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Treatment of Therapy-resistant Alopecia Areata with Fumaric Acid Esters

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Abstract:
Background: Alopecia areata is a cosmetically very disfiguring clinical picture and can be a great emotional burden to the patient, especially when persisting for a longer period of time.
Patients and Methods: 10 patients with an alopecia resistant to therapy were treated within the bounds of an open, non-placebo controlled pilot study with fumaric acid esters (FAE´s, Fumaderm®) for a period of six months and a maximum dose of 120 mg dimethyfumarate per day. The shortest space of time between persistent Alopecia areata and the start of the therapy with FAE was between six months and 17 years.
Results: Six patients took benefit from the six months therapy with FAE. In three of them very good results could be observed, presenting an almost entire remission, one patient showed a good success with a focal remission. With two patients a mediocre to moderate outcome was observed with growth of partly diffuse spread or very thin hair. Four patients took no benefit from the FAE therapy at all.
Conclusions: FAE can be useful in the treatment of therapy-resistant Alopecia areata. This therapy approach should be validated in a multi-centre study.

Key words: Therapy-resistant Alopecia areata, fumaric acid esters, t-lymphocytes, chronic (peri-)follicular inflammation reaction

Introduction

Alopecia areata (Aa) is defined as a potentially reversible, suddenly appearing, circular hairless on the capillitium, the eyebrows, the eyelashes, the hair of the beard and/or the pubic hair.

Special forms of the Alopecia areata are the Aa diffusa with diffusely bordered hairless areals, the Aa of the Ophiasis type which is localized in the border area of the hair, mainly occipito-retroauricular, the Aa totalis with affection of the whole capillitium and the Aa universalis which shows a complete loss of hair in any haired region of the body. The pathogensis of the Aa is still not completely revealed. Sometimes a family accumulation can be observed which stresses the thesis that Aa in these cases is genetically determined.

Coincidences with atopic disposition and autoimmunological illnesses can be found [13, 14]. Infectreactive factors are discussed. Aethiologically immunological-inflammatorical mechanisms dominate via cytokine-mediated t-cell-reactions. Hairfollicle-keratinocyte-cytokines with proinflammatoric effect play an important role. These proinflammatoric cytokines are INF-γ, IL-1, IL-2, IL-5, IL-12 and TNF-α.

The cytokine-mediated T-cell-reaction leads to an activation of langerhans-cells and macrophages, inducing new inflammation stimuli which cause a chronic-perifollicular inflammation in terms of a vicious circle [2, 4, 6, 8, 9].

An average of 35% of the patients had a spontaneous remission within 6 months, 20-30% underwent remission within 12 months therapy. Relapses have been observed frequently. 30% of the patients suffer from persisting Aa.

As we are dealing with a chronic, perifollicular inflammation caused by cytokine-mediated T-cell-reaction we need drugs able to interfere selectively into this inflammatoric cycle.

Fumaric acid ($C_4H_4O_4$) is a nonsaturated, aliphatic, dicarbonic acid which can be found in all plants and is produced in the human organism by degradation of phenylalanine to tyrosine in the citric acidcycle and ureacycle. In the human organism fumaric acid cannot be resorbed. For oral application lipidsoluble, well absorbable fumaric acidesters (FAE) and their salts are used.

Due to inhibition of the cytokines INF-γ, IL-2, IL-12 and TNF-α FAE inhibits T-suppressorcells and T-helpercells (especially type-1 helpercells). Furthermore FAE blocks the proliferation of keratinocytes and ICAM [4, 12, 13, 17, 18].

Patients and Methods

A total of 10 patients (5 male, 5 female) suffering from Aa resistant to therapy were enrolled in an open, non-placebo controlled pilot study with FAE (daily application for 6 months). Highest applied dosis was 720 mg dimethylfumarate per day.

Patients who were diagnosed with Aa at least 6 months ago and who already underwent 3 or more common therapies without success were classified as resistant to therapy and could be enrolled in the study.

