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EFFICACY OF METHOTREXATE MICROINFUSION IN SCALP LESIONS OF PATIENTS WITH FIBROSING FRONTAL ALOPECIA: A PROSPECTIVE CONTROLLED TRIAL

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Original Article

EFFICACY OF METHOTREXATE MICROINFUSION IN SCALP LESIONS OF PATIENTS WITH FIBROSING FRONTAL ALOPECIA: A PROSPECTIVE CONTROLLED TRIAL.

EFICÁCIA DA MICROINFUSÃO DE METOTREXATO EM LESÕES DO COURO DE PACIENTES COM ALOPECIA FIBROSANTE: ENSAIO CLÍNICO PROSPECTIVO CONTROLADO.

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ABSTRACT - *Introduction*: Frontal fibrosing alopecia (FFA) is lymphocytic scarring, with hair loss through the frontal implantation line of the scalp and other body areas. Topical and systemic drugs, such as methotrexate (MTX), do not control disease activity in most of the cases showing the need for new therapies. ***Aim*****:** To evaluate the effectiveness of methotrexate microinfusion in AFF. ***Methods***: Prospective, controlled clinical trial, carried out with 17 volunteers with

clinical and histological diagnosis of FFA. Applications of MTX by MMP® (microinfusion of drugs into the skin method) were made every 30 days, in a total of 3 applications, in the right half of the alopecia area; the other half served as a control. The frontal-glabella and frontal temporo-parietal measurements, dermoscopy photos analyzed by blind and external evaluators, patient's perceptions of signs and symptoms and the Lichen Planopilaris Activity Index (LPPAI) were evaluated. Total blood count and liver function tests were also measured. ***Results***: There was a significant reduction in frontal-glabella and frontal temporo-parietal measurements at treated site while in the untreated site the AAF increased. Patient's referred improvement of pruritus and desquamation but not in hair loss and local erythema. Analysis of the dermoscopic photos and the LPPAI calculation did not show relevant changes. About 95% of the participants were satisfied or very satisfied with the results and none of them had alteration in the laboratory test results. ***Conclusion***: The MTX application by MMP®, improved symptoms associated with AFF, and the frontal-glabella and frontal temporo-parietal measurements. This technique proved to be safe and well tolerated.
KEYWORDS - Frontal fibrosing alopecia. Lichen planus pilaris. Baldness. Scalp. Methotrexate.

RESUMO - *Introdução*: A alopecia frontal fibrosante (AFF) é cicatricial linfocítica, com queda de cabelo pela linha de implantação frontal do couro cabeludo e outras áreas do corpo. Drogas tópicas e sistêmicas, como o metotrexato (MTX), não controlam a atividade da doença na maioria dos casos, mostrando a necessidade de novas terapias. ***Objetivo***: Avaliar a eficácia da microinfusão de metotrexato em AFF. ***Métodos***: Ensaio clínico prospectivo, controlado, realizado com 17 voluntários com diagnóstico clínico e histológico de AFF. As aplicações de MTX por MMP® (método de microinfusão de drogas na pele) foram feitas a cada 30 dias, totalizando 3 aplicações, na metade direita da área da alopecia; a outra metade serviu como controle. Foram avaliadas as medidas frontoglabela e frontal temporoparietal. Fotos de dermatoscopia foram analisadas por avaliadores cegos e externos com percepção de sinais e sintomas do paciente e o Índice de Atividade do Líquen Planopilar (LPPAI). Hemograma total e testes de função hepática também foram medidos. ***Resultado***s: Houve redução significativa nas medidas frontoglabela e frontal temporoparietal no local tratado, enquanto no não tratado a AAF aumentou. Houve melhora do prurido e descamação, mas não da queda de cabelo e eritema local. A análise das fotos dermatoscópicas e o cálculo do LPPAI não mostraram alterações relevantes. Cerca de 95% dos participantes ficaram satisfeitos ou muito satisfeitos com os resultados e nenhum deles teve alteração nos resultados dos exames laboratoriais. ***Conclusão***: A aplicação de MTX por MMP® melhorou os sintomas associados à AFF e as medidas frontoglabela e frontoparietal. Esta técnica mostrou-se segura e bem tolerada.
DESCRITORES - Alopecia frontal fibrosante. Líquen plano pilar. Calvície. Couro cabeludo. Metotrexato.

