

# Can microinfusion of methotrexate in scalp lesions help in the relief of frontal fibrosing alopecia?

*Microinfusão de metotrexato nas lesões de couro cabeludo podem auxiliar no alívio da alopecia frontal fibrosante?*

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## ABSTRACT

**Introduction:** Frontal fibrosing alopecia is a form of primary lymphocytic cicatricial alopecia, with loss of hair in the frontal implantation line of the scalp and other body areas. It consists of a systemic and multifactorial disease, with genetic, hormonal, environmental, racial and, sometimes, gender influence. The technique of microinfusion of microparticles through the skin (MMP®) is minimally invasive and minimally painful or painless.

**Objective:** To review the effectiveness of this technique with methotrexate in frontal fibrosing alopecia.

**Method:** The literature review was carried out by collecting information published on virtual platforms searched for descriptors related to the topic, identified through DeCS, such as: "frontal fibrosing alopecia, lichen planopilaris, baldness, scalp, and methotrexate" with search AND or OR, considering the title and/or abstract. Afterwards, considering only those that were most related to the topic, the full texts were read.

**Results:** 39 articles were included.

**Conclusion:** The application of MTX by MMP® showed a significant reduction in symptoms associated with frontal fibrosing alopecia, and improvement in frontoglabbellar and frontotemporal measurements. The technique proved to be safe and was well tolerated.

**KEYWORDS:** Alopecia. Scalp. Methotrexate.



Frontal fibrosing alopecia

## Central Message

Frontal fibrosing alopecia is a form of primary lymphocytic scarring alopecia, with hair loss at the frontal implantation line of the scalp and other body areas. It consists of a systemic and multifactorial disease, with genetic, hormonal, environmental, racial and sometimes gender influences. The microparticle through the skin (MMP®) technique is minimally invasive and not very painful or painless. This review sought to survey the scientific evidence of its efficacy from the existing literature.

## Perspective

Regarding the technique of microinfusion of MTX through MMP®, there is a need for a greater number of clinical trials in relation to the number of sessions and the time interval between treatments. Thus, based on new studies, patients with AFF will be able to have a better therapeutic arsenal, with specific guidelines for follow-up and management in early treatment, aiming at controlling the disease that causes unaesthetic damage and has a negative impact on quality of life.

## RESUMO

**Introdução:** A alopecia frontal fibrosante é forma de alopecia cicatricial linfocítica primária, com perda de pelos na linha de implantação frontal do couro cabeludo e outras áreas corporais. Consiste em doença sistêmica e multifatorial, com influência genética, hormonal, ambiental, racial e, por vezes, de gênero. A técnica de microinfusão de micropartículas através da pele (MMP®) é minimamente invasiva e pouco dolorosa ou indolor.

**Objetivo:** Revisar a eficácia dessa técnica com metotrexato na alopecia frontal fibrosante.

**Método:** A revisão da literatura foi feita colhendo informações publicadas em plataformas virtuais buscada por descritores relacionados ao tema, identificados por meio do DeCS, como: "alopecia frontal fibrosante, líquen plano pilar, calvície, couro cabeludo, e metotrexato" com busca AND ou OR, considerando o título e/ou resumo. Após, considerando-se somente os que tinham maior relação ao tema, foi realizada a leitura da íntegra dos textos.

**Resultados:** Foram incluídos 39 artigos.

**Conclusão:** A aplicação de MTX por MMP® mostrou redução significativa dos sintomas associados à alopecia frontal fibrosante, e melhora nas medidas frontoglabbellares e frontotemporais. A técnica mostrou-se segura e foi bem tolerada.

**PALAVRAS-CHAVE:** Alopecia. Couro cabeludo. Metotrexato.

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## INTRODUCTION

**F**rontal fibrosing alopecia (AFF) is scarring, inflammatory, progressive, and chronic with predominant lymphocytic infiltrate. It consists of a variant form of lichen planus pilaris and has unknown etiopathogenesis. It was described by Kossard S in 1994 and was characterized by the presence of progressive cicatricial alopecia, affecting the hairline in the frontotemporal region and eyebrows. Today, it is known that it involves hair loss in other regions of the body, such as the armpits, inguinal, upper and lower limbs, and eyelashes. Initially, it was described only in postmenopausal women, most of whom were Caucasian and correlated with androgenic activity of the period and its action on the hair follicle, inflaming it and leading to hair loss.<sup>1</sup> However, several cases have been diagnosed and reported in young or premenopausal women, as well as in men.

Since the first reports, its diagnosis has been made based on clinical suspicion, by hair loss in the frontal implantation line of the scalp or loss of eyebrows. As the disease became epidemic, new publications allowed us to verify that AFF is an inflammatory disease that can also be associated with other lesions, such as brownish spots on malar - configuring itself as lichen planus pigmentosum, and facial normochromic papules. Although it is an asymptomatic dermatosis, it can course with changes in sensitivity in the scalp and present pain or itching, characterizing trichodinea.

Trichoscopy is an important noninvasive method for diagnostic evaluation. Based on characteristic findings, such as erythema, desquamation, and perifollicular hyperchromia, a presumptive diagnosis of AFF can be made and the degree of inflammation and disease activity can be assessed.<sup>2</sup> Scalp biopsy is the diagnostic method of certainty, showing a reduction in the number of terminal hair follicles in the dermis, perifollicular concentric fibrosis, lymphocytic infiltrate in the follicular isthmus, presence of necrotic keratinocytes, in addition to fibrotic tracts and the scarring pattern of alopecia.<sup>3</sup>

As a result, careful evaluation is necessary to define the activity of the AFF. Through the response to treatment, scores, dermoscopy, biopsy, traction test of anagen hairs, comparative clinical evolution (density and hair implantation), and symptoms on the scalp, the progression of inflammation and hair loss can be evaluated.<sup>4</sup> However, there is no method that has been completely validated or considered the gold standard for assessing prognosis.

