1 year of therapy with anti-IL-23 agent. MiR-146a and miR-155 are considered to be the prototypical "inflamma-miR" [8], whose expression levels are significantly modulated in numerous pathologies sharing a pro-inflammatory condition. High levels of miR-146a have been observed in the skin, serum and in peripheral blood mononuclear cells (PBMCs) of psoriatic patients, showing a strong positive correlation with IL-17 level [21, 22]. In addition, Taganov et al. found that miR-146a was upregulated by NF-kB in the late phase of inflammation through negative feedback, contributing to the self-limiting of NF-kB signaling involving IL-1 receptor-associated kinase 1 (IRAK1) and TNF-receptor associated factor (TRAF) [23]. Therefore, it has been argued that the miR-146a upregulation in psoriasis is a compensatory mechanism to overcome the exacerbated inflammatory response caused by upregulation of IL-17 so that when inflammation is suppressed by biologic therapy, there is a decrease in miR-146a expression in serum, plasma and PBMCs [7, 22, 24].

MiR-155 levels could promote, through a positive feedback loop, the production of TNF-α [25] and the differentiation of T cells towards a Th1 phenotype [18]. We performed pathway analysis to focus on the involvement of miR-146a and miR-155 in the alteration of psoriasis-related inflammatory signaling. NF-kB, one of the major contributors to the pathogenesis of psoriasis [26], is also a significant target of both miR-155 and miR-146a, and decreased levels of these miRNAs after treatment with risankizumab might be due to the effect of the therapy on the NF-kB pathway.

Also, in untreated patients, miR-210 and miR-378 showed a positive statistically significant correlation with the PGA score. The PGA is a composite tool and can be an alternative to the PASI; it is considered a sensitive tool for

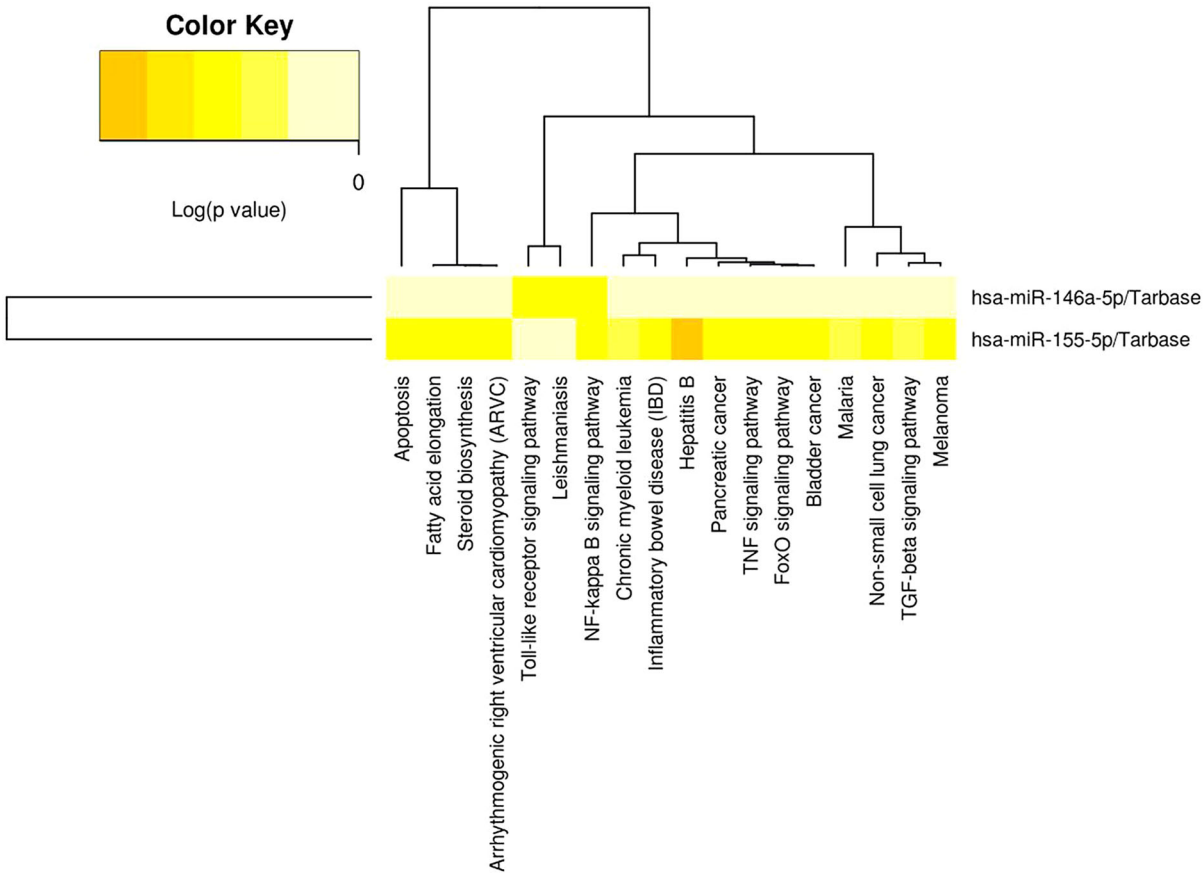

Fig. 3 KEGG pathways enriched in miR-155 and miR-146a target genes. The heatmap of the significant interaction between each miRNA and the target pathway was generated by the DIANA-miRPath tool [15]

assessing psoriasis severity and response to therapy [27, 28].