INTRODUCTION

Fibrosing frontal alopecia (FFA) is a progressive and chronic cicatricial alopecia of unknown etiology considered to be a form of the lichen planopilaris.[1]

This is an inflammatory disease that affects not only scalp and eyebrows, but also other regions of the body causing hair loss, local pain (trichodynia) and pruritus. FFA occurs mainly in post-menopausal women and may be associated with the appearance of lichen planus pigmentosum and normochromic facial papules.[2-4] Although FFA may be detected clinically, the trichoscopy is an important noninvasive method that helps not only in the diagnostic evaluation showing scalp erythema, desquamation and perifollicular hyperchromy but, also, in the evaluation of the inflammation degree.[5] Nevertheless, the best diagnostic tool is the biopsy that shows reduction in the number of terminal hair follicles in the dermis, perifollicular concentric fibrosis, lymphocytic infiltrate in the follicular isthmus, presence of necrotic keratinocytes, as well as the scarring pattern of the alopecia. An early diagnosis and treatment can modify the evolution of the disease, preventing its progression.[6-10]

FFA treatment is done with oral, intralesional and topic glucocorticoids, antimalarials, methotrexate, acitretin, mycophenolate mophetyl, finasteride, naltrexone, pioglitazone, doxycycline and tofacitinib. Other used medications are cyclosporine, thalidomide and griseofulvin, with variable results.[11-13]

Methotrexate is used orally and as subcutaneous or intramuscular injections. However, the systemic use of this drug is associated with several side effects such as gastrointestinal intolerance, hepatotoxicity, myelosuppression and teratogenicity. Moreover, the bioavailability of this drug is limited due to important metabolization through the first liver passage.[15] Local use minimizes such complications but the MTX, being hydro soluble, has limited capacity to permeate the corneal extract of the skin. In psoriasis, techniques such as electroporation, iontophoresis and ablative lasers have been used to increase the drug penetration in the skin.[16]

The micro infusion of microparticles into the skin, MMP®, consists of a micro needling of the skin, with instillation of active ingredients through these needles. The depth of the micro needling is previously adjusted according to the disease to be treated. Infusions of MTX through MMP® technique has shown good results in psoriasis with excellent tolerability. The drug when injected percutaneously has potent local effect and its inactivation due to first hepatic passage is prevented.[17]

Considering that the treatment of FFA is challenging, this study aims to evaluate the efficacy and safety of methotrexate infusion (MTX) through the MMP® technique on the scalp through a prospective controlled trial.

METHODS

This study was approved by the Ethics Committee on the Use of Animals of Faculdade Evangélica Mackenzie do Paraná, Curitiba, PR, Brazil under CAAE no. 09928919100000103). To be included, patients should be older than 18 years of age, and have FFA diagnosis proved through clinic, trichoscopic examination and biopsy. Patients with abnormal liver function tests, history of chronic hepatitis, renal failure, hemolytic anemia and pregnant were excluded. Individuals that have had treatment with corticosteroid infiltration, systemic MTX or that used any micro infusion treatment in the last 4 months were also excluded. All included patients signed consent.

Data collection

Epidemiological data

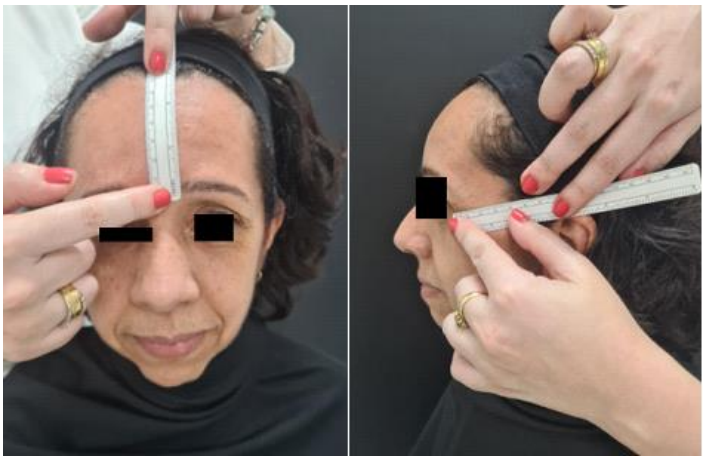
Age, years of formal study, occupation, marital status, and if the patient was pre- or post-menopausal when the disease started.

Symptoms

Pruritus, desquamation and burning.

Physical examination

Fitzpatrick phototype, hair fall in other areas of the body, frontal-glabella measurement and determination of frontal temporo-parietal distance.[18] The frontal-glabella measurement evaluates the distance between the frontal hairline, excluding lonely hair, and the glabellar crease; the frontal temporo-parietal evaluates the distance between lateral eye epicanthus and implantation hairline at temporo-parietal region.[19] These measurements were done with a flexible and manual ruler which was appropriate to the convex region of the forehead and collected at day 0 and 30 days after the last application. The examiner measuring these distances was blind to which side was being treated (Figure 1).



