CysLT1 receptor inhibition in patients with Raynaud's phenomenon – capillaroscopic evidence of the role of leukotriene

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ABSTRACT

Objective: To assess the effect of the leukotriene receptor inhibitor (montelukast) on vascular alterations in fingers of patients with Raynaud's phenomenon. **Methods:** Patients with Raynaud's phenomenon of the hands secondary to inflammatory connective tissue disease were selected, and those with the following characteristics were excluded: smokers, arterial hypertension, and diabetes mellitus. All patients maintained their previous medications and started the use of montelukast, 10 mg/day, for 60 days. Naifold capillaroscopy of fingers was performed before the use of medication and after 30 and 60 days. Statistical analysis was performed with percentage, media, standard deviation, Fisher exact test, with 95% of confidence interval. **Results:** The study assessed five Caucasian, female patients with Raynaud's phenomenon secondary to inflammatory connective tissue disease (three with scleroderma and two with mixed connective tissue disease), aged 42.4 ± 11.5 years, and with 9.6 ± 4.8 years of disease duration. Patients were on nifedipine and pentoxifylline, and those with mixed connective tissue disease were also on prednisone. The medications were maintained. After using montelukast for two months, nailfold capillaroscopy showed a reduction in edema and pallor, and normalization of capillary number, size, and distribution. **Conclusion:** The use of montelukast modified the capillary abnormalities observed on nailfold capillaroscopy of patients with Raynaud's phenomenon.

Keywords: Raynaud's disease, advanced treatment, leukotriene receptor antagonists, leukotrienes.

INTRODUCTION

An episodic observation about the use of leukotriene receptor inhibitor selective for the CysLT1 receptor (montelukast) in a female patient with bronchial asthma secondary to the use of aspirin and with triphasic Raynaud's phenomenon has evidenced disappearance of the respiratory disease and of vascular signs and symptoms, and normalization of her nailfold capillaroscopic findings.[1]

In Raynaud's phenomenon, the abnormality of vascular regulation stands out, with microcirculation spasm, edema, and cellular infiltration.[2–4] Several substances participate, directly or indirectly, in the vasoconstriction process; leukotrienes, which participate actively through receptors and adhering to endothelial cells, are potent bronchoconstrictors and vasoconstrictors.[5]

A research project was then established to assess the use of montelukast in patients with inflammatory connective tissue disease and Raynaud's phenomenon of difficult control, with capillaroscopy before and after the use of the medication. The project aimed at assessing whether the use of the leukotriene inhibitor in patients with the Raynaud's phenomenon could modify the abnormal nailfold capillaroscopic findings.

The study was carried out at the Rheumatology Service, Hospital Clementino Fraga Filho, Universidade Federal do Rio de Janeiro (HUCFF-UFRJ). It was an open, observational, non-randomized, prospective study with a reduced group of

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patients with triphasic Raynaud's phenomenon and systemic inflammatory disease of immunological origin. The project was submitted to the Ethics Committee on Research of the HUCFF-UFRJ and approved. The patients used one tablet of montelukast (10 mg) per day, for two months. That drug is used to treat bronchial asthma and has few side effects. Patients were instructed about the drug and advised to look for researchers whenever necessary. All patients provided written informed consent and maintained their medications to control their underlying diseases. The essential requirements to participate in the study were as follows: diagnosis of inflammatory connective tissue disease; treatment of that disease for more than one year; and Raynaud's phenomenon difficult to control and with repeated crises.

Patients underwent nailfold capillaroscopy of fingers to characterize the capillary changes found in Raynaud's phenomenon. Nailfold capillaroscopy was performed by two examiners at 30-day intervals. The criteria of improvement on capillaroscopy were as follows: a reduction in the alterations of the form and function of the capillaries by assessing the reduction in vasospasticity, which was recognized due to changes in capillary branches; increased number of capillary loops per field studied; regression of the edema; field coloration; and capillary form, distribution, and size.[3]

Female patients with Raynaud's phenomenon of difficult control were included in the study according to their order of arrival for medical consultation, independently of their underlying disease, duration of disease, and medications being used. Patients with the following characteristics were excluded: smokers; arterial hypertension; and diabetes mellitus. Regarding therapy, the medical prescription being used was maintained. Patients underwent nailfold capillaroscopy, with appropriate care, and new capillaroscopies were scheduled for 30 and 60 days. Leukotriene receptor inhibitor CysLT 10 mg/day was initiated, in addition to the medication already in use. The total time of medication use was 60 days, due to the previous observation of the successful use of montelukast by the female patient with asthma and vascular syndrome. Results were assessed considering only the change in the capillary morphology on capillaroscopy after the use of montelukast, and the following were not considered: clinical evolution; diagnosis; duration of disease; medications being used; and laboratory tests. Statistical analysis was performed by use of mean, standard deviation, percentage, and Fisher exact test. The confidence interval of 95% was considered, and $P < 0.05$ was the statistical significance level adopted.