Different therapeutic forms are known, but with variable results, since their treatment is controversial and often not very effective. Because it is scarring alopecia, the main goal of treatment is to prevent the progression of inflammation and disease activity. Early diagnosis, through clinical evaluation, trichoscopy, biopsy, associated with the initial

intervention, can modify the evolution, preventing its progression.<sup>5</sup>

Topical, intralesional, and systemic corticosteroids are some of the treatment options, as well as others, such as cyclosporine, thalidomide, and griseofulvin, which have already been described and have shown variable responses. The association of these therapies has shown promise and superior to monotherapy. There are also reports in the literature about the benefit of the association with low-level laser (excimer laser and carbon dioxide).<sup>7</sup>

Hair transplantation is considered in AFF, as well as in other forms of inflammatory alopecia, only in cases where there is stability of the disease for more than 2 years.<sup>8</sup>

Methotrexate (MTX), administered intramuscularly, orally or subcutaneously, is part of the therapeutic arsenal, either because of its anti-inflammatory mechanisms or because it behaves as a steroid-sparing agent. However, the systemic risks involved limit its use, since it is associated with gastrointestinal intolerance, risk of myelosuppression, hepatotoxicity, and is also teratogenic. Its bioavailability is limited orally due to incomplete absorption by the gastrointestinal tract, hepatic metabolism, and releasing into the systemic circulation small concentrations of the drug despite ingestion of high doses. In addition, because it is water-soluble, MTX has a limited capacity to permeate the stratum corneum, and its use in intact skin becomes ineffective.<sup>9</sup> For this reason, techniques such as electroporation, iontophoresis, and ablative lasers have been used to increase its permeation through the skin, with a therapeutic response in the treatment of psoriasis in studies carried out.<sup>10</sup>

Microparticle microinfusion into the skin (MMP®) consists of superficial microneedling, at the same time as the infusion of the active ingredients by needles. The depth of microneedling is previously adjusted, according to the disease to be treated. The materials used consist of disposable and sterile tips and needles, in addition to the machine that applies the active ingredient to the skin. All materials are low cost and those released for use in Brazil are certified by ANVISA.<sup>11</sup> MMP® was based on existing drug injection techniques, initially from a single needle used for scar treatment and, later, with refinement of the method, a tattoo device with more needles. Through this technique, it was possible to infuse MTX directly into the psoriasis lesions, with good tolerance of the patients evaluated and remission of the lesions. The drug injected percutaneously has a potent local effect and manages to avoid hepatic first-pass metabolism. As a result, it reaches the systemic circulation in a low concentration, undetectable, but sufficient to obtain a therapeutic response, treating patients with moderate to severe psoriasis and, also, lesions resistant to other therapies, without side effects.

Considering that the treatment of AFF is challenging, this review aimed to verify the efficacy

of MTX infusion through the MMP® technique on the scalp and to point out its possible adverse effects.

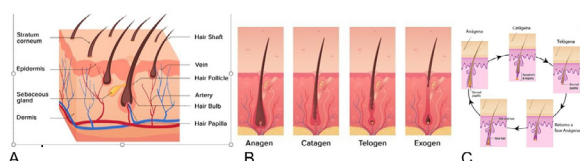
## METHOD

The literature review was carried out by collecting information published on virtual platforms, in Portuguese and English, selected from the SciELO, Google Scholar, Pubmed and Scopus platforms. Initially, a search was carried out for descriptors related to the theme, identified through DeCS, using the following terms: “frontal fibrosing alopecia, lichen planus pilaris, baldness, scalp, and methotrexate” with an AND or OR search, considering the title and/or abstract. Afterwards, considering only those that were more related to the theme, the full texts were read and finally 39 articles were included.

## DISCUSSION

### Frontal fibrosing alopecia Follicular cycle

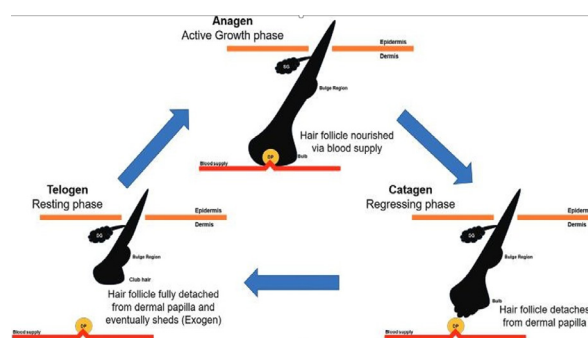
Human hair grows in a cyclical and continuous pattern and rest, known as the growth cycle, which is composed of phases: anagen (growth), catagen (transition), telogen (rest), and exogenous (shedding). During the anagen phase, the follicle is divided into 2 parts: the upper or permanent portion, composed of the infundibulum and isthmus, and the lower or temporary portion, whose lower limit is the follicular bulb.<sup>12</sup> It is below the bulb that the hair strands begin to be formed by the keratinocytes of the matrix, which receive the nutrients from the dermal papilla and proliferate intensely, at the same time that they receive pigment from the follicular melanocytes interspersed with each other. As a result, the bulb generates an average of 1 cm of new hair per month, while the follicle remains in the anagen phase, it can last up to 25 years, with an average of 3-8 years<sup>13</sup> (Figure 1).