The patients were seen by a dermatologist regularly and clinical findings as well as laboratoric changes (relevant laboratoric parameters were the T-lymphocytes) were controlled.

During therapy, kidney- and liver-specific parameters as well as the differential blood count were observed very critically.

Results

After six months treatment with FAE six out of ten patients with therapy resistant Aa showed positive results (Table 1).

Three patients had very good results with an almost complete remission of the clinical symptoms (Figs. 3, 4, 5), one patient had a good effect, showing a focal remission (Fig. 5).

Two patients had fair to moderate effects with diffuse growth of thin hair (Figs. 1, 2).

After six months treatment with FAE four patients showed no growth of hair in the area of focus.

All in all FAE was well tolerable, two patients reported gastrointestinal complaints which were tolerated. There were no drop outs during therapy.

The number of CD4+- (Fig. 8a) as well as of CD8+-T-lymphocytes (Fig. 8b) decreased during therapy with FAE. In the group of patients with no benefit from FAE treatment the CD4+-T-lymphocytes were reduced by 35%, the CD8+-T-lymphocytes by 40% after six months therapy.

Among the patients with benefit from FAE treatment a reduction of 26% for the CD4+-T-lymphocytes and of 27% for the CD8+-T-lymphocytes could be observed.

Discussion

Knowing Aa is an unspecific, chronic inflammatoric reaction, bound to follicles and maintained by cytokine-mediated TH_1-reactions [2, 4, 8, 13] we treated 10 patients with therapy-resistant Aa in an open, non-placebo controlled pilot study with FAE for six months.

For the very first time, clinical cases of patients diagnosed with Aa and treated with FAE are presented in this paper. Fumaric acid shows broad antiproliferative and immunmodulatoric effects, based upon its influence on T-suppressor- and T-helpercells. Fumaric acid reduces the count of both, T-suppressor- and T-helpercells [6]. Native T-helpercells (TH_0) develop into T-helpercells of the type 1 (TH_1) or type 2 (TH_2). The main effect of TH_1 is predominately directly cytolytic, based upon activation of macrophages and the furtherance of inflammation. The differentiation of TH_0 to TH_1 is forced by INF-γ and IL-12. The activity of TH_1 is IL-2, INF-γ and IL-12 dependent. IL-2 and IL-10 stimulate the differentiation of TH_0 to TH_2, its activity depends on IL-4, IL-5 and IL-10. TH_1 play an important role in the maintenance of the inflammatoric reaction.

Fumaric acid supports the production of TH_2 -cytokines (IL-4, IL-5 and IL-10) and induces TH_0 to develop to the benefit of TH_2.

Furthermore an inhibition of INF-γ, IL-2, IL-12, TNF-α, lymphocytes, endothelial keratintocytes, as well as a repression of the ICAM-expression could be proved [13, 17].

In Germany, fumaric acids are available on the market as Fumaderm® (fumaric aciddimethylesters, calcium, magnesium, and zinc) and are used for therapy of severe forms of psoriasis. The specific stimulation of fumaric acids on TH_2 and the suppression of TH_1 is made responsible for its positive results in the therapy of psoriasis [7, 9].

This study deals with the clinical picture of Alopecia areata refracture to therapy.

The causing factors for Aa are not completely revealed, but immunological factors are ascribed great importance in the pathogenesis of Aa [2, 4].

Histologically, the Aa regularly shows a peri- and intrabulbic, immunocytic infiltrate of lymphocytes and a movement of the quantitative ratio to the better of the

Table 1. Patient data, daily dose of Fumaric acid esters and responds of Alopecia areata to Fumaric acid esters after six months therapy.

