

Pemphigus foliaceus patients (Fogo Selvagem) treated with kinesiotherapy presented lower levels of proinflammatory cytokines

Rodolfo Pessato Timóteo^{1,*}, Helioswilton Sales-Campos², Marcos Vinicius Silva¹, Djalma Alexandre Alves da Silva¹, Jonatas Da Silva Catarino¹, Marlos Aureliano Dias de Sousa¹, Virmondos Rodrigues Júnior¹, Leonardo Eurípedes de Andrade e Silva¹, Ana Carolina Silva Bittencourt³, Élide Mara Carneiro³, Carlo José Freire Oliveira¹

¹Federal University of Triângulo Mineiro, Uberaba, Brazil

²Federal University of Goiás, Goiânia, Brazil

³Physiotherapy Division (EBSERH/UFTM). Clinical Hospital of Federal University of Triângulo Mineiro, Uberaba, Brazil

Fogo Selvagem (FS) is a rare autoimmune disease characterized by acantholysis and inflammation of the epidermis. It was evidenced in this disease the increase of pro-inflammatory cytokines levels which can be influenced by physical activities. Kinesiotherapy, as physiotherapeutic interventions, was associated improvement levels of the quality of life, mainly the pain. Understanding the impact of such methodology in immunology of the FS, may constitute an alternative and effective approach. We compare the levels of serum cytokines and chemokines between nine patients with FS submitted to kinesiotherapy for 12 weeks and ten patients not submitted to kinesiotherapy. The kinesiotherapy was composed by self-stretching followed by a resistance training for upper and lower limbs. The protocol was carried out in three sections of eight to ten repetitions with 70% of the maximum load measured by test maximum of ten repetitions. After strengthening period patients

performed a passive stretching. The training sessions lasted 50 min and were performed 3 times a week at least 12 weeks. Cytokines and chemokines were assessed in plasma using enzyme-linked immunosorbent assay and/or cytometric bead array. Patients with FS were being kinesiotherapy presented minors levels of interferon- γ , interleukin (IL)-17, IL-22, and IL-15 when compared to those not submitted to kinesiotherapy. No differences were observed for the detection of the chemokines chemokine ligand (CCL)-2, CCL-3, CCL-5, CCL-11, C-X-C motif chemokine 8 (CXCL-8), and CXCL-10. These results suggest that kinesiotherapy had a positive impact on inflammatory markers that are associated with disease worsening in FS.

Keywords: Kinesiotherapy, Pemphigus foliaceus, Cytokines, Chemokines


INTRODUCTION

Pemphigus foliaceus (PF) is a disorder from a group of immune-mediated diseases characterized by the production of IgG₄ antibodies targeting desmoglein-1, which causes loss of cell adhesion in the epidermis, thus leading to the formation of discrete fluid-containing blisters in the skin (Grando, 2012). This process triggers a painful, disabling inflammatory process and reduces the quality of life of patients (Timóteo et al., 2010). The endemic form of PF is known as “Fogo Selvagem” (FS) and presents partic-

ularities in the Southeast and Midwest regions in Brazil, reaching up to 3% of the entire population (Aoki et al., 2015; Culton et al., 2008).

The immune system of patients with FS is locally and systemically disturbed. FS activity seems to be correlated with higher levels of interleukin (IL)-6, tumor necrosis factor (TNF)- α , IL-17, IL-1 and interferon (IFN)- γ in skin (Arakawa et al., 2009; López-Robles et al., 2001; Rodrigues et al., 2009; Timóteo et al., 2017; Tojo et al., 2013), and IL-22 and IL-8 in serum. Furthermore, an imbalance in the lymphocytes T helper (Th)1/Th2 ratio with a

*Corresponding author: Rodolfo Pessato Timóteo

 <https://orcid.org/0000-0002-4273-8201>

Federal University of Triângulo Mineiro, Av. Getúlio Guaritá S/N, Laboratory of Immunology, Uberaba, Minas Gerais, 38015-050, Brazil

E-mail: rodolfo_pessa@hotmail.com

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trend towards a Th2 response have already been identified in cells isolated from patients with FS under corticosteroid therapy (Rocha-Rodrigues et al., 2003).