**FIGURE 1** — Hair structure: A) hair follicle and hair shaft; B) phases: anagen (growth), catagen (transition), telogen (rest), exogenous (shedding); C) hair cycle

After the end of the anagen phase, the follicle enters the catagen phase, in which the keratinocytes of the matrix stop proliferating, block the entry of pigment from the melanocytes and undergo apoptosis, generating a white end in the hair that is preparing to fall out. The anatomy of the follicle changes rapidly at this stage. After 10-14 days, the bulb disappears and the entire lower portion undergoes involution, leaving in its path the trail of blood vessels, called fibrous tracts, and, above these, the telogen wire.<sup>13</sup> The telogen phase then begins, which lasts 3 months. It is also called the

resting phase, because the telogenized follicle does not grow. This definition, however, is inappropriate, since during these 3 months the formation of a new hair follicle will occur. Although imperceptible in macroscopy of the scalp, during the telogen phase, the keratinocytes of the follicular bulb, located at the lower limit of the isthmus, begin to proliferate, forming a structure with a characteristic aspect: the telogen germinal unit. This structure aims to find the vessels of the fibrous tract and delimit a new dermal papilla, thus forming a new anagen bulb, initially small and superficial, but which gradually increases its diameter, as it deepens along the path of the fibrous tract. At the same time as the bulb deepens, a new hair begins to be produced and grows towards the epidermis. When the tip of this new hair is exteriorized, the telogen hair of the predecessor follicle is expelled, performing a perfect exchange and leaving no empty ostia on the scalp. The new follicle, already with a diameter and depth similar to the previous one, will remain in the anagen phase for years, until it enters the catagen phase and so on.<sup>13</sup> (Figure 2).

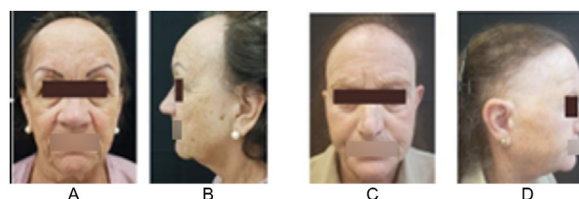


Source: International Immunology, 2019

**FIGURE 2** — Illustration of the hair growth cycle

### Epidemiology

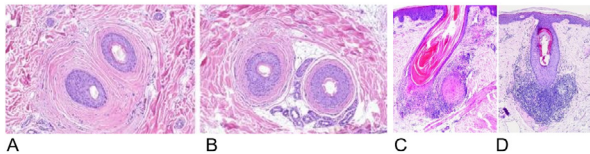
AFF has become an epidemic disease described worldwide and with increasing numbers. It is more prevalent in Caucasian women and after 50 years of age, in the postmenopausal period.<sup>14,15</sup> More recently, there has been an increase in cases in African-American and Asian women (Figure 3) and also in young women in the premenopausal period who probably initially received another diagnosis, for example, alopecia due to androgenetic traction. Increasing numbers of cases have also been reported in young men, who often present, as an initial sign, eyebrow loss.



**FIGURE 3** — Frontal fibrosing alopecia: A and B) hair loss in the frontal implantation line of the scalp; C and D) eyebrow loss

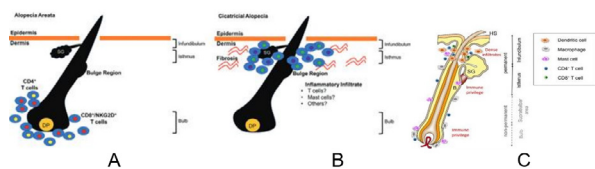
## Etiopathogenesis

AFF is primary scarring alopecia, which means that, after the inflammatory process around the follicular isthmus, there is definitive replacement of this tissue by fibrotic tracts and the absence of new hair follicles in this scar area. Therefore, there is no hair repilation after hair loss<sup>16</sup> (Figure 4).



Source: J AM Acad Dermatol 2017 (A and B); Hautarzt, Dermatologie, Allergologie und Phlebologie, 2016 (C & D)

**FIGURE 4** – Frontal fibrosing alopecia (A and B) and perifollicular clear lymphocytic inflammation (C and D): A) reticular dermis; B) dermal subcutaneous junction with fibrosis extending beyond the isthmus; C) normal interfollicular epidermis; D) greater magnification with intrafollicular lymphocytes, dyskeratosis and perifollicular fibrosis



Source: International Immunology, 2019 (A and B); Exp Dermatol. 2020 (C)

**FIGURE 5** – Illustration of the histological presentation: A) non-scarring alopecia; B) scarring alopecia; C) morphology and immunology of the pilosebaceous follicle

The inflammatory infiltrate is predominantly TCD8+17 lymphocytes in the follicular isthmus (Figure 5), a region of the hair where hair stem cells are located, which makes it impossible to recover hair growth in these affected areas. One hypothesis that has been accepted refers to the loss of immune privilege, as occurs in alopecia areata. Consequently, there is a deficiency of the peroxisome activating receptor (PPAR- $\gamma$ ), which has great antifibrotic activity, enabling autoimmune attack on the infundibular isthmus with permanent destruction. The factors that lead to the loss of this immune privilege are unknown, so far.<sup>18</sup>

In lichen planus there is an association with the HLA-DR1 gene and, although AFF is a variant of it, until recently no alleles were found that correlated with AFF. However, new studies demonstrate that the mutation of the gene CYP21A2 p.<sup>V281L</sup> can be used as a genetic marker for susceptibility to familial frontal fibrosing alopecia.<sup>19</sup>

In addition, hormonal action is also suggested as a possible triggering factor for AFF, mainly because this alopecia is more prevalent in postmenopausal women. In this sense, over the years, the drop in DHEA (dihedral-epi-androsterone) and DHEA sulfate - hormones that are precursors of testosterone and essential for PPAR- activity - could explain the loss of immune privilege that occurs in AFF. It is due to

possible androgenic involvement that therapeutic response to 5 -reductase would be expected.<sup>20</sup>

Scalp sensitivity, clinically manifested in some patients with AFF, could be explained by the reduction of substance P and increase in peptide related to the calcitonin gene.

