Review of the Use of Fumaric Acid Esters in Dermatology

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Abstract

Background: Fumaric acid esters (FAE) have been used as a drug since 1959. The therapeutic preparation containing FAE has been one of the prominent drugs used for the systemic treatment of psoriasis since 1994 in Germany. FAE have been used in the treatment of sarcoidosis, granuloma annulare, necrobiosis lipoidica, chelitis granulomatosa, annular elastic giant cell granuloma, malignant melanoma, pityriasis rubra pilaris, alopecia areata, hidradenitis suppurativa, and lupus erythematosus with different success rates.

The results obtained from research articles, case reports or case series of the used FAE of dermatological diseases were revised in this article. FAE can be an effective and safe first-line treatment alternative in the treatment of psoriasis. It also can be beneficial to granulomatous skin diseases, lupus erythematosus, malignant melanoma, pityriasis rubra pilaris, alopecia areata, and hidradenitis suppurativa in patients unresponsive to first line therapies.

Introduction

Fumaric acid (FA) is a simple organic dicarboxylic acid with a simple structure widely used in the food, agriculture, pharmaceutical and chemical industries today [1]. In humans, it plays a role in an important step of the citric acid cycle. It has been also in use as a drug since 1959 when it was discovered to be effective in the treatment of psoriasis. Schweckendiek, a German chemist, suggested that the lack of FA may play a role in the etiopathogenesis of psoriasis. Using an oral mixture made of FA esters (FAE) he developed himself, Schweckendiek has cured his own psoriatic lesions and shown the efficacy of the FAEs in psoriasis [2, 3].

When administered through the oral route, the bioavailability of FA is not satisfactory and it may cause gastrointestinal irritation. Therefore, the FAE used for treatment is manufactured in the form of enteric-coated tablets. There are three types of FAE, namely dimethyl fumarate (DMF), methyl hydrogen fumarate (MHF) and ethyl hydrogen fumarate (EHF) [2]. The therapeutic preparation containing FAEs have been one of the prominent drugs used for the systemic treatment of psoriasis since 1994 in Germany. The preparation includes DMF and a blend of the three monoethyl fumarate (MEF) salts (Table 1). Under the brand name Fumaderm®, it is presented in two different strengths including a low-dose starting treatment and a high-dose tablet. The active ingredient effective for the treatment is DMF [3].

(continued on next page)
Pharmacokinetics

Following the oral administration, FAE is almost completely absorbed through the small intestine. From the enteric-coated tablets, the DMF is released in the small intestine and a portion of it is hydrolysed to MMF in the alkaline pH environment of the intestines. In the pH 7.4 environment consistent with the human serum, DMF is rapidly hydrolysed to its active metabolite monomethyl fumarate (MMF). This hydrolysis does not occur in an acidic environment [3, 4]. The half-life of DMF is 12 minutes and it is not detectable in the plasma. Following the oral intake, its metabolite MMF is detected in the plasma [5]. The plasma concentrations of DMF and fumaric acid are negligible. In a study conducted on the pharmacokinetics of FAEs on healthy volunteers, the postprandial pharmacokinetics of a single tablet containing 120 mg DMF and 95 mg calcium monoethyl fumarate was observed to greatly vary between individuals. Therefore, fumarate doses were recommended to be taken before meals [6]. Following the oral intake, the peak plasma MMF levels are reached within 5-6 hours. In the serum, 50% of MMF is bound to proteins and its half life is 36 hours. No teratogenicity was observed in the therapeutic doses in animal studies. MMF enters the citrate cycle and is metabolised to carbondioxide and water. It main route of excretion is through respiration. A small fraction is excreted through the urine and faeces [7].

Mechanism of Action

The mechanism of action of the FAEs has not been fully understood. Their effects on various cells have been demonstrated in patients with psoriasis. They are suggested to play their role through their effect on the keratinocytes, T-lymphocytes, dermal fibroblasts, mast cells, endothelial cells, dendritic cells and other antigen presenting cells.