Patient	Age beginn of therapy	Alopecia areata since	FAE-dose/d[mg]	Response* after 6 months Therapy with FAE
1. f	43	11 years	720	No respond
2. m	33	17 years	360	No respond
3. f	32	1 years	600	Initial fokal respond
4. m	18	13 months	720	Fokal good respond up to very good response
5. f	32	1 year	720	Fokal moderate to good response
6. m	40	7 years	720	Fokal good respond
7. f	23	8 months	360	Fokal good respond to very good response
8. f	39	6 months	720	Fokal good respond
9. m	17	1 year	720	Fokal good response up to very good response
10. m	44	1,5 years	720	No respond

*Very good respond: complete grow again of the hair.
Good respond: up to 50% grow again of the hair.
Slight respond: 25%-50% grow again of hair.
Less respond: till 25% grow again of the hair.
No respond: no grow again of the hair.

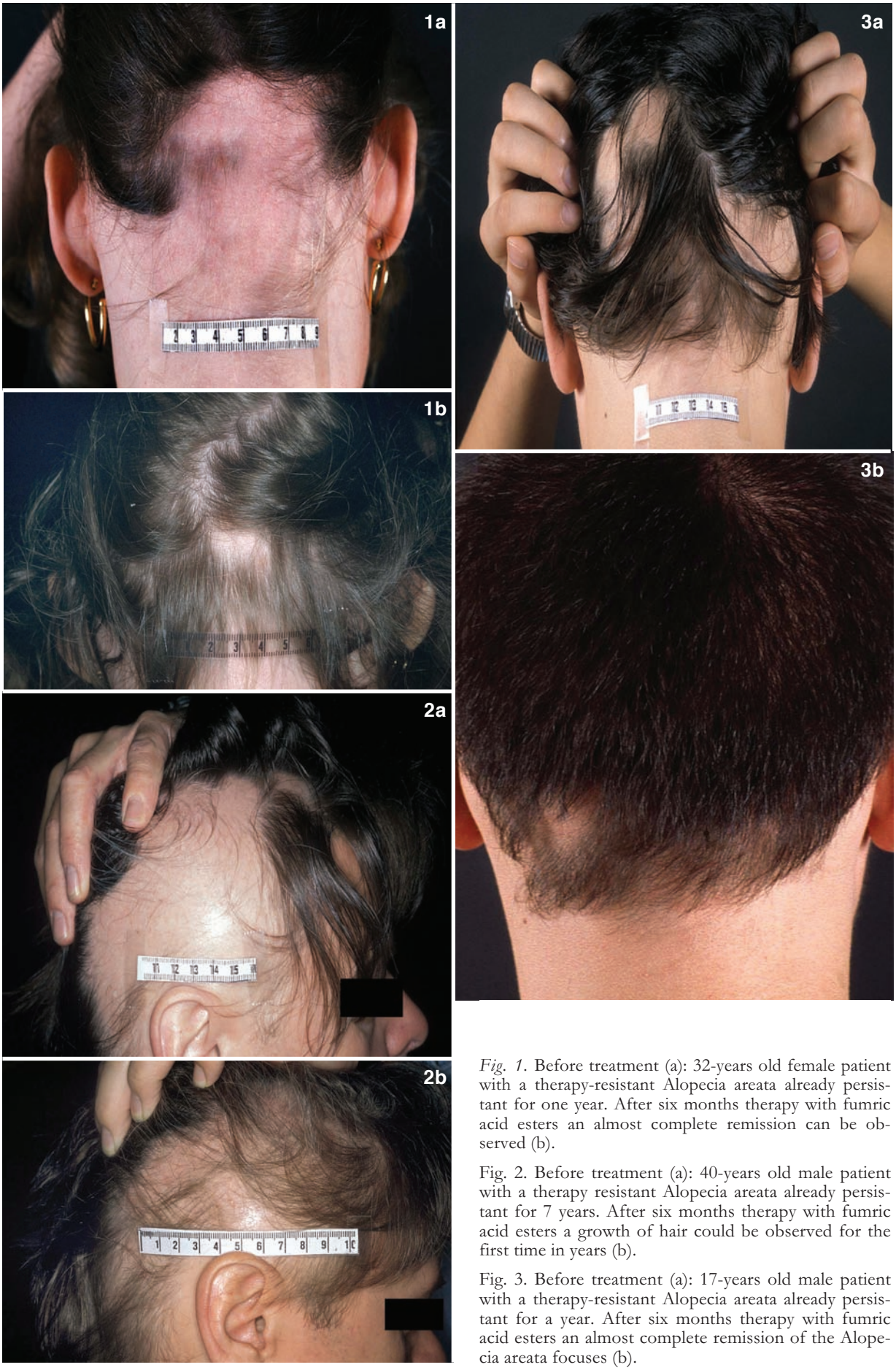
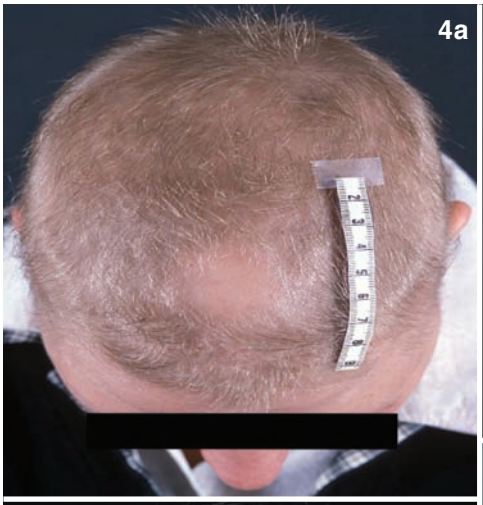
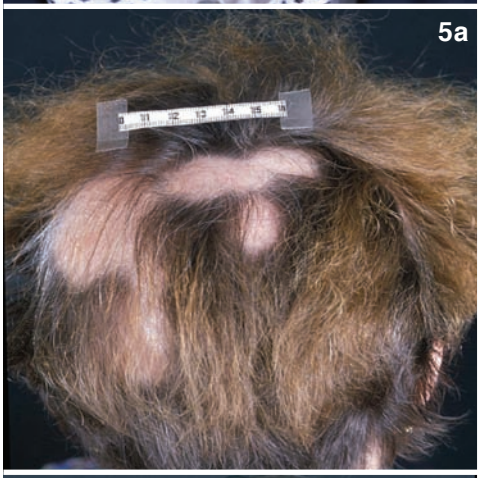