Regarding possible external triggers, for some time it was thought that sunscreens or other cosmetics – such as makeup, for example – when applied close to the frontal implantation line, could trigger the follicular inflammatory process, leading to definitive hair loss.<sup>21</sup> However, there is no evidence linking the pathogenesis of AFF with the use of cosmetics, traction methods, or scalp maceration (use of hats, caps, or caps).<sup>22</sup>

## Clinical manifestations and diagnosis

In the clinical diagnosis, in addition to the area of alopecia in the frontal and frontotemporal implantation line, the texture of the skin that is atrophic in this region is evaluated, allowing greater visualization of blood vessels due to the loss of the dermal portion. With its scar progression, the color of the skin becomes lighter in relation to the forehead. It is also evaluated whether there is an increase in the distance between the eyebrows and the frontal hair implantation line, as well as an increase in the distance between the lateral epicorners of the eyes to the frontotemporal hair implantation line. Hair loss or reduction in hair density in other areas of the body, such as eyelashes, eyebrows, limbs, armpits, inguinal, are also evaluated. Erythema on the scalp and the pseudofringe sign are clinical signs that also signal the investigation of FNA. Brownish plaques on the malars may lead to suspicion of lichen planus pigmentosum, which is part of the AFF spectrum, especially in patients with a higher Fitzpatrick phototype (Figure 6).

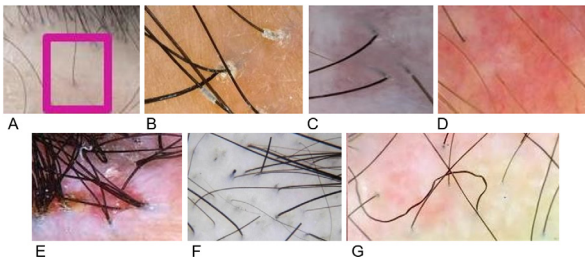


**FIGURE 6** – A and B) Association between lichen planus pigmentosum; C and D) frontal fibrosing alopecia

A positive traction test of anagen hairs signals inflammatory activity of the disease. Symptoms such as scalp pain, increased sensitivity or itching can also occur in the condition of AFF.

## Trichoscopy

By handheld trichoscopy, it is possible to increase the area to be examined from 10-20x of the original size. Digital dermoscopy, on the other hand, can magnify it by up to 40x and, as a result, the diagnostic clinical accuracy is increased.<sup>23</sup>



**FIGURE 7** — Trichoscopic findings in frontal fibrosing alopecia: A) lonely hair; B) peripapillary scaling; C) peripapillary erythema; D) erythema and telangiectasia on the scalp; E) crusts; F) tufts; G) Pili torti

Some findings, such as lonely hair (isolated hair in an area of atrophy in the frontal implantation line), perifollicular desquamation and erythema, peripilar hyperchromia (in higher phototypes), are characteristic of AFF.<sup>23</sup> Pili torti (dystrophic hair) and broken hair (black or broken) can also be found, the latter resulting from the breakage of the hair. Telangiectasias on the scalp, as well as diffuse erythema, may also be found in AAF23 (Figure 7).

### Histology

According to the stages of AFF, a characteristic histological pattern is observed. In the initial picture, lymphohistiocytic and lichenoid infiltrate is evidenced around the outer root sheath in the region of the follicular isthmus, in addition to mild perifollicular lamellar fibrosis. In the later stages, more pronounced follicular fibrosis is observed, with reduction of hair follicles, and replacement of the attached glands by fibrous tissue.

### Treatments

Different therapeutic forms are known, but with variable results because the treatment of AFF is controversial and often not very effective. Because it is scarring alopecia, the main goal of treatment is to prevent the progression of inflammation and disease activity. Early diagnosis, through clinical evaluation, trichoscopy, biopsy and with initial intervention, can modify the evolution of the disease, preventing its progression.<sup>24</sup>

In addition to topical, intralesional, and systemic corticosteroids, there are other treatment options, such as hydroxychloroquine, methotrexate, acitretin, isotretinoin, mycophenolate-mofetil, finasteride, naltrexone, pioglitazone, doxycycline, tofacitinib.<sup>6</sup> More recently, oral minoxidil and bicaludam have also been used. Other options, such as cyclosporine, thalidomide, and griseofulvin, have already been described and have shown variable response. The association of these therapies has shown promise and superior to monotherapy. There are also reports in the literature about the benefit of the association with low-level laser (excimer laser and carbon dioxide).<sup>10</sup> Hair transplantation is considered in AFF, as well as in other forms of inflammatory alopecia, only in cases where the disease is stable for more than 2 years.<sup>8</sup>

In turn, MTX, administered intramuscularly, orally or subcutaneously, is part of the therapeutic arsenal of AFF already described,<sup>25</sup> either because of its anti-inflammatory mechanisms or because it behaves as a steroid-sparing agent.

### Methotrexate and its routes of administration and bioavailability

MTX is an analogue of folic acid, which competitively inhibits dihydrofolate reductase (DHFR), an enzyme that converts dihydrofolate into tetrahydrofolate, which is a necessary cofactor in the synthesis of thymidylate and purine nucleotides, which are required in DNA/RNA synthesis. This inhibition may be partially reduced by the concomitant administration of folic acid.<sup>26</sup> MTX also performs a partially reversible inhibition cascade of thymidylate synthetase, inhibiting cell division in the S phase. Although it was originally believed to suppress keratinocyte proliferation, it is more likely to inhibit DNA synthesis in immunologically active cells.<sup>26</sup>

It is a drug used orally, subcutaneously or intramuscularly. In dermatology, it is indicated for the treatment of inflammatory dermatoses such as psoriasis, atopic dermatitis, dermatomyositis, pityriasis rubra pilaris. It can also be used as a steroid-sparing agent, and in the elderly, weekly monotherapy is an option for the treatment of bullous pemphigoid. In addition to being associated with gastrointestinal intolerance, it presents a risk of myelosuppression, hepatotoxicity, and is a teratogenic drug.<sup>26</sup>