A B

FIGURE 1 – A) Frontal-glabella measurement using the line between the eyebrows and the frontal capillary implantation area, excluding lonely hair; B) frontal temporo-parietal measurement at left side using the distance between the left epicanthus and the left frontal temporo-parietal hairline implantation.

LLPAI or Lichen Planopilaris Activity Index.

This index evaluates symptoms (pain, pruritus and local burning sensation), local findings (such as desquamation, diffuse and perifollicular erythema), anagen traction test and alopecia progression. It ranges from 0 to 10 where 0 is the best and 10 the worst scenario.[20] LLPAI was evaluated at day 0 and 30 days after the last treatment.

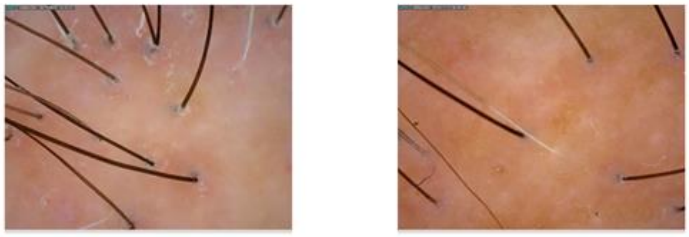
Trichoscopy

For the trichoscopy study, the frontal line of the scalp was divided in 8 regions, 3 cm from each other (named A, B, C, D on the right and E, F, G, H on the left, Figure 2). The examination was done at day 0 and 30 days after the last treatment and performed by 2 certified examiners, blind to the treated side using videodermatoscopy Dino Lite®.

FIGURE 2 – Scalp division of the frontal and parietal region for evaluation of trichoscopic findings. A, B, C and D areas were treated and E, F, G, H were used as control

External evaluation of results through photos

Trichoscopic findings were photographed (Canon® EOS Rebel T7 Ef-S 18-55 F/3.5-5.6 Is II) in the above mentioned 8 regions (Figure 2) at day 0 and 30 days after treatment. The photos were standardized with the same lighting conditions, in the same place and with the same distance of 30 cm from the participant. The pre and post treatment imagens were placed side by side (Figure 3) and evaluated by 3 certified dermatologists, blind to treated side, using the following classification: -1 (worsening), 0 (no changes) and +1 (improvement). The following parameters were evaluated: scalp and perifollicular erythema, telangiectasis, desquamation and alterations in pigmentation.



A A´

FIGURE 3 - Trichoscopic findings as presented to the 3 dermatologists for evaluation: A) pre-treatment; A´) post-treatment

Laboratory evaluation

Total blood cell count, transaminases (GOT and GPT), creatinine, blood urea nitrogen, prothrombin time, hepatitis B and C serologies and BHCG were done at day 0 and 30 days after each application.

Treatment procedures

Prior to the injection scalp, inspection and 0,2% chlorhexidine antisepsis were performed at the locations to be treated. Three applications of 1 ml of methotrexate (50 mg/2 ml) were done through MMP® technique using a Magnum 23 tip of a Cheyenne MMP® dispositive, with 30 days of interval between sessions. This procedure was done by just one dermatologist that applied the medication in right side of the alopecia area; the left area - that served as control – doesn't received any treatment.

Procedures were performed by a single investigator, only in the half of the alopecia area (on the right side) serving the other half (left side), as control. A

mild erythema was expected in the treated region. Each sector of the treated area (divided according to the Figure 2) received an equal amount of 0.25 ml of MTX. Patients were instructed not to wash the treated area for the period of 24 hrs and to start using SPF 30 sunscreen 72 hrs after the procedure.

Patient's satisfaction evaluation

The overall degree of patient satisfaction was assessed with a questionnaire on the obtained results (size of the alopecia area, hair thickness, hair loss and density) as well as about local or systemic symptoms associated with the treatment. This evaluation was done 30 days after the last treatment session.

Statistical analysis

Obtained data were collected in frequency and contingency tables. Central tendency was expressed as mean and standard deviation as all numerical data were parametric. Comparison of nominal data was done through Fisher and chi-squared tests and of numerical data through student t test. The adopted significance was 5%. The tests were calculated using the software SPSS (version 17.0, USA).

RESULTS

Description of the studied sample

Seventeen female patients were included. Table 1 shows the main characteristics of this sample that had mainly middle-aged individuals with phototype III and IV. This table also shows that the most common clinical findings were pruritus and desquamation and that almost 2/3 of the sample had hair loss in some other part of the body.