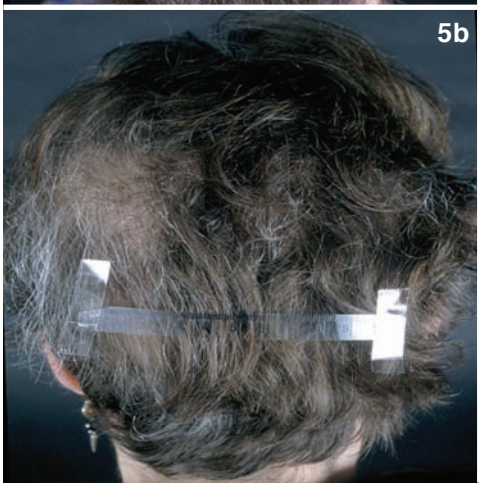
Fig. 1. Before treatment (a): 32-years old female patient with a therapy-resistant Alopecia areata already persistant for one year. After six months therapy with fumric acid esters an almost complete remission can be observed (b).

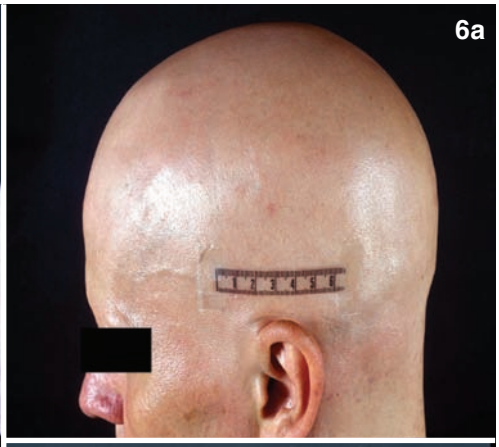
Fig. 2. Before treatment (a): 40-years old male patient with a therapy resistant Alopecia areata already persistant for 7 years. After six months therapy with fumric acid esters a growth of hair could be observed for the first time in years (b).