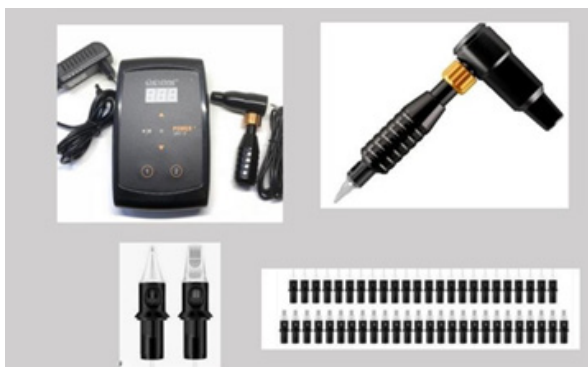
Its bioavailability by the oral route is limited due to incomplete absorption by the gastrointestinal tract, in addition to metabolization in the first hepatic passage, releasing small concentrations of the drug into the systemic circulation despite the ingestion of high doses. Administered orally, it is rapidly absorbed and reaches peak serum levels within 1-2 h. After intramuscular injection, plasma peaks are detected in approximately half of this period.<sup>27</sup> MTX diffuses and accumulates in red blood cells. In serum, about 50% of the drug is reversibly bound to albumin, which means that the concomitant use of other drugs that also bind to proteins can increase their hematological toxicity.<sup>28</sup> Once absorbed, its levels in plasma have a three-phase reduction: the first, rapid distribution, is followed by the second of 2-4 h reflecting renal excretion; the third, represents a terminal half-life of 10-27 h and is secondary to the enterohepatic circulation.<sup>This</sup> terminal half-life, if unduly prolonged as a result of renal failure, may be responsible for the drug's major toxic effects on the bone marrow and gastrointestinal tract.<sup>29</sup>

The enzyme reduced folate carrier 1 (RFC1), a ubiquitous transmembrane carrier protein, can limit the oral absorption of MTX when saturated, which occurs from 15 mg.<sup>30</sup> As an alternative, some studies have investigated the possibility of its topical use, which would reduce the occurrence of side effects, and could increase bioavailability without increasing the risk of toxicity. However, because MTX is water-soluble, it has a limited capacity to permeate the stratum corneum, and

its use in intact skin becomes ineffective.<sup>10</sup> Therefore, techniques such as electroporation, iontophoresis and ablative lasers were used to increase its permeation through the skin with a therapeutic response in the treatment of psoriasis in a study carried out.

### Microparticle microinfusion (MMP®)

The MMP® (microparticle microinfusion) technique, first published in 2013<sup>11</sup>, consists of performing micropunctures on the skin beyond the stratum corneum, increasing the delivery of certain active ingredients (depending on what is to be treated), from a device containing microneedles that deliver medication (Figure 8).



Source: Cheyenne, captured in <https://tattooaja.com.br/>

**FIGURE 8** — Kit for microinfusion of microparticles into the skin: source, handles, executor, executor at higher magnification, 23 Magnum tip and other tips available.

In MMP®, ablation of the corneal layer and removal of the most superficial layers of the epidermis occurs, facilitating the entry of active substances into the deeper layers.<sup>11</sup> Naeini et al. (2006)<sup>32</sup> infused bleomycin into keloids and hypertrophic scars, while Sadeghinia et al (2012)<sup>32</sup> infused 5-FU into keloids. Both studies showed satisfactory results in terms of improvement in the appearance of the lesions. There are few publications that use the MMP® technique with MTX infusion. However, authors<sup>32</sup> performed the technique in 2 patients with clinical improvement of plaque psoriasis lesions after monthly applications of MTX, and one of the 2 treated underwent 3 sessions of MMP® with MTX 25 mg/ml with complete remission of the lesions. No serum MTX levels were detected on the day after application, nor complaints of side effects. In the other patient, 1 application of MMP® with MTX was performed on the lesions of the left back and arm with 25 mg/ml, promoting remission of the lesions, without detection of the medication in the circulation and without side effects in the individuals evaluated.

Regarding the infusion of medications through MMP® in scarring and non-scarring alopecia, there are few publications in the literature, but with favorable results. In androgenetic alopecia, the administration of minoxidil 5% through MMP® was tried with a cosmetically satisfactory response. This infusion proved to be an effective and low-complexity option, with a comfortable dosage, and can even be performed in an outpatient setting.

## Evaluation of therapy and follow-up

### AFF evaluation scores

#### LPPAI

The Lichen Planopilaris Activity Index (LPPAI) proved to be a good measure for monitoring the effectiveness of AFF treatments. However, it has limitations, as it does not assess the extent of the disease, but only quantifies signs and symptoms. This score evaluates symptoms (itching, pain, and burning), signs (diffuse erythema, erythema, and perifollicular keratosis), anagen traction test (activity measurement), and progression or not of alopecia. Weight of 30% is given for symptoms, 30% for signs, 25% for the traction test, and 15% for alopecia progression.<sup>33</sup>

#### FFASI

The Frontal Fibrosing Alopecia Severity Index (FFASI) (0-100)<sup>24</sup> is based on a standardized picture of images that demonstrate the recess of the frontal line, divided into 4 sessions (frontal, right and left lateral, and posterior) and graded in 5 degrees of severity. Each grade receives a score (grade I = 4; grade II = 8; grade III = 12, grade IV = 16 and grade V = 20). The degree of inflammation (erythema and perifollicular keratosis) of the frontal band is also evaluated: no inflammation, normal density = 0; with inflammation or reduced density = 2; with inflammation and reduced density = 4. In this session, the maximum score is 84. Other hair loss (eyebrows, eyelashes, flexures, upper and lower limbs) are no loss = 0; partial loss = 1; total loss = 2; maximum score of 10. Additional features (typical scalp of lichen planus pilaris, papules of the face, cutaneous lichen planus and variants, lichen planus of the oral, genital and nail mucosa): absence = 0; presence = 1; maximum score = 6.

