

Use of fumaric acid esters in psoriasis

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ABSTRACT

Fumaric acid esters (FAE) are chemical compounds derived from the unsaturated dicarboxylic acid fumaric acid. The usage of FAEs in treatment of psoriasis was introduced in the late 1950's. In the 1980s more standardized oral preparations of FAEs were developed containing dimethylfumarate (DMF) and salts of monoethylfumarate (MEF) as main compounds. In 1994, Fumaderm® an enteric-coated tablet containing DMF and calcium, magnesium, and zinc salts of MEF was approved for the treatment of psoriasis in Germany and since then has become the most commonly used systemic therapy in this country. Fumaric acids have been proven to be an effective therapy in patients with psoriasis even though the mechanisms of action are not completely understood. About 50-70% of the patients achieve PASI 75 improvement within four months of treatment and without any long-term toxicity, immunosuppressive effects, or increased risk of infection or malignancy. Tolerance is limited by gastrointestinal side effects and flushing of the skin. This article reviews pharmacokinetics, uses, contraindications, dosages, and side effects of treatment with FAEs.

Key Words: Fumaric acid ester, Psoriasis

Fumaric acid esters (FAE) are chemical compounds derived from the unsaturated dicarboxylic acid, fumaric acid. Fumaric acid is a white crystalline powder with a characteristic acidic taste. It is used as a food additive and is commonly found as flavoring agent in cakes and sweets. Fumaric acid is poorly absorbed and believed to pass through the body without causing any effects. However, esters of fumaric acid (FAEs), such as monoethylfumarate (MEF), monomethylfumarate (MMF), diethylfumarate (DEF) and dimethylfumarate (DMF) are potent chemicals and have been used in the treatment of psoriasis in European countries for over 30 years.

The use of FAEs in the treatment of psoriasis was first introduced in the late 1950s by a German chemist named Schweckendiek. A 'fumaric acid' protocol for psoriasis was introduced that proposed the use of FAEs as oral and topical treatment (ointment and bathing solution).^[1] In the 1980s, more standardized oral preparations of FAEs

were developed containing dimethylfumarate (DMF) and salts of monoethylfumarate (MEF) as the main ingredients. These were used in thousands of patients in different European countries including Germany, Switzerland and The Netherlands. In 1994, Fumaderm®, an enteric-coated tablet containing DMF and calcium, magnesium and zinc salts of MEF was approved for the treatment of psoriasis in Germany and since then has become the most commonly used systemic therapy in this country.^[2] DMF is rapidly metabolized to monomethyl fumarate (MMF) which, together with DMF, is regarded as the main bioactive metabolite.

Although data from controlled clinical trials is limited, available studies suggest that up to 50% of patients treated with Fumaderm® achieve at least 75% reduction of their baseline 'psoriasis area and severity index' (PASI) after 12-16 weeks of treatment.^[3,4] The most common side effects during induction therapy are flushing and

How to cite this article: Roll A, Reich K, Böer A. Use of fumaric acid esters in psoriasis. *Indian J Dermatol Venereol Leprol* 2007;73:133-7.

Received: December, 2006. **Accepted:** February, 2007. **Source of Support:** Nil. **Conflict of Interest:** None declared.

gastrointestinal side effects such as nausea, vomiting and diarrhea which may lead to treatment discontinuation in as many as 30% of the patients. One major advantage of Fumaderm® is its excellent efficacy and tolerability during long-term treatment. In long-term studies, 50-70% of the patients experience improvements of $\geq 70\%$ after 1 year of therapy.^[5-8] In Germany, large numbers of responding patients have been treated for several years and patients with successful continuous therapy for 10 or more years are not uncommon. Leukopenia (particularly lymphopenia) is a concern during long-term FAE treatment. However in contrast to methotrexate (MTX), lymphopenia is usually not significant, not associated with signs of immunosuppression and is reversible within weeks after cessation of treatment. Impairment of renal function has been observed in some patients in the days of non-standardized FAE therapy and is a very rare event now with Fumaderm®. Nonetheless, control of creatinine levels is mandatory during treatment with FAEs and therapy should be stopped if increased creatinine levels are noticed. Fumaderm® is effective in patients who can not be successfully treated with either UV phototherapy with or without retinoids or MTX or cyclosporine.^[3] There is also evidence for the synergistic effects of the combination of Fumaderm® with topical therapies, especially calcipotriol.^[9]