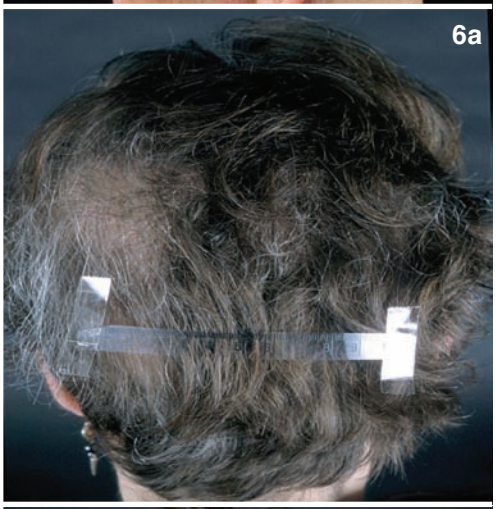
Fig. 3. Before treatment (a): 17-years old male patient with a therapy-resistant Alopecia areata already persistant for a year. After six months therapy with fumric acid esters an almost complete remission of the Alopecia areata focuses (b).











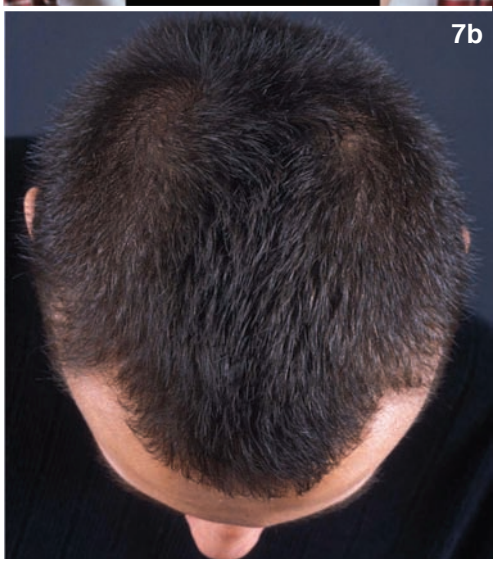


Fig. 4. Before treatment (a): 23-years old female patient with therapy-resistant Alopecia areata already persistant for 8 months. After six months therapy with fumric acid esters complete remission (b).

Fig. 5. Before treatment (a): 39-years old female patient with a therapy-resistant Alopecia areata already persistant for 6 months. After six months therapy with fumric acid esters an almost complete remission of Alopecia areata (b).

Fig. 6. Before treatment (a): 44-years old male patient with therapy-restistant Alopecia areata already persistant for 1,5 years. After six months therapy with fumric acid esters no growth of hair (b).

Fig. 7. Before treatment (a). 18-years old male patient with therapy-resistant Alopecia areata already perstistant for 13 months. After six months therapy with fumric acid esters complete remission of Alopecia areata focuses.