### Use of scores

One of the ways to evaluate the response to treatment is the use of the 2 indices mentioned: LPPAI, FFASI based on the degree of inflammation of the scalp, symptoms that the patient mentions during the questionnaire and progression of the disease.

In a Brazilian study that included 22 patients with AFF treated and evaluated using the LPPAI and FFASI scales, it was shown that they are not satisfactory if applied separately, because the final score of both is not directly correlated, but only complements each other.

### Frontotemporal and frontoglabellar measurements

Another way used to evaluate the response to treatment is based on the frontoglabellar, right and left frontotemporal measurements before and after treatment, a methodology already described in the literature.<sup>27</sup> The study by Rakowska et al. <sup>27</sup> showed the cessation of FNA progression after discontinuation of isotretinoin or acitretin from frontoglabellar measurements (excluding lonely hair) and clinical photos after 6, 12 and 24 months.

### Clinical photos and trichoscopy

From semiannual clinical photos, trichoscopy photos, it is possible to make adequate follow-up and evaluation of the arrest or not of the progression of AFF inflammation. Clinical photographs should follow the

same standardization of distance, luminosity, positions (front and profiles) and use the same camera<sup>22</sup> (Figure 9).



**FIGURE 9** – Clinical photos: A) right profile; B) left profile; C) frontal photo

AFF, as it is primary and progressive lymphocytic cicatricial alopecia, has a clinical evolution that is still obscure and treatment in monotherapy is discouraged because it is a multifactorial systemic disease. According to de Souza et al<sup>38</sup>, for a therapeutic response to occur, it is necessary that the treatment of AFF be done with a combination of drugs and, even so, with the use of different routes of administration.

Vañó-Galván et al (2017)<sup>34</sup> point out that there is a lack of randomized clinical trials on the best treatment for AFF; however, the available evidence provides guidance on the potential of the therapeutic approaches already described. Regarding the use of MTX through the MMP® technique for the treatment of AFF, there are some cases reporting its oral use in patients with AFF, with mixed results.<sup>6</sup> A study conducted at Duke University, USA, 3 patients with AFF were treated with oral MTX, and only 1 achieved disease stabilization.<sup>35</sup> Similarly, another study done at the Mayo Clinic, USA, with only 2 patients treated with MTX systemically, showed that the drug was able to prevent the progression of the disease.<sup>36-39</sup>

We already know that MTX, being a water-soluble molecule, has a limited capacity to permeate the stratum corneum and topical use on intact skin is ineffective.<sup>10</sup> For this reason, techniques such as electroporation, iontophoresis, and ablative lasers were used with the aim of increasing the penetration of this drug through the skin. Arbache et al.<sup>11</sup> described MMP® with drug delivery of MTX for the treatment of plaque psoriasis, with complete remission of the lesions of 2 patients after 3 sessions, with an interval of 2 weeks between each one. In the present study, this technique showed improvement in pruritus and desquamation on the treated side ( $p < 0.05$ ), with no progression of the frontal implantation line, which can be interpreted as a halt in the progression of the disease, with a positive impact on quality of life.

In a study by Brazilian authors, the way used to evaluate the response to treatment was the frontoglabellar, right and left frontotemporal measurements, before and after treatment. It was observed that the treatment prevented the progression of the retraction of the frontoglabellar implantation line. This evaluation methodology had already been described by Rakowska et al.<sup>27</sup> evidencing the cessation of the progression of AFF even after the suspension of the medications in use (in this case, isotretinoin and acitretin), from the frontoglabellar

measurement (excluding lonely hair), as well as the clinical photos after 6, 12 and 24 months.

Currently, in the comparative analysis between the treated and untreated sides, it was observed that the frontoglabellar and right frontoparietal measurements had a significant reduction, while the left frontoparietal had a significant increase. Therefore, it is observed that, in accordance with the literature, the evaluation of the measurements between the epicanthus and the frontal implantation line, as well as the glabella and the frontal alopecia band, are the most important metric parameters to evaluate the progression of this fibrosing disease.

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

Regarding the use of trichoscopy as a measure to evaluate AFFA activity, to date there are no studies demonstrating the correspondence between trichoscopy and histology findings in relation to AFFA activity. According to Starace et al.<sup>37</sup> the best way to assess the progression of AFF would be the presence of symptoms, such as hair loss, itching, erythema, desquamation, and increased scalp sensitivity.

Regarding the analysis of the MMP® technique in the treatment of AFF, there are no reports in the literature on its use to treat scarring alopecia, but there are no reports in the literature on its use to treat scarring alopecia, but there is a description of this treatment modality in other diseases. Other authors<sup>38</sup> evaluated the use of MMP® with 5% minoxidil for the treatment of androgenetic alopecia, with a total of 3 monthly sessions, showing that it is an effective and low-complexity option, with a comfortable dosage, and can be performed in an outpatient setting.

Laboratory evaluation after the 3 sessions of MMP® with drug delivery of MTX showed no changes in serum levels of transaminases, bilirubins or organic, renal and hematological dysfunctions, which allows inferring the no, or little, systemic absorption of MTX, which makes the procedure a safe treatment.

De Souza et al.<sup>38</sup> were able to demonstrate, with some novelty, that the technique is promising in controlling the progression of AFF, with low risks associated with MMP® or the possible systemic absorption of MTX. In addition, the treatment has a comfortable dosage, low cost – both technique and the drug used – in addition to being a procedure with low complexity.<sup>39</sup>

However, further studies should be oriented towards comparative results of the various treatments, in order to confirm which one or which are the most appropriate.