Effects on the T-lymphocytes

FAE has been reported to exert strong effects on the T-lymphocytes. During the treatment of 16 patients with severe psoriasis using FAE, leukocytopenia was observed in 94% of the patients. In the study where a 26.6% mean reduction in the leukocyte count was observed, CD4+ T lymphocytes were decreased by 45.4% and the CD8+ T-cells were decreased by 44.5% [2]. In psoriatic patients without concurrent disease or infection and treated with FAE, a significant reduction was observed in the CD3+, CD4+ and CD19+ lymphocyte counts. However, the citric acid cycle and the intracellular ATP levels were shown to be unaffected by the FAE [8, 9]. The reduction in the T-lymphocyte count in the peripheral blood goes parallel to the reduction of the T-lymphocytes on the skin of the patients with psoriasis lesions [2].

The common point of the mechanism of action of FAE in psoriasis and multiple sclerosis has been investigated. Studies have shown that the type 2 dendritic cells producing IL-10 are increased through FAE. The stimulation of the type 2 dendritic cells inhibits the T helper 1 and T helper 17 cells producing IL-12 and IL-23, while the T helper 2 cells producing IL-4 are induced. This effect has been suggested to bring about the action of FAE in psoriasis and multiple sclerosis [10, 11].

Effects on the Epidermal Keratinocytes

In cultured human keratocytes, production of the chemokins and cytokins such as IL-8, IL-20, CXCL1, CXCL8, CXCL9, CXCL10 and

| Table 1. The Contents of The Preparation of Fumaric Acid Esters |
|-----------------|-----------------|-----------------|-----------------|
| Dimethylfumarate (mg) | Mono-ethylfumarate Ca-salt (mg) | Mono-ethylfumarate Mg-salt (mg) | Mono-ethylfumarate Zn-salt (mg) |
| Fumaderm Initial | 30 | 67 | 5 | 3 |
| Fumaderm | 120 | 87 | 5 | 3 |
CXCL11 is observed to be strongly suppressed in the presence of DMF \[12, 13\]. In the skin biopsies of the psoriatic patients treated with FAE, acanthosis was observed to be rapidly reduced at the beginning while the effect slowed down in time \[14\]. In the keratinocyte cell cultures incubated with DMF, the mitogen-activated protein kinase (MAPK) 1 and 2 activation, which is thought to play a role in the pathogenesis of psoriasis, was observed to be suppressed. Thus, the gene transcription induced by the NF-kappa B transactivated MAPK 1 and 2 is also inhibited \[15\].

**Inhibition of the Angiogenesis**

Angiogenesis is a factor playing an important role in chronic inflammatory conditions and tumour formation. DMF exerts its antipsoriatic and antitumorigenic activity through the inhibition of angiogenesis. FAE leads to the inhibition of angiogenesis both in the in vitro and in vivo environments by affecting various steps of angiogenesis \[16\]. A major part of its angiogenetic effect is realised through the inhibition of the endothelial VEGFR-2 expression. Thus, it also inhibits the development of the capillary-like structures induced by VEGF \[17\].

**Induction of Apoptosis**

The nuclear transcription factor, production of the NF-kappaB1 inflammatory cytokins and cell differentiation play a major role in apoptosis. DMF has been shown to be a potent inhibitor for NF-kappaB1 and to lead apoptosis in various cells through this inhibition \[18\]. The induction of the apoptosis of the T-lymphocytes has been suggested as a mechanism of action in psoriasis \[19\]. In recent years, DMF was shown to cause apoptosis in mast cells and the mast cell apoptosis has been reported to contribute to the curative effect in psoriasis and MS \[20\].