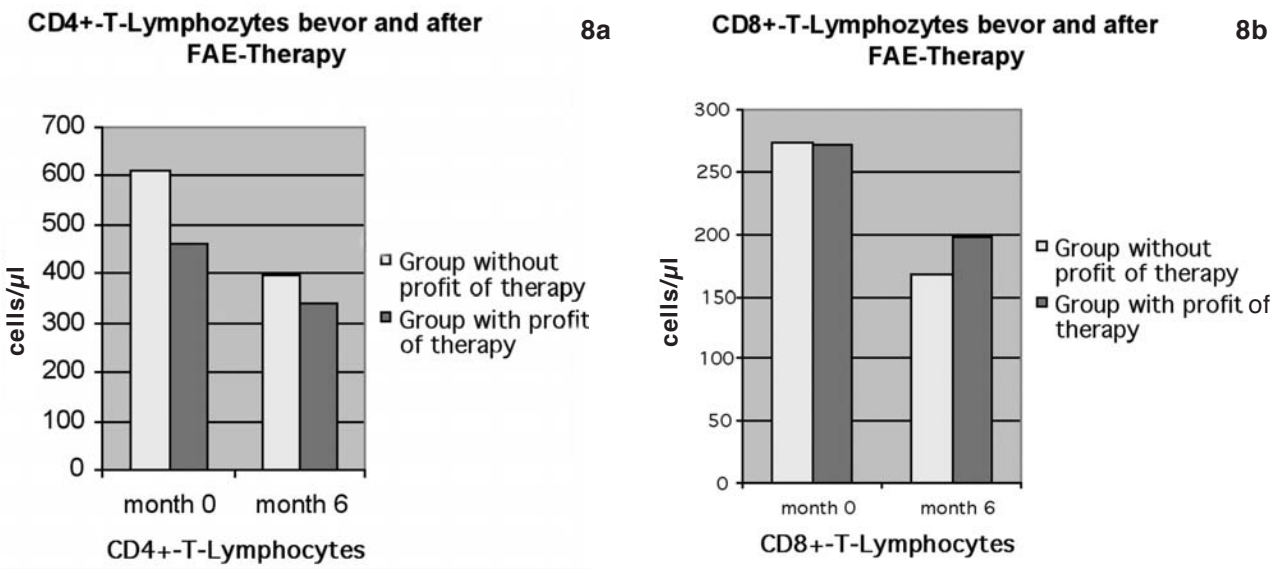


Fig. 8. Development of the CD4+-T-Lymphocytes (a) and the CD8+-T-Lymphocytes (b) under therapy with fumric acid esters (FAE). Among the group of patients with no therapeutical success the number of CD4+-T-Lymphocytes decreased from 613/µl to 398/µl (equals 38%), after the six months therapy with FAE.
Among the group of patients with good therapeutical success the number of CD4+-T-Lymphocytes decreased from 461/µl to 339/µl (equals 26%). The number of CD8+-T-Lymphocytes decreased from 273/µl to 163/µl (equals 40%) after six months therapy among the group with no therapeutical outcome and among the group with good therapeutical success from 271/µl to 198/µl (equals 27%).

T-helpercells with a reduction of T-suppressorcells (4:1) [6].

Endogenous and exogenous stimuli leading to a release of proinflammatoric cytokines from hairfolliclekeratinocytes cause the chronic inflammation, bound to the follicles.

The release of the proinflammatoric cytokines INF-γ, IL-1, IL-2, IL-8, IL-12 and TNF-α lead to an activation of vascular endothelial cells with an activation of adhesionmolecules (ICAM-1) as well as of langerhanscells, macrophages and T-lymphocytes [2, 4, 13, 14, 15, 17]. Therefore the chronic inflammation proceeds like a vicious circle.

The circle consists of the release of proinflammatoric cytokines and consecutively the cascade of unspecific inflammation sequences.

In this study, 60% of the patients took benefit from the six-months therapy with FAE. 40% had no benefit after six-months treatment with FAE.

The most relevant question is not how long Aa has been there but rather how the pathogenesis of Aa is functioning. Although histologically an inflammed infiltrate bound to the bulbar could regularly be observed, not all patients took the same benefit from treatment with FAE.

In cases of Aa where the inflammatoric circle can be broken, FAE is a sanguine therapeutic approach.

Conclusion

Alopecia areata is, depending on the peculiarity, a cosmetically very disfiguring clinical picture and very cumbering for the patient, especially when persisting over longer periods of time.

In cases of therapy resistance for longer than six months fumaric acids can be applied. With longer durations of persistence of the Alopecia areata a less successful therapeutic outcome has to be assumed caused by the chronic, perifollicular inflammation and a continuous atrophy of the follicle.

This study shall prompt further investigations on the therapeutic potential of fumaric acids in Aa resistant to therapy. These studies should be multi-centric, randomized and placebo controlled.

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