## CONCLUSION

The treatment of MMP® with MTX has been shown to be an effective, well-tolerated, and safe option in the treatment of AFF, with a significant reduction in associated symptoms, in addition to preventing the progression of the disease. Trichoscopy and LPPAI were not good

instruments to assess response to treatment. On the other hand, the bilateral frontoglabbellar and frontotemporal measurements were statistically satisfactory to evaluate the therapeutic outcome.

#### Authors' contributions

Conceptualization: Tatiane Elen e Souza  
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## REFERENCES

- Kossard S, Lee MS, Wilkinson B. Postmenopausal frontal fibrosing alopecia: a variant of lichen planopilaris. *J Am Acad Dermatol.* 1997;36(1):59-66. Doi: 10.1016/s0190-9622(97)70326-8
- Anzai A, Pirmez R, Vincenzi C, Fabbrocini G, Romiti R, Tosti A. Trichoscopy findings of frontal fibrosing alopecia on the eyebrows: A study of 151 cases. *J Am Acad Dermatol.* 2021;85(5):1130-4. Doi: 10.1016/j.jaad.2019.12.023
- Tavakolpour S, Mahmoudi H, Abedini R, Hesari KK, Kiani A, Daneshpazhoo M. Frontal fibrosing alopecia: An update on the hypothesis of pathogenesis and treatment. *Int J Womens Dermatol.* 2019;5(2):116-23. Doi: 10.1016/j.ijwd.2018.11.003
- Photiou L, Nixon RL, Tam M, Green J, Yip L. An update of the pathogenesis of frontal fibrosing alopecia: What does the current evidence tell us? *Australas J Dermatol.* 2019;60(2):99-104. Doi: 10.1111/ajd.12945.
- Kossard S, An update of the pathogenesis of frontal fibrosing alopecia: What does the current evidence tell us? *Australas J Dermatol.* 2019;60(4):335-6. Doi: 10.1111/ajd.13128
- Imhof R, Tolkachjov SN. Optimal Management of Frontal Fibrosing Alopecia: A Practical Guide. *Clin Cosmetol Invest Dermatol.* 2020;13:897-910. Doi: 10.2147/CCID.S235980
- Ferting R, Tosti A. Frontal fibrosing alopecia treatment options. *Intractable Rare Dis Res.* 2016;5(4):314-315. Doi: 10.5582/irdr.2016.01065
- Scribel M, Dutra H, Trueb RM. Autologous Hair Transplantation in Frontal Fibrosing Alopecia. *Int J Trichology.* 2018;10(4):169-171. Doi: 10.4103/ijt.ijt\_37\_18
- Schiff MH, Jaffe SJ, Freundlich B, Head-to-head, randomised, crossover study of oral versus subcutaneous methotrexate in patients with rheumatoid arthritis: drug-exposure limitations of oral methotrexate at doses  $\geq 15$  mg may be overcome with subcutaneous administration. *Ann Rheum Dis.* 2014;73(8):1549-51. Doi: 10.1136/annrheumdis-2014-205228
- Taudorf EH, Lerche CM, Vissing AC, Philipsen PA, Hannibal J, D'Alvise J, et al. Topically applied methotrexate is rapidly delivered into skin by fractional laser ablation. *Expert Opin Drug Deliv.* 2015;12(7):1059-69. Doi: 10.1517/17425247.2015.1031216
- Arbache S, Roth D, Steiner D, Breunig J, Michalany NS, Arbache ST, et al. Activation of melanocytes in idiopathic guttate hypomelanosis after 5-fluorouracil infusion using a tattoo machine: Preliminary analysis of a randomized, split-body, single blinded, placebo controlled clinical trial. *J Am Acad Dermatol.* 2018;78(1):212-215. Doi: 10.1016/j.jaad.2017.08.019.
- Harland DP, Introduction to Hair Development. *Adv Exp Med Biol.* 2018;1054:89-96. Doi: 10.1007/978-981-10-8195-8\_8
- Oh JW, Kloepper J, Lagan EA, Kim Y, Yeo J, Kim MJ, et al. A Guide to Studying Human Hair Follicle Cycling In Vivo. *J Invest Dermatol.* 2016;136(1):34-44. Doi: 10.1038/JID.2015.354
- Morgado-Carrasco D, Fustá-Novell X. Frontal Fibrosing Alopecia. *JAMA Dermatol.* 2020;156(2):92. Doi: 10.1001/jamadermatol.2019.3110
- Kanti V, Constantinou A, Reygagne P, Vogt A, Kottner J, Blume-Peytavi U. Frontal fibrosing alopecia: demographic and clinical characteristics of 490 cases. *J Eur Acad Dermatol Venereol.* 2019;33(10):1976-83. Doi: 10.1111/jdv.15735
- Wong D, Goldberg LJ. The depth of inflammation in frontal fibrosing alopecia and lichen planopilaris: A potential distinguishing feature. *J Am Acad Dermatol.* 2017;76(6):1183-4. Doi: 10.1016/j.jaad.2016.10.011
- Pindado-Ortega C, Perna C, Saceda-Corralo D, Fernández-Nieto D, Jaén-Olasolo P, Vaño-Galván S. Frontal fibrosing alopecia: histopathological, immunohistochemical and hormonal study of clinically unaffected scalp areas. *J Eur Acad Dermatol Venereol.* 2020;34(2):e84-5. Doi: 10.1111/jdv.15977
- Bertolini M, McElwee K, Gilhar A, Bulfone-Paus S, Paus R.