Because of the central role of immune system in the disease onset and outcome, immunosuppressive drugs, like corticosteroids and immunobiologicals, have been used to treat FS (Kasperkiewicz et al., 2017). Though these therapeutic approaches have been experienced, more studies are required to clarify their safeness and effectiveness. Alongside pharmacological therapy, kinesiotherapy is a complementary intervention initially used to improve the quality of life of patients in distinct diseases. The influence of physical exercise on immune responses is not fully understood, however, changes in circulating cytokines are noticeable soon after, few hours later or even days after physical training (Leicht et al., 2013). The influence of physical exercise in immune response was verified after strenuous exercise in humans (Perandini et al., 2012), and after moderate physical activity in animal models of systemic lupus erythematosus (Aqel et al., 2017). Additionally, a reduction of pain, improvement of physical aspects and in quality of life was observed in patients with PF under immunosuppressive therapy and physical exercise protocol (kinesiotherapy) (Timóteo et al., 2010).

Despite these evidences regarding the beneficial role of physical activity/kinesiotherapy in the modulation of immune system in different scenarios, there are no studies that can clarify if this improvement is related to significant changes in immunological parameters, especially cytokines and chemokines. Therefore, this study aimed to verify the putative differences in circulating cytokines and chemokines in patients with FS submitted or not to kinesiotherapy.

MATERIALS AND METHODS

Study design

This was an exploratory and quantitative study that evaluated the levels of cytokines and chemokines in patients with FS submitted or not to kinesiotherapy. All patients undergoing kinesiotherapy were under this treatment for at least 12 weeks. This physical intervention was part of the hospital routine for patients who accepted, based on patients' choice, to participate in the proposed therapy. Therefore, kinesiotherapy was not proposed in the context of adjuvant treatment of patients with FS, since it is only an option if the patient has an interest in participating in some activity during hospitalization. The others patients with FS were not submitted to kinesiotherapy by option or because they were

unable to go to the hospital to perform it. All FS patients submitted or not to kinesiotherapy were under drug treatment. A control group with healthy subjects was also used. All participants agreed to participate in the study by signing the free and informed consent form. This study was conducted in accordance with the Declaration of Helsinki and the protocol approved by the Ethics Committee of the Federal University of Triângulo Mineiro with protocol number 1.341.124.

Participants

For this study 10 healthy subjects, 10 patients with FS under immunosuppressive treatment, and nine patients with FS under immunosuppressive therapy and submitted to kinesiotherapy protocol, were included. Were included in the submitted kinesiotherapy group patients undergoing kinesiotherapy for at least 12 weeks. For the group not submitted to kinesiotherapy, were randomly included patients were only on medication treatment and did not perform any type of regular physical activity.

Chemokine and cytokine production

The production of IL-1 β , IL-5, IL-12, IL-13, IL-15, IL-22, IL-23, IL-33, chemokine (C-C motif) ligand 2 (CCL2) also referred to as monocyte chemoattractant protein 1 (MCP1), C-X-C motif chemokine 10 (CXCL-10) also referred to as Interferon Gamma-Induced Protein 10 (IP-10), and CCL-11 (Eotaxin-1) was assessed in plasma using the enzyme-linked immunosorbent assay (R&D Systems, San Diego, CA, USA), following the manufacturer's instructions. Cytometric Bead Array (BD Bioscience, San Jose, CA, USA) was used for detection of TNF- α , IFN- γ , transforming growth factor beta, IL-2, IL-4, IL-6, IL-9, IL-10, IL-17A, CCL-5 (RANTES), C-X-C motif chemokine 8 (CXCL8) (IL-8) and CCL3 (MIP-1 α).

Kinesiotherapy protocol

The 12-week kinesiotherapy protocol was performed three times a week for approximately sixty minutes under the supervision and guidance of a physiotherapist. Kinesiotherapy was composed of resistive exercises and active stretches for all parts of the body. For the resisted exercises, loads with up to 70% of the maximum load evaluated by the test of 10 maximum repetitions (Alexanderson et al., 2007) were used and performed in three sets of 10 repetitions, according to the protocol of American College of Sports (American College of Sports Medicine, 2009). The active stretches were performed at the beginning and at the end of each session with a total of three sets of stretching for a period of ap-

proximately twenty seconds/each. The same physiotherapist supervised all kinesiotherapy sessions. Blood samples were collected in the morning (between 8:00 a.m. and 11:00 p.m.) 48 hr after the last session of exercises and 12 weeks after the beginning of the protocol.