**Effects on Oxidative Stress**

The effects of DMF on the intracellular thiol depend on time. In case of long term exposure to DMF, the interaction with the intracellular thiols has been reported to lead to an increase in the glutation levels. Increased levels of glutation inhibit the redox-sensitive kinases, reducing the oxidative stress \[2\]. Within the cell, DMF and MMF rapidly react with glutation (GSH) and are transformed into S-glutation forms. In vivo, the GSH-adducts are catalysed into mercapturic acids through enzymatic reactions and are excreted through urine. DMF is thought to cause the apoptosis of the cell through the repletion of the intracellular GSH. The reduction of the intracellular GSH leads to the downregulation of the Th 1 cytokins. Consequently, one of the effect mechanisms of FAE may be the release of the anti-inflammatory cytokins from the immune cells and/or the induction of apoptosis due to the depletion of the intracellular GSH \[21\].

**The Clinical Uses of FAEs in Dermatology**

(Table 2)

**Psoriasis:**

For more than fifty years, FAE has been in use as a safe and effective treatment for psoriasis in Western European countries including primarily Germany and the Netherlands. It has been shown to exert its effect in the treatment of psoriasis through its immunomodulatory, antiproliferative and anti-inflammatory effects and apoptosis in the active T-cells \[22\].

The first placebo-controlled, double-blind, randomised clinical efficiency study on FAE was conducted by Nuyteren-Huying et al \[23\]. In this study where 39 psoriatic were treated for 16 weeks, the combination of DMF and MEF salts were observed to lead to a significantly greater improvement compared to placebo. The subsequent first multi-centre, double-blind, placebo-controlled study by Altmeier et al. has demonstrated that FAE is significantly more effective than placebo in the treatment of psoriasis \[24\].

In a multi-centred and prospective study, Mrowietz et al. \[25\] have investigated the efficiency and safety of FAEs and observed an 80% decrease in the PASI values in comparison to the baseline values in the patients who have completed the four months treatment period. Side effects were observed in 69% of the patients who participated in the study. In general, it was observed that all the patients during the...
course of the treatment. The most commonly observed side effect were complaints related to the gastrointestinal system and flushing, which were generally observed to be dose-dependent. In 1999, Mrowietz et al. [26] have published a guideline reporting that FAEs are an effective and safe treatment alternative in the treatment of psoriasis.

Studies focussing on the effects of the FAEs in the treatment of psoriasis have also been conducted in countries outside Germany. It has been reported that 58.6-71.0% of the patients treated with FAEs in Ireland had good or excellent outcomes. In this study, one fifth of the patients could not tolerate the drug [22, 27]. In a retrospective study from the United Kingdom where 55 patients with severe psoriasis were evaluated, improvement was observed in 55% of the patients whereas 28% showed no response and the condition was worsened in 16% [28]. Similarly to the other countries, also in Italy, partial or complete healing was reported in 82.5% of the patients with severe psoriasis treated with FAE [29]. All the studies reported that FAE is an effective and safe alternative in the first line systemic treatment of psoriasis.

The effects of FAE have been compared with the other systemic treatments for psoriasis. Both in retrospective and prospective randomised and controlled studies, FAE was observed to have a similar effect with methotrexate in the treatment of psoriasis. Discontinuation rates of the therapy due to side effects were also reportedly similar [30, 31]. FAE has been used concurrently with another antipsoriatic treatment in the patients with plaque-type refractory psoriasis. In this study, 36% of the patients have discontinued and 25% have reduced the dose of the other antipsoriatic drug at the end of the 3 month treatment period [32]. FAE has also been found effective when used in combination with methotrexate, cyclosporine, acitretin and hydroxyurea and no significant drug interaction has been observed. Thus, in case of a lack of a response to the other systemic treatments or side effects, FAE can be added to the therapy and the side effects of the other drug can be reduced by a dose adjustment. Still, it must be borne in mind that the experience with combination therapy is limited and care must be taken during the treatment [33].

When used as monotherapy in palmoplantar pustular psoriasis, a higher dose was required and the treatment was found to be less effective compared to the other types of psoriasis [34]. Successful results were reported in nail psoriasis unresponsive to the other therapies [35]. It is not recommended to be used in psoriatic arthritis due to its lack of effect [5, 22].