Capillaroscopy was performed by two examiners with a nailfold capillaroscopy device (Wild M3C), at room temperature (25 °C). Five Caucasian female patients (mean age, 42.4 ± 12.4 years; disease duration, 9.6 ± 4.8 years) with Raynaud's phenomenon secondary to systemic scleroderma[3] and mixed connective tissue disease were assessed.[2] The patients were on vasodilating and anti-inflammatory medication as follows: prednisone up to 20 mg/day (patients with mixed connective tissue disease); nifedipine up to 30 mg/day; and pentoxifylline up to 1,200 mg/day. Neither aspirin nor anticoagulants were used. All patients received one tablet of montelukast per day for 60 days.

Table 1
Changes in the nailfold capillaroscopy of the fingers before and after using montelukast in patients with Raynaud's phenomenon (n = 5)

	Before montelukast			After montelukast		
Nail bed	**Presence**	**Absence**	**P**	**Presence**	**Absence**	**P**
Pallor	77.3% (4)	22.7% (1)	0.009	22.7% (0)	77.3% (5)	0.009
Edema	100% (5)	0% (0)	0.001	0% (0)	100% (5)	0.001
Capillaries	**Normal**	**Abnormal**	**P**	**Normal**	**Altered**	**P**
Number	22.7% (2)	77.3% (3)	0.009	100% (5)	0% (0)	0.001
Size	22.7% (2)	77.3% (3)	0.009	77.3% (3)	22.7% (2)	0.009
Form	44.4% (2)	55.6% (3)	0.5	55.6% (3)	44.4% (2)	0.5
Distribution	44.4% (2)	55.6% (3)	0.5	100% (5)	0% (0)	0.009

Fisher exact test. Confidence interval: 95%. Statistical significance: $P < 0.05$.

DISCUSSION

The capillaroscopic assessment of Raynaud's phenomenon requires the characterization of the spasticity of capillaries by use of parameters such as pallor and edema in the field, and capillary form, number and distribution. The presence of edema stands out, caused by fluid leaking from the nail bed, which, along with capillary spasm, cases pallor. In the group studied, significant pallor was observed in the capillaroscopic field, demonstrating that, despite the diversity of diseases, that parameter was almost constant (observed in 80% of the sample). The capillary morphology was altered, but with no significant differences regarding capillary form, number, size and distribution, being secondary to the dynamics of the physiopathogenesis. More marked abnormalities were observed regarding the form and color of the afferent branches. In the sample studied, such capillaroscopic alterations characterize a functional alteration of blood vessels.

Vascular abnormality is one characteristic among the several processes involved in the development of Raynaud's phenomenon, with alterations in vascular structure and function. Those alterations cause capillary damage and activate mast cells through macrophages and T cells, which, along with heparin, compromise the endothelial cells, causing endothelial proliferation, edema, and vascular instability.[2,6] In more than 50% of the sera of patients with scleroderma and Raynaud's phenomenon, circulating endothelial cytotoxic activity was found. One of the main factors for developing that process is the presence of leukotriene B4 (LTB4) bound to low-molecular-weight protein.[7] Among pathogenic actions of leukotrienes, it is worth noting their potent vasoconstrictor and bronchoconstrictor action, with stimulation of endothelial cytotoxicity and mitogenic effect.[8]

For the intervention in the leukotriene pathway, antagonists of leukotriene cell receptors are currently used. They efficiently block the bronchial constriction specifically induced by leukotrienes, and reduce, after 48 hours, the number of basophils and lymphocytes in the bronchoalveolar lavage fluid, as well as histamine concentration, but without acting on eosinophils and macrophages.[9,10] Based on this evidence, the hypothesis raised was that such substance could influence positively the vascular instability of Raynaud's phenomenon.

The results of the capillaroscopic monitoring (Table 1) showed that the use of the leukotriene receptor inhibitor was significantly efficient in reducing the pallor of the field, which can be explained by the improvement in capillary flow and by the reduction in both spasticity and edema. In addition, significant normalization was observed in the number, size and distribution of the capillaries in the nail bed, without, however, significantly influencing the capillary form. Improvement began to appear before 30 days of montelukast use. Difference was evidenced neither in the underlying diseases, nor in the development of side effects.

In conclusion, the use of a leukotriene receptor inhibitor could modify the capillaroscopic characteristics of the nail bed of patients with Raynaud's phenomenon, characterizing the participation of the prostanoid in the physiopathogenesis of that syndrome. Because Raynaud's phenomenon can affect other organs, the use of the leukotriene receptor inhibitor could provide systemic clinical improvement, requiring, however, further directed and randomized studies.

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