Data analysis and statistics

For all variables normal distribution and homogeneous variance were tested. The D'Agostino-Pearson test was used to assess normality for all variables. In cases of non Gaussian distribution of data, the nonparametric Mann-Whitney test was applied. Multiple comparisons relating to the medians of values for more than two groups were made using the Kruskal-Wallis nonparametric test followed by Dunn test. The observed differences were considered significant when $P < 0.05$ (5%). For correlations the Spearman test was used. Statistical analysis was performed using the software Graphpad Prism (GraphPad Software 6.0, La Jolla, CA, USA).

RESULTS

Participants

Groups were considered homogeneous relative to age, gender, skin color and residence type (Table 1). All patients with FS presented lesions that reached cutaneous involvement between 18% and 45% of the body surface (Rule of nine of Wallace) with lesions in phase of re-epithelialization and/or granulation and hy-

Table 1. Age, gender, skin color, and housing area of pemphigus foliaceus patients and control groups

Variable	Control	PF under pharmacological therapy	PF with pharmacological therapy and kinesiotherapy	P-value
Age (yr), mean ± SD	30 ± 9.54	27 ± 12.55	42 ± 15.70	0.086
Gender (n)				> 0.999
Female	7	5	6	
Male	3	5	3	
Skin colors (n)				> 0.999
Mulattoes	5	1	4	
White	2	5	4	
Black	3	4	1	
Housing área (n)				> 0.999
Urban	5	5	3	
Urban with rural area	4	3	4	
Rural area	1	2	2	

PF, pemphigus foliaceus; SD, standard deviation.

perpigmentation. All patients were treated with prednisone with dosages ranging from 10 mg to 60 mg/day (Supplementary Table 1). No correlation was found between the cutaneous involvement and the glucocorticoid dosage in both patients groups. As well no correlations was found between medical treatment period and glucocorticoid dosage. Was verified only a correlation between cutaneous involvement and medical treatment period in PF under pharmacological therapy group ($P = 0.009$, $r = 0.835$; Spearman test).

Kinesiotherapy modulates key cytokines in serum of patients with the endemic form of PF

Patients with FS who underwent kinesiotherapy had reduced levels of IFN- γ , IL-17, and IL-22 when compared to the group of patients receiving immunosuppressive therapy alone (Fig. 1A, B, G, and H, respectively). No differences were observed for the production of IL-6 (Fig. 1C), IL-5 (Fig. 1D), IL-13 (Fig. 1E), and IL-10 (Fig. 1F). These results indicate that kinesiotherapy may induce a reduction in key cytokines in the development of FS. The kinesiotherapy protocol appeared to have no influence on the production of IL-4 (data not show).

Kinesiotherapy induced a reduction in the production of IL-15 when compared to patients with FS not submitted to kinesiotherapy, reinforcing the anti-inflammatory role of physical intervention in this scenario (Fig. 2D, F). No differences were observed for IL-2 (Fig. 2A), TNF- α (Fig. 2B), IL-12 (Fig. 2C), and IL-33 (Fig. 2E). Cytokines IL-4, IL-23, and IL-1 β were not detected in plasma of healthy subjects or PF patients submitted or not to kinesiotherapy (data not shown).

Kinesiotherapy seems not to be effective in the modulation of chemokines in FS

No differences were detected for the levels of CXCL8 (Fig. 3A), CCL2 (Fig. 3B), CCL5 (Fig. 3C), CCL11 (Fig. 3D), and CCL10 (Fig. 3E). MIP- α was not detected (data not shown).