The onset of the response to FAE treatment is observed within 5-6 weeks and complete
is usually achieved in 15 months [28]. The long term efficacy and safety of FAE was investigated in a multi-centred, retrospective study conducted on 984 patients for a mean treatment period of 44 months. At the end of 6 months 67%, at the end of 24 months 78%, and at the end of 36 months 82% healing was observed. Among the patients, 90% did not show any significant side effects necessitating a change in the therapy [36]. In recent years, studies have been conducted on the use of FAE in pediatric psoriatic patients. FAE was generally well tolerated in children and only 2 children discontinued the treatment due to side effects [37]. In a prospective study including 6 pediatric psoriatic patients, a PASI 100 response was observed in 3 children, PASI 90 was observed in one child and PASI 75 was observed in 2 children at the 12th week [38]. These studies have reported that FAE can be a treatment alternative in pediatric patients.

In a large-scale, multi-centred, prospective study on the use of Fumaderm®, a 75% DQLI reduction was observed in adult psoriatic patients at the end of the 12 month treatment period. This improvement in the DQLI has been found comparable to biological treatments [39]. In a retrospective study, the mean duration of the medication in 249 patients treated with FAE was 64 months. The ratio of the patients who continued the treatment for four years was 60%, while this ratio was 40% for etanercept and 70% for infliximab [40]. In conclusion, FAE can be an effective and safe first-line treatment alternative in the treatment of psoriasis.

Granulomatous Diseases:

Non-infectious granulomatous diseases are chronic diseases of unknown etiology. Experience on FAE in the treatment of granulomatous diseases is limited with case reports or case series.

Sarcoidosis:

Between 1998 and 2014, FAE was used in a total of 20 patients with sarcoidosis reported either in case reports or patient series. Among these patients, 6 had cutaneous sarcoidosis and 14 had pulmonary and cutaneous sarcoidosis. Standard doses used in psoriasis treatment were used in the treatment of sarcoidosis with FAE. In 10 patients in the literature, in terms of complete healing in cutaneous sarcoidosis, 5 had a partial response while no response could be achieved in 5 patients [41]. Nowack et al. [42] have observed full remission with FAE in 3 female patients with sarcoidosis unresponsive to treatment with chlorokin and corticosteroids. Full remission was achieved between 4 and 12 months of therapy.

In patients with pulmonary involvement treated with FAE for the cutaneous lesions, the pulmonary changes were improved in parallel to the skin symptoms and the serum angiotensin converting enzyme levels returned to normal. The cutaneous and pulmonary changes were observed after 11-12 months of therapy [43, 44].

Granuloma Annulare:

Disseminated granuloma annulare (DGA) tends to be more chronic and refractory to treatment than localised granuloma annulare. It is usually unresponsive to topical treatments. Patients with DGA unresponsive to other therapies have been treated with FAE and cases with successful outcome have been reported. In these patients, FAE was used in the standard dose used for psoriasis [45, 46, 47]. Older lesions have been reported to require longer healing periods than newer lesions [46]. Weber et al. [48] have investigated the efficacy and safety of the treatment with low-dose FAE in 8 patients with DGA. Significant improvement was achieved in approximately 63% of the patients using low-dose fumarate treatment. Low-dose FAE used in the treatment of DGA had much less side effects than high-dose therapy and was better tolerated.

Wollina et al. [49] have compared the efficacy of the combination of FAE + PUVA against PUVA monotherapy in patients with DGA. In the group treated with FAE plus PUVA, the cumulative dose of PUVA was significantly lower and the complete healing rate was higher. The combination of PUVA with low-dose FAE has been reported to be beneficial in patients unresponsive to PUVA therapy.
Necrobiosis Lipoidica:

Necrobiosis lipoidica (NL) is an idiopathic skin disease observed usually concurrently with diabetes mellitus. More than one third of the lesions lead to ulcerations. While non-ulcerative NL causes dysesthesia and cosmetic problems, ulcerated lesions cause severe pain and morbidity. Gambichler et al. [50] observed complete clearance after a 6-month treatment with FAE in a 50-year-old female patient with a 15-year history of recalcitrant NL of the pretibial skin on the leg. Kreuter et al. [51] have investigated the results of the FAE treatment in NL patients unresponsive to the other treatments. In 15 patients who used DMF at the doses used in standard psoriasis treatment for a minimum of 6 months, the clinical results were satisfactory both for the physician and the patients. The clinical improvement was also verified histopathologically and using 20 M-Hz ultrasound. No progression was observed in the lesions during the 6-month follow up after the treatment was discontinued.