MiR-210 can contribute to the modulation of inflammation by interfering with the immunosuppressive effects of regulatory T cells [29]. In addition, miR-378a expression level has been reported to be elevated in psoriatic lesions and decreased after treatment with methotrexate or narrow-band ultraviolet B [30].

Overall, our results suggest that miR-155 and miR-146a are related to treatment response whereas miR-210 and miR-378 are positively correlated with disease severity. These results support the increasing research efforts on circulating miRNAs relevance as diagnostic/prognostic biomarkers, and as markers of response to treatments. Further studies are needed to better disentangle the mechanisms underpinning the modulation of miRNAs in psoriasis.

Although our findings on miRNA modulation in the present study are in agreement with those reported in most of the studies published to date, there is one study with opposite results. Shen et al. found that, in psoriatic patients, the decrease in miR-146a and miR-146b levels correlates with exacerbated disease activity, and their longitude increment relates to anti-TNF-α etanercept response [31]. However, the authors cannot justify these results and hypothesize that the different biological samples from which the miRNAs were extracted (plasma, serum or PBMCs) could justify these variations. Furthermore, it needs to be clarified where the authors searched for miRNAs, as the Materials and methods section of their article specifies

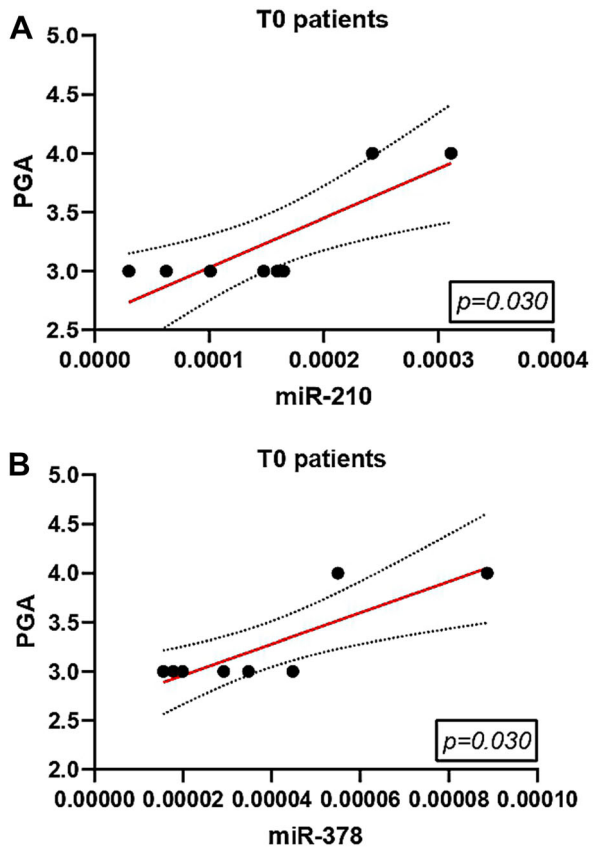

Fig. 4 Correlation between miRNA expression levels and PGA score in pre-treated patients. Spearman correlation between PGA and miR-210 (**A**; $r = 0.756$, $p = 0.030$) and miR- 378 (**B**; $r = 0.756$, $p = 0.030$). PGA Physician Global Assessment

plasma as the source, while the Discussion section mentions PBMCs. Nevertheless, the study does show the pivotal role of miRNAs in regulating inflammation and thereby the potential role of these molecules as biomarkers; as such this study cannot not be neglected.

LIMITATIONS

The main limitation of the present study is the limited size of the study population. Larger, multicenter and possibly prospective studies are needed to identify the cutoff values of the selected miRNAs.

CONCLUSIONS

In summary, of the five miRNAs selected from literature as being related to psoriasis, namely miR-21, miR-146a, miR-155, miR-210 and miR-378, only miR-146a and miR-155 were associated with the 1-year rizankizumab treatment response, whereas miR-210 and miR-378 were positively correlated with disease severity at T0 (untreated patients). These results suggest that specific circulating miRNAs could be not only diagnostic/prognostic biomarkers of psoriatic disease but also potential biomarkers of treatment response.

ACKNOWLEDGEMENTS

The authors thank the participants of the study.

Funding. No funding or sponsorship was received for this study or publication of this article. The Rapid Service Fee was funded by the authors.

Author Contributions. Conceptualization: FD and GM. Methodology: FD and GM. Writing—original draft preparation: FD and GMD. Writing—review and editing: FD and GM. Visualization: AC and JS. Supervision: FO and AO. All authors have read and agreed to the published version of the manuscript.

Ethics and Compliance Guidelines. This study was performed in accordance with the Helsinki Declaration of 1964 and its later amendments. The ethics committee of UNIVPM approved the study protocol and all enrolled participants provided written informed consent. The patients reported in this manuscript have provided written informed consent to the publication of their case details.

Disclosures. The authors have nothing to disclose.

Data Availability. The datasets generated during and/or analyzed during the current

study are available from the corresponding author on reasonable request.

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