DISCUSSION

In recent years, a great number of researchers have sought to investigate new alternatives of treatment or complementary therapies for FS. One of the main goals of such approaches relies on improving the effectiveness in the modulation of immune system thus, favoring a reduction in inflammation, prolonging the periods of remission and a promising outcome. Despite this observation, the role of kinesiotherapy has never been addressed in this

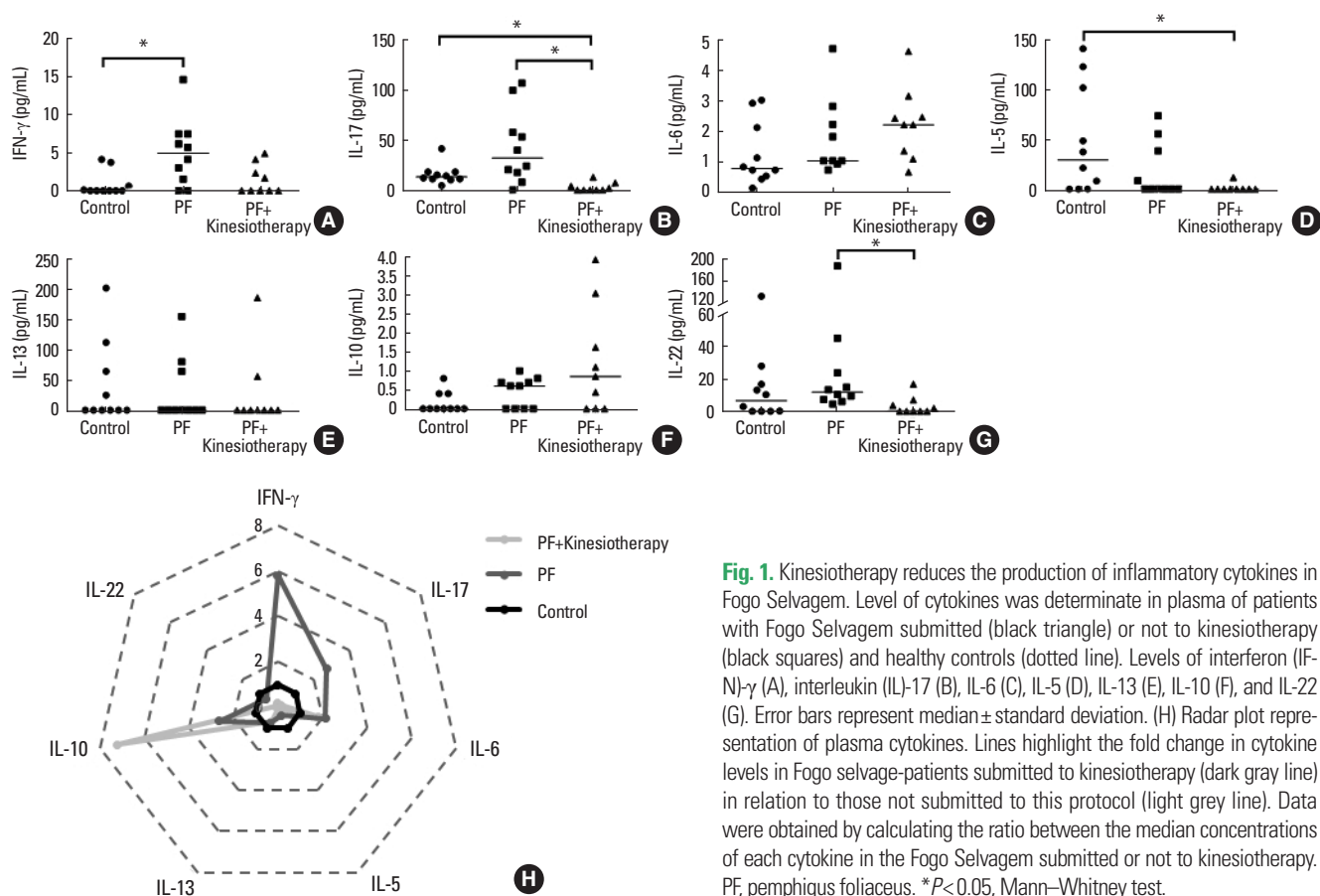


Fig. 1. Kinesiotherapy reduces the production of inflammatory cytokines in Fogo Selvagem. Level of cytokines was determined in plasma of patients with Fogo Selvagem submitted (black triangle) or not to kinesiotherapy (black squares) and healthy controls (dotted line). Levels of interferon (IFN)- γ (A), interleukin (IL)-17 (B), IL-6 (C), IL-5 (D), IL-13 (E), IL-10 (F), and IL-22 (G). Error bars represent median \pm standard deviation. (H) Radar plot representation of plasma cytokines. Lines highlight the fold change in cytokine levels in Fogo selvagem-patients submitted to kinesiotherapy (dark gray line) in relation to those not submitted to this protocol (light gray line). Data were obtained by calculating the ratio between the median concentrations of each cytokine in the Fogo Selvagem submitted or not to kinesiotherapy. PF, pemphigus foliaceus. * $P < 0.05$, Mann–Whitney test.

scenario. Thus, our results pointed to a beneficial role of kinesiotherapy as adjuvant treatment besides of its ability to reduce the levels of IFN- γ , IL-22, IL-17, and IL-15 in FS. However, kinesiotherapy seems not to affect the levels of chemokines in plasma of patients with FS.