TABLE 1 – Epidemiological and clinical data of studied sample (17 females with fibrosing frontal alopecia)

Female gender (n)		17/17 (100%)
Mean age (years)±SD		59.6±8.4
Mean symptoms duration (years) ±SD		9,7±4,9
Fitzpatrick phototypes		
	II	3 (18%)
	III	4 (24%)
	IV	6 (35%)
	V	2 (12%)
	VI	2 (12%)
Disease beginning prior to menopause		14 (82%0
Symptoms		
	Pruritus	13 (76%)
	Burning sensation	5 (29%)
	Desquamation	11 (64%)
	Erythema	5 (29%)
Hair loss in other region of the body		
	Any other part of the body	12 (71%)
	Eyelash fall	7 (41%)
	Eyebrow fall	11 (65%)
	Axillary hair fall	4 (24%)
	Superior limb hair loss	4 (24%0
	Loss of pubic hair	3 (18%)
	Inferior limb hair loss	2 (12%)
Used treatments		
	Topical clobetasol	17 (100%)
	Hydroxychloroquine	13 (76.4%)

	Minoxidil	16 (94.1%)
	Finasteride	5 (29.4%)
	Topical tacrolimus	1 (5.8%)

n=number; SD=standard deviation.

Treatment results

The results of the comparison of frontal-glabella and frontal temporo-parietal distances are on Table 2. This table shows that the frontal-glabellar distance and right frontal temporo-parietal distance had important reduction while the left front-temporo-parietal had a significative increase.

TABLE 2 - Comparison of frontal glabella and frontal temporo-parietal distances (in cm) prior and after treatment

	Before treatment	**After treatment**	**p**
Frontal-glabella	8,30±1,59	8,12±1,53	0.01
Right frontal temporo-parietal	6.85±1.42	6.70±1.43	0.001
Left frontal temporo-parietal	6.99±1.91	7.05±1.92	0.01

No differences were noted in the comparison of frontal temporo-parietal measurements right and left prior to treatment (p=0.80) neither after treatment (p=0.73). The comparison of symptoms and clinical findings pre- and post-treatment is on Table 3 that shows improvement in the pruritus and desquamation. Prior to treatment, the LPPAI at right side (treated area) had a mean value of 4.61±1.86 and after of 4.15±1.62 com p=0.45.

The direct comparison of trichoscopic findings between treated (right) side (A, B, C, D) and untreated (left) side (D, E, F, G) did not show any differences, neither the comparison done through photography by external evaluators (all with p>0.05).

TABLE 3 – Comparison of symptoms and signs of patients with frontal fibrosing alopecia after treatment with MMP with methotrexate

	Improvement		**Worsening**		**No changes**		**p**
	n	**%**	**n**	**%**	**n**	**%**	
Hair loss	5	29	3	18	9	53	0.34
Pruritus	9	53	3	17	5	29	**0,03**
Erythema	1	6	4	23	12	71	0.17
Desquamation	10	59	3	18	4	23	**0.01**

n=number; MMP=micro infusion of microparticles

The procedure was well tolerated. Table 4 shows the symptoms referred by the patients during and after the MTX application.

TABLE 4 - Patient's perception towards MTX application with MMP

Pain (n)		
Local pain during procedure	None	8 (47%)
	Light	7 (41%)
	Moderated	2 (12%)
	Strong	0
Local pain after procedure (n)	None	12 (71%)
	Light	4 (24%)
	Moderated	1 (6%)
	Strong	0
Headache after procedure (n)	None	15 (88%)
	Light	2 (12%)
	Moderated	1 (6%)

	Strong	0
Pruritus (n)		
During treatment	None	12 (71%)
	Light	4 (24%)
	Moderated	0
	Strong	0
After treatment	None	15 (88%)
	Light	2 (24%)
	Moderated	0
	Strong	0
Signs		
	None	7 (41%)
	Scalp erythema	6 (35%)
	Hyperchromia	2 (12%)
	Ecchymosis	1 (6%)
	Pustules	1 (6%)

Concerning patient's satisfaction with treatment results the results are on Figure 4. None of them were unsatisfied.

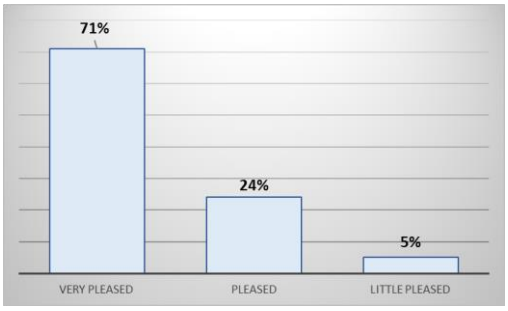


FIGURE 4 - Patient's perception of treatment results

No alterations in blood cell count, liver and renal function tests were observed.