PHARMACOKINETICS

Little is known about the pharmacokinetics of FAEs. Recent in vitro data suggests that hydrolysis of DMF to the bioactive metabolite MMF occurs rapidly at pH 8 (simulating the alkaline pH found in the small intestines) but not at pH 1, which is the pH found in the stomach.^[10] This indicates that hydrolysis of DMF occurs mainly in the small intestine. Most likely, MMF and MEF are then absorbed into the blood circulation where they interact with blood cells. MMF and MEF may also influence inflammatory cells in psoriatic lesions. In humans, serum concentrations of MMF after oral intake reach peak levels within 5-6 hours. MMF is further metabolized to fumaric acid and finally to H₂O and CO₂, the latter being eliminated via respiration where it is detectable as early as 80 minutes after oral intake.^[11]

MECHANISM OF ACTION

The major current hypothesis of the pharmacodynamic effect of FAEs is based on the concept that DMF and MMF influence pro-inflammatory signal transduction pathways through modulation of the intracellular redox

system.^[6-7] There is evidence that changes in this system contribute to a decreased translocation of nuclear factor kappa B leading to an inhibition of the expression of pro-inflammatory cytokines including TNF- α , interleukin (IL)-8 and IL-1 β . Through this and other activities, FAEs modulate a variety of events involved in the exaggerated immune response in psoriasis. It has been concluded mostly from in vitro experiments that FAEs mediate the following anti-inflammatory, immune-modulatory and anti-proliferative effects:

1. Inhibition of the cytokine-induced expression of adhesion molecules such as ICAM-1, VCAM-1 and E-selectin on dermal fibroblasts^[12,13] and endothelial cells.^[14]
2. Suppression of not only the production of T helper type-1 and pro-inflammatory mediators such as TNF- α and IFN- γ but enhancement of the formation of cytokines with anti-inflammatory properties such as IL-10 and IL-1RA.^[15,16]
3. Decrease of the maturation and T helper type-1-inducing capacity of dendritic and other antigen presenting cells and promotion of apoptosis in these cells; the stimulation of T helper type-2 cytokine production seems to be less affected.^[17-20]
4. Induction of apoptosis not only in antigen presenting cells but in various other immune cells including activated T cells which is accompanied by a strong induction of the anti-inflammatory stress protein heme oxygenase 1 (HO-1).^[21,22]

On the other hand, FAEs have no effects on the production of superoxide anions, which are components of the innate defense against microorganisms.^[23]

USES

Plaque-type psoriasis

There is substantial evidence from at least eight clinical studies conducted between 1987 and 2004 mostly in patients with severe psoriasis, that monotherapy with FAEs is an effective treatment of this condition.^[4]

Pustular psoriasis

There are a few reports of successful treatment of pustular psoriasis with FAEs.^[24,25]

Psoriasis capitis

Due to the lack of controlled clinical trials, efficacy of FAEs in this manifestation of psoriasis has not been documented. In clinical experience, FAEs can be helpful in controlling severe cases of psoriasis capitis presenting incomplete response to topical therapy alone.

Psoriatic arthritis (PsA)

There is evidence that FAEs have some efficacy in the treatment of psoriatic arthritis.^[26] In clinical practice, FAEs are useful in patients with plaque-type psoriasis and mild PsA. In more aggressive cases of PsA or if PsA is the predominant manifestation of psoriasis, other therapies such as MTX or TNF antagonists are more appropriate.

Nail psoriasis

This often very-difficult-to-treat manifestation of psoriasis shows at least some improvement during long-term treatment with FAEs in many patients.^[27] However, controlled trials are not available.

Uses other than psoriasis

Disseminated granuloma annulare

There are case reports describing successful treatment of patients with disseminated granuloma annulare with FAEs.^[28-31] FAEs may represent a therapeutic option in more severe cases unresponsive to treatment with PUVA and potent topical corticosteroids.

Sarcoidosis

Some authors claim to have observed a positive effect of FAEs in cutaneous and systemic sarcoidosis.^[32,33]

Necrobiosis lipoidica

There is data for the treatment of eighteen patients with histopathologically proven necrobiosis lipoidica with FAEs according to the standard schedule for psoriasis (see below).^[34] After a mean treatment period of 7.7 months, a significant decrease in the mean clinical score was observed. The improvement remained stable over six months of follow-up.

CONTRAINDICATIONS

FAEs should not be used in patients with significant gastrointestinal diseases such as chronic gastritis or active or recent gastric or duodenal ulcers. Patients suffering from severe liver or kidney diseases, patients under the age of 18 and women during pregnancy or lactation should also not be treated with FAEs.^[4,35,36]

DOSAGES

The established treatment regimen of FAEs in psoriasis proposes