Despite of the limited patients' number in our study, both groups were considered homogeneous relative to age, gender, skin color, and residence type. This homogeneity between patient groups was probably of the Brazilian epidemiological and environmental factors cited in previous study of our group and others studies (Hans-Filho et al., 2018; Timóteo et al., 2010). Clinical characteristics as medical treatment time, concomitant medication dosage and cutaneous involvement did not present correlations between the patients groups studied. These characteristics may be due to the limited number of patients between the groups, individualization in the pharmacological treatment and/or different responses to different dosages of corticosteroids.

Different studies have addressed the impact of kinesiotherapy as a complementary therapy on the treatment of immune-mediated diseases. Such approach has been used in systemic lupus erythe-

matusos (Rodríguez Huerta et al., 2016; Walsh et al., 2011), psoriasis, psoriatic arthritis (Kimball et al., 2008), and rheumatoid arthritis (Brenol et al., 2013). In these cases, the intervention with physical exercise was associated with improvement of clinical signs of disease. Despite the amelioration observed the immune-mechanisms involved in clinical improvement were poorly explored.

The participation of specific cytokines in the pathogenesis of FS is a matter of debate and some of them present conflicting role depending on the location they are analyzed. Higher levels of IFN- γ can be associated either with disease worsening or amelioration. Locally in skin, higher levels of IFN- γ in the inflammatory exudate of lesions in FS, together with TNF- α and IL-1, were implicated in mechanisms of tissue injury (Rodrigues et al., 2009). On the other hand, a recent publication from our group, suggested that higher plasma levels of IFN- γ might have a putative protective role in FS progression (Timóteo et al., 2017). In this present study, the reduction in IFN- γ in plasma was observed in patients with FS submitted to kinesiotherapy protocol. One hypothesis to explain this controversial result, may rely on the adjuvant