FAE has been used in a female patient with long-term, bilateral ulcerative NL in which no improvement was achieved through topical corticosteroids and tacrolimus, systemic corticosteroids and phototherapy. After six months of DMF treatment, the ulcers were healed and the pain and dysesthesia were improved. It has been suggested that the anti-inflammatory effect brought about by FAE in the endothelial cells may contribute to the healing in the treatment of NL [52].

Malignant Melanoma:

DMF’s antiangiogenic activity is also thought to have antitumoral and antimetastatic effects besides its antipsoriatic activity. Therefore, it may be a potential therapeutic agent in case of malignancies where angiogenesis plays a role [16]. Although there is no data obtained from humans, DMF was investigated for the treatment of malignant melanoma in animals. Loewe et al. [53] have studied the potential antitumorigenic activity of DMF on a mouse model. DMF administered three times the standard dose used in the treatment of psoriasis was found to delay the growth of nodular melanoma and the slow down the lymphogenic tumour dissemination in metastatic melanoma. DMF stopped the cell cycle at G2-M boundary. The proapoptotic effect of DMF was also shown in this study and its antiproliferative and proapoptotic features are thought to be effective in delaying tumour growth and metastases. In another study, DMF was shown to inhibit the NF-kappaB, which plays a role in tumour progression, cell invasion and metastasis; and the metastasis of the melanoma cells through the suppression of the activity and expression of matrix metalloproteinases. Therefore, it has been suggested to be beneficial as a metastasis preventive agent in the treatment of malignant melanoma [54]. For this purpose, Valero et al. [55] have investigated the effects of dacarbazine plus FAE compared to dacarbazine monotherapy on a severe combined immune deficiency (SCID) mouse model. In mice xenografted with human melanoma cells metastasized to the sentinel lymph nodes, the sentinel lymph node metastases were significantly delayed in the group treated with FAE + dacarbazine compared to the dacarbazine monotherapy group. Also, the density of the lymph vessel in the primary tumour was observed to be significantly reduced with the combination of FAE and dacarbazine.

In spite of the successful results obtained from animal studies and cell cultures, malignant melanoma has been reported to develop in 2 patients treated with FAE due to psoriasis [56]. However, it is unclear if these tumours are coincidental or therapy-related. A greater number of case reports and studies on the immunologic effects may shed light to this question.

Other Dermatological Diseases:

Positive results have been reported with FAE in patients with different types of lupus erythematosus unresponsive to other treatment methods. A female patient with severe discoid lupus erythematosus (DLE), in which treatment with topical corticosteroids, topical tacrolimus, klorokin, hydroxychloroquin and altretinoin was ineffective, was successfully treated with low-dose Fumaderm over 6 months [57]. Another patient with chronic DLE was treated with FAE and hydroxychloroquin for 73 months and the disease remai-
ned stable [58]. In lupus erythematosus tumidus, complete healing was reported after a 3-month therapy with FAE at a psoriasis dose. In systemic lupus erythematosus unresponsive to systemic prednisolone, hydroxychloroquin ad cyclosporine therapy, FAE was used in combination with 10 mg/day of prednisolone and healing was achieved after a 3 month therapy [59]. These case reports demonstrate that the healing period with FAE in lupus erythematosus may be dose-dependent.

In a 15-year old male patient with atypical juvenile pityriasis rubra pilaris unresponsive to classical treatments, the FAE dose used in psoriasis was used and his lesions were improved, although relapse was observed after the discontinuation of the treatment [60].