DISCUSSION

There are almost no clinical trials on FFA treatment; none on MTX use through MMP technique, being this the first description on its use for this disease. MTX has been used systemically for FFA but the results are poorly documented.[9] In the review by IMHOF et al. 2 cases are documented with controversial results. A study from Duke University reported 3 patients with FFA treated with oral MTX and just 1 had stabilization of the disease. Another work by Mayo Clinic, in just 2 patients, showed that systemic MTX was able to arrest the disease progression.[21]

Arbache et al. reported the use of MTX drug delivery with MMP technique for vulgar psoriasis treatment in two patients, with complete remission of skin lesions after 3 applications.[22] In the present work, this technique has shown improvement of pruritus and desquamation as well as it arrested the progression of alopecia measured by frontal-glabella and right frontal temporo-parietal measurements having a positive impact in patients' well-being.

In the present study, the LPPAI used to evaluate the treatment response, did not show any improvement of signs and symptoms with the proposed treatment. According to Andrade et al., that studied 22 patients with FFA treated and assessed by LPPAI and FFASI (Frontal Fibrosing Alopecia Severity Index), these 2 scales, if applied separately, are not satisfactory because their final

scores do not correlate directly; they only complement each other. So, it is possible to conclude that a good tool to study FFA severity is not available.[23]

According to the frontal-glabella and frontal temporo-parietal measurements, the currently used treatment avoided progression of retraction of the frontal glabellar implantation line. This methodology has been already used by Rakowska et al., while studying the use of isotretinoin and acitretin in patients with FFA. These authors' study showed that this evaluation tool was able to demonstrate that there was no progression of AAF even after stopping medications.[19] At present, comparing treated and untreated sides, the right frontal-glabella and frontal temporo-parietal distances had significant reduction while the left frontal temporo-parietal distance progressed, showing that these metric parameters are the most important for assessing the progression of this fibrosing disease.

The comparison of symptoms and clinical findings before and after treatment demonstrated significant improvement of pruritus and desquamation, being those findings more present on the untreated side (on the left), which allows us to infer that treatment improved these complaints on the treated side (on the right). Erythema and hair loss were not important parameters to evaluate treatment response.

Concerning the use of trichoscopy as a tool to evaluate AAF activity, no studies that shows correspondence between trichoscopy and histological findings in relation to AFF activity as been done so far. According to STARACE et al. the best way to assess the progression of AFF would be the presence of symptoms such as hair fall, itching, erythema, desquamation and increased scalp sensitivity.[24]

As already mentioned, no studies using MMP technique in the FFA treatment have been done before but there is a description of the use of this treatment modality in other situations. Contin evaluated the use of MMP® with 5% Minoxidil for the treatment of androgenetic alopecia with a total of 3 monthly sessions, verifying that this is an effective and low complexity option, and that can be easily performed in an outpatient setting.[25] The present study corroborates these findings because it also showed a comfortable and well-tolerated technique, besides its low cost. Moreover, this technique proved to be quite safe, especially because it did not present any severe side effects, without triggering Köebner phenomenon or worsening of FFA after the MPM sessions.
No biochemical alterations were verified after three applications of MTX in drug delivery with total blood count, liver and renal function were preserved suggesting that this procedure is safe.

Patient's satisfaction was also a positive item observed currently, as most of them were pleased with the results; the technique was well tolerated without causing important pain and pruritus.

Limitations of the present study are the small sample and uncertainty as to the number of applications to be used as well as to the interval between them. The relative rarity of the disease and the strict exclusion criteria justify the small sample. The ideal number of applications as well the intervals between them are a knowledge in construction as this is the first report on MTX use through MMP® in FFA. More studies are needed to answer these questions. Another point to be taken into account is that the degree of systemic absorption of the MTX is unknown and this drug may have spread to the untreated side.

As positive points this work shows, in an unprecedented way, the use of a new technique for the treatment of AAF that has good results, low cost and it is easily performed.

CONCLUSION

The use of MTX in drug delivery through MMP® showed the ability to reduce symptoms and to avoid progression of AAF. Trichoscopy and LPPAI were not good instruments to evaluate treatment response but the frontal glabella and bilateral frontal temporo-parietal measurements were satisfactory. The procedure was safe and well tolerated offering a new option for treatment of AFF patients.

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