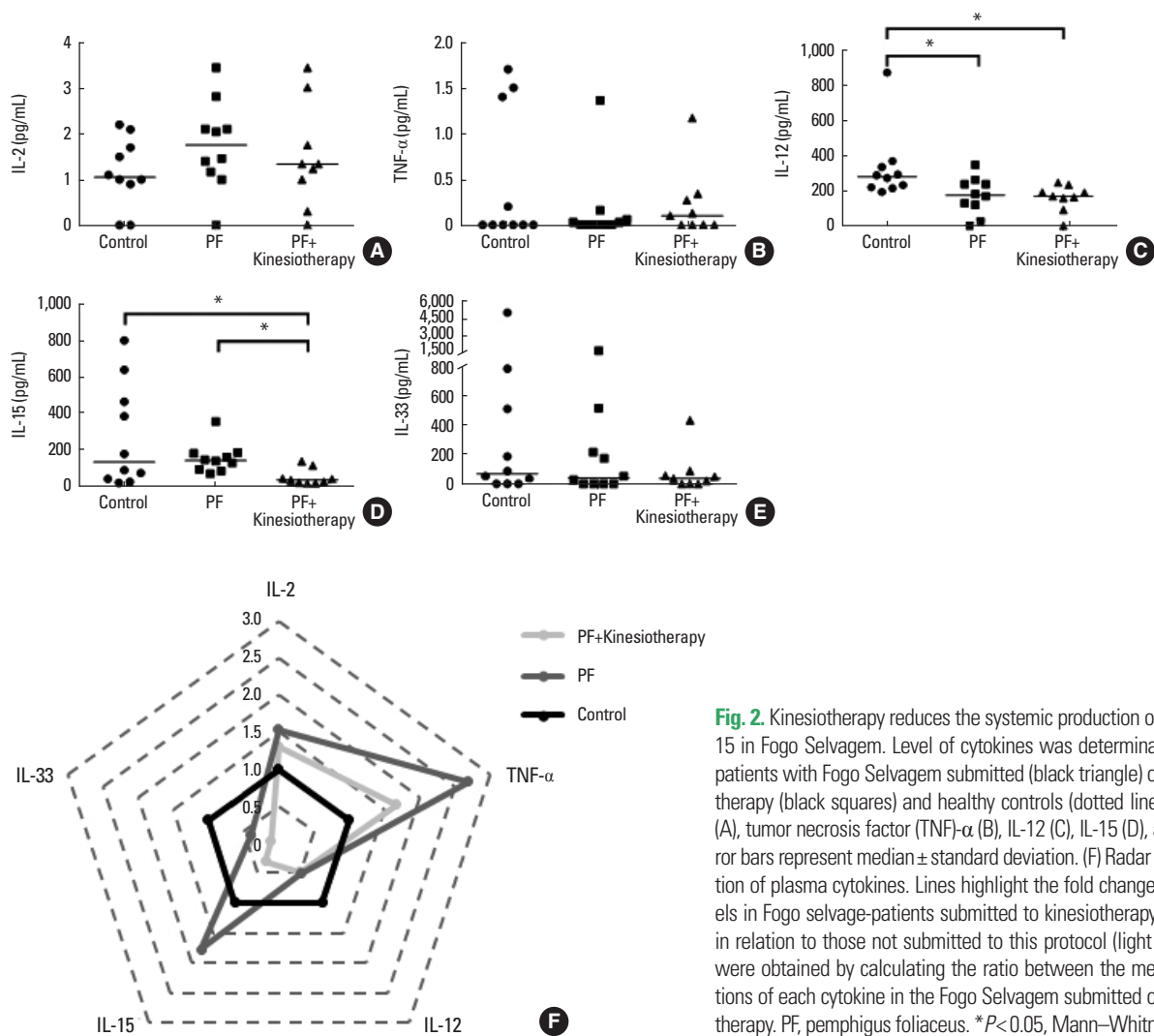


Fig. 2. Kinesiotherapy reduces the systemic production of interleukin (IL)-15 in Fogo Selvagem. Level of cytokines was determined in plasma of patients with Fogo Selvagem submitted (black triangle) or not to kinesiotherapy (black squares) and healthy controls (dotted line). Levels of IL-2 (A), tumor necrosis factor (TNF)- α (B), IL-12 (C), IL-15 (D), and IL-33 (E). Error bars represent median \pm standard deviation. (F) Radar plot representation of plasma cytokines. Lines highlight the fold change in cytokine levels in Fogo selvagem-patients submitted to kinesiotherapy (dark gray line) in relation to those not submitted to this protocol (light gray line). Data were obtained by calculating the ratio between the median concentrations of each cytokine in the Fogo Selvagem submitted or not to kinesiotherapy. PF, pemphigus foliaceus. * $P < 0.05$, Mann-Whitney test.

anti-inflammatory role of kinesiotherapy that have induced a reduction in key inflammatory cytokines such as IL-17 and IL-22, which are clearly associated to disease worsening. Thus, the modulation of these cytokines may have down regulated the systemic production of IFN- γ .