FAE was used in 3 patients with annular elastolytic giant cell granuloma and good treatment response was observed in two patients, although one remained unresponsive. No healing was achieved in a patient with granulomatous cheilitis after 5 months of treatment [61].

FAE was used for 6 months in 10 patients with refractory alopecia areata. Full remission was achieved in three patients, while good response was observed in one patients and partial response was achieved in two patients. The remaining four patients showed no improvement [62].

Recently, the effectiveness and short-term tolerability of fumarates in patients with moderate to severe hidradenitis suppurativa who were refractory to conventional hidradenitis suppurativa therapies were assessed in a prospective, single-centre, open-label pilot study. It was shown that fumarates induced clinically meaningful improvement in three out of seven patients with recalcitrant moderate to severe hidradenitis suppurativa in the study [63].

A hand creme containing 5% Fumaric acid used twice daily was compared to a creme containing 0.1% triamcinolone used twice daily in hand eczema and was found to be less effective than the 0.1% triamcinolone creme. This result may be explained with the poor absorption of FA and the low concentration of 5% [64].

Side Effects:

Side effects with FAE are frequent but mild. Organ toxicity is lower than the licensed products such as methotrexate or cyclosporine [32, 65]. The frequency of side effects in studies was reported as 52-74% [22, 32, 66]. Side effects are most frequently observed during the first months of the therapy and approximately 30-40% of the patients have to discontinue treatment due to side effects [22, 32, 65]. The most frequently observed side effects are complaints related to the gastrointestinal system and flushing. Flushing and gastrointestinal side effects are more common among the patients with good treatment response [5, 7, 65]. Gastrointestinal side effects are observed in two-thirds of the patients and comprise abdominal pain, increased frequency of stool and tenesmus, bloating, diarrhea and nausea. The other reported side effects include headaches, malaise, fatigue, hair loss, exacerbation of the disease and palpitations [28].

A significant decrease in lymphocyte count is observed in 94% of the patients and necessitates a dose adjustment in 3.1% of the patients. Lymphopenia is also parallel to the efficacy of the drug and reduces both the T and B cells [7, 13]. Approximately half of the patients develop temporary eosinophilia. Elevations in the liver enzymes were observed in psoriatic patients under long-term treatment [7].

Acute kidney failure was reported in patients under treatment with FAE. Kidney failure is more frequent in female patients and was associated with high doses [67].

Method of Administration and Dose:

In order to minimize the side effects, standard treatment with FAE is stared at low doses and increased stepwise to the therapeutic dose [28]. The first week, therapy is initiated with Fumaderm initial® once a day and the treatment is continued with Fumaderm initial® twice a day through the second and third weeks. On the fourth week, Fumaderm® tablet is administered once a day and the dose increased to Fumaderm® tablet twice a day during the fifth week and three times a day in the sixth week. The dose is recommended to
be increased at weekly intervals. The maximum dose is 1.2g/day (6 strength tablets). After the treatment response is achieved, the dose is adjusted according to the individual [5, 7].

Patients under treatment with FAE should be followed up through monthly laboratory tests during the first 6 months and tests should be repeated every two months after this period. The routine hematological tests including serum creatinine, blood urea nitrogen, alanine and aspartate aminotransferases, gamma glutamyl transferase and the white blood count a complete urine test are among the parameters to be examined during the follow up visits. If the leukocyte count is below 3x109/L, lymphocyte count is 0.5x109/L and the eosinophil count is above 25%, the serum creatinine is 30% above the baseline value and proteinurea is observed, the dose should be reduced. If abnormal laboratory parameters prevail after the dose adjustment, the treatment should be discontinued [7].

No evidence of teratogenicity or mutagenicity was found in the toxicology studies with FAE. Still, since the data at hand is limited, it should not be prescribed during gestation and the lactation period. No metabolic interaction would not be prescribed during gestation and

References