- Porriño-Bustamante ML, López-Nevo MA, Aneiros-Fernández J, Casado-Ruiz J, García-Linares S, Pedrinacci-Rodríguez S, et al. Study of Human Leukocyte Antigen (HLA) in 13 cases of familial frontal fibrosing alopecia: CYP21A2 gene p.V281L mutation from congenital adrenal hyperplasia linked to HLA class I haplotype HLA-A\*33:01; B\*14:02; C\*08:02 as a genetic marker. *Australasian Journal of Dermatology.* 2019;60:e195-200. Doi: 10.1111/ajd.12985
- Gaspar NK. DHEA and frontal fibrosing alopecia: molecular and physiopathological mechanisms. *An Bras Dermatol.* 2016;91(6):776-780. Doi: 10.1590/abd1806-4841.20165029
- Robinson G, McMichael A, Wang SQ, Lim HW. Sunscreen and frontal fibrosing alopecia: A review. *J Am Acad Dermatol.* 2020;82(3):723-8. Doi: 10.1016/j.jaad.2019.09.085
- Kusano LDC, Brenner FAM. Frontal fibrosing alopecia: follow-up of a Brazilian group. *An Bras Dermatol.* 2019;94(3):365-6. Doi: 10.1590/abd1806-4841.20197941
- Alessandrini A, Bruni F, Piraccini BM, Starace M. Common causes of hair loss - clinical manifestations, trichoscopy and therapy. *J Eur Acad Dermatol Venereol.* 2021;35(3):629-40. Doi: 10.1111/jdv.17079
- Holmes S, Ryan T, Young D, Harries M, Hair B, Nails Society. Frontal Fibrosing Alopecia Severity Index (FFASI): a validated scoring system for assessing frontal fibrosing alopecia. *Br J Dermatol.* 2016;175(1):203-7. Doi: 10.1111/bjd.14445. Epub 2016 May 27
- Babahosseini H, Tavakolpour S, Mahmoudi HR, Balighi K, Teimourpour A, Ghodsi SZ, Abedini R, et al. Lichen planopilaris: retrospective study on the characteristics and treatment of 291 patients. *J Dermatolog Treat.* 2019;30(6):598-604. Doi: 10.1080/09546634.2018.1542480
- Ramos PM, Anzai A, Duque-Estrada B, Melo DF, Stenberg F, Santos LDN, et al. Consensus on the treatment of alopecia areata - Brazilian Society of Dermatology. 2020;95(Suppl 1):39-52. Doi: 10.1016/j.abd.2020.05.006
- Rakowska A, Gradzinska A, Olszewska M, Rudnicka L. Efficacy of Isotretinoin and Acitretin in Treatment of Frontal Fibrosing Alopecia: Retrospective Analysis of 54 Cases. *J Drugs Dermatol.* 2017;16(10):988-92.
- Puig L. Methotrexate: new therapeutic approaches. *Actas Dermosifiliogr.* 2014;105(6):589-9. Doi: 10.1016/j.ad.2012.11.017
- Jeric B, Maksimovic N, Damnjanovic T. Methotrexate pharmacogenetics in the treatment of rheumatoid arthritis. *Pharmacogenomics.* 2019;20(17):1235-45. Doi: 10.2217/pgs-2019-0121
- Pannu AK. Methotrexate overdose in clinical practice. *Curr Drug Metab.* 2019;20(9):714-19. Doi: 10.2174/1389200220666190806140844
- Naeini FF, Najafian J, Ahmadpour K. Bleomycin tattooing as a promising therapeutic modality in large keloids and hypertrophic scars. *Dermatol Surg.* 2006;32(8):1032-9. Doi: 10.1111/j.1524-4725.2006.32225.x
- Sadghinia A, Sadghinia S. Comparison of the efficacy of intralesional triamcinolone acetonide and 5-fluorouracil tattooing for the treatment of keloids. *Dermatol Surg.* 2012;38(1):104-9. Doi: 10.1111/j.1524-4725.2011.02137.x
- Kaur H, Nikam BP, Jamale VP, Kale MS. Lichen Planus Severity Index: A new, valid scoring system to assess the severity of cutaneous lichen planus. *Indian J Dermatol Venereol Leprol.* 2020;86(2):169-75. Doi: 10.4103/ijdv.IJDVL\_650\_17
- Vañó-Galván S, Camacho F. New Treatments for Hair Loss. *Actas Dermosifiliogr.* 2017;108(3):221-8. Doi: 10.1016/j.ad.2016.11.010
- Ladizinski B, Bazakas A, Selim MA, Olsen EA. Frontal fibrosing alopecia: a retrospective review of 19 patients seen at Duke University. *J Am Acad Dermatol.* 2013;68(5):749-55. Doi: 10.1016/j.jaad.2012.09.043
- Alegre-Sánchez A, Saceda-Corralo D, Bernádez C, Molina-Ruiz AM, Arias-Santiago S, Vaño-Galván S. Frontal fibrosing alopecia in male patients: a report of 12 cases. *J Eur Acad Dermatol Venereol.* 2017;31(2):e112-4. Doi: 10.1111/jdv.13855
- Starace M, Orlando G, Alessandrini A, Baraldi C, Bruni F, Piraccini BM. Diffuse variants of scalp lichen planopilaris: Clinical, trichoscopic, and histopathologic features of 40 patients. *J Am Acad Dermatol.* 2020;83(6):1659-67. Doi: 10.1016/j.jaad.2019.11.006
- de Souza TE, Fabre AB, Medeiros KB, Skare TL, Lourenço C de M, de Souza ACM, et al. Efficacy of methotrexate microinfusion in scalp lesions of patients with fibrosing frontal alopecia: a prospective controlled trial. *SciELO Preprints.* Doi: 10.1590/SciELOPreprints.4313
- Frare E, Kahlow BS, Skare TL. Artrite reumatoide: associação entre atividade da doença, funcionalidade, qualidade de vida e conhecimento dos pacientes. 2022;80(2):70-3. Doi: 10.55684/80.2.16