IL-22 is associated to the regulation of tissue cells in skin, small intestine, liver, colon, and respiratory system (Wolk et al., 2004). Th17 and Th22 cells mostly produce this cytokine (Trifari et al., 2009). Despite its physiological role, IL-22 may also be involved in inflammatory process. Different studies have demonstrated a positive correlation between higher levels of IL-22 and inflammatory disorders in skin, such as psoriasis (Benham et al., 2013) and atopic dermatitis (Nogralles et al., 2009). In a recent publication, our group demonstrated that FS is characterized by systemic production of IL-22 (Timóteo et al., 2017). Though the role of IL-22

in FS is still poorly addressed, we cannot underestimate its importance in disease pathogenesis. In this present study, patients with FS submitted to kinesiotherapy, had lowered the levels of IL-22, which suggests the importance of such adjuvant therapy in the amelioration of disease. However, the mechanisms behind this observation still demand further clarification.

IL-17 is a cytokine detected in different inflammatory diseases and is closely involved in chronic inflammation observed during the pathogenesis of some immune-mediated diseases. Th17 cells are the main source of IL-17, and several molecules associated to this lymphocyte are strongly implicated in the pathogenesis of psoriatic skin lesions (Johansen et al., 2009). Because of the role of IL-17 in this scenario, it has been used as a potential treatment target in psoriasis (Greig, 2016; Markham, 2016). Though the role of IL-17 in FS has not yet been demonstrated, it is known

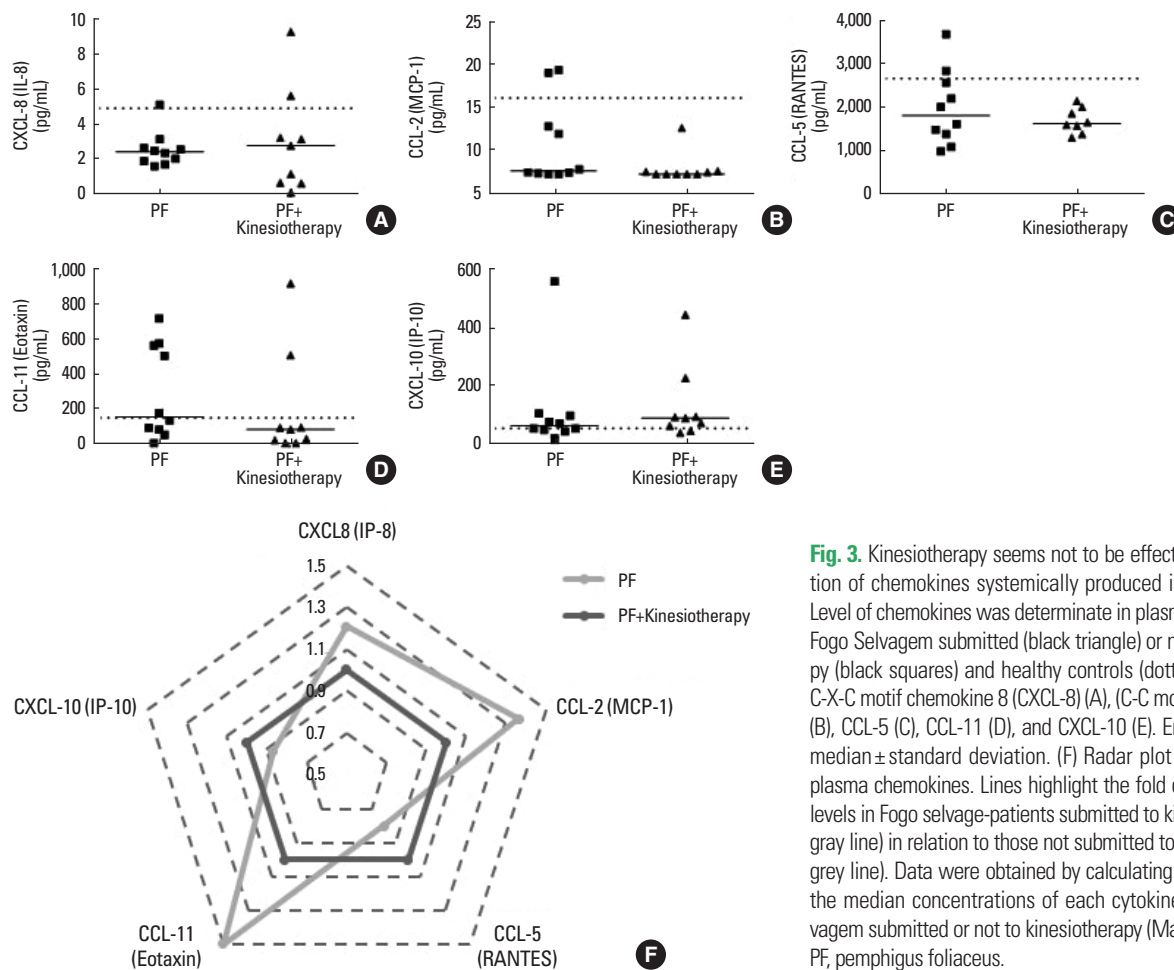


Fig. 3. Kinesiotherapy seems not to be effective in the modulation of chemokines systemically produced in Fogo Selvagem. Level of chemokines was determined in plasma of patients with Fogo Selvagem submitted (black triangle) or not to kinesiotherapy (black squares) and healthy controls (dotted line). Levels of C-X-C motif chemokine 8 (CXCL-8) (A), (C-C motif) ligand 2 (CCL2) (B), CCL-5 (C), CCL-11 (D), and CXCL-10 (E). Error bars represent median \pm standard deviation. (F) Radar plot representation of plasma chemokines. Lines highlight the fold change in cytokine levels in Fogo selvagem-patients submitted to kinesiotherapy (dark gray line) in relation to those not submitted to this protocol (light gray line). Data were obtained by calculating the ratio between the median concentrations of each cytokine in the Fogo Selvagem submitted or not to kinesiotherapy (Mann-Whitney test). PF, pemphigus foliaceus.

that this molecule is increased in *Pemphigus vulgaris* (Timóteo et al., 2017). The results observed in the present study, suggest that kinesiotherapy can be effectively used as adjuvant therapy as well as is able to lower the levels of IL-17 in FS. Despite the scarcity of data regarding the role of IL-17 in the pathogenesis of FS and based on its function in other pathologies of skin, it is feasible to assume that therapies aiming at modulating this cytokine, especially in combination with kinesiotherapy, may present promising results.

Increased levels of different cytokines, including IL-15, characterize chronic inflammation, like that observed in FS. This cytokine is produced by several types of cells like antigen-presenting cells, epidermal skin cells, keratinocytes, and intestinal epithelial cells (Fehniger and Caligiuri, 2001). Furthermore, IL-15 is able to induce the production of other inflammatory cytokines such as IL-17 and TNF- α , besides of influencing angiogenesis, recruitment of phagocytes and acanthosis (Dunphy and Gardiner, 2011). IL-15 has similar biological effects as IL-2, however, distinct key

roles were identified during development and function of CD8+ T cells, natural killer cells, invariant natural killer-T cells, and intestinal intraepithelial lymphocytes (Castillo and Schluns, 2012). High serum levels of IL-15 were implicated in the pathogenesis of pustular palmoplantar psoriasis (Lesiak et al., 2016), which is an infrequent type of psoriasis disturbing primarily distal parts of the limbs. Likewise, higher levels of IL-15 were correlated with the activity of NK cells in the pathogenesis of psoriatic arthritis (Tang et al., 2013). Additionally, IL-15 is also implicated in the pathogenesis of psoriasis through the protection of keratinocytes from apoptosis by the activation of ERK1/2 and PI3 kinase (Waldmann, 2013). Though the role of IL-15 is not clarified in FS, the reduction observed in patients submitted to kinesiotherapy could be beneficial to disease outcome.

Our results indicate how a number of cytokines can behave in front of the practice of physical activity for rehabilitation of an autoimmune disease which can be enlightening for other diseases with the same profile. Therefore, for the first time, we suggest

that kinesiotherapy can be safely and effectively used as adjuvant therapy to treat FS and reestablish immune balance for having been associated the reduction of pro-inflammatory cytokines related to the disease. More prospective studies are needed to assess the levels of cytokines and their relationship to disease activity and quality of life parameters of patients with FS.

CONFLICT OF INTEREST

No potential conflict of interest relevant to this article was reported.

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SUPPLEMENTARY MATERIAL

Supplementary Table 1 can be found via <https://doi.org/10.12965/jer.1938146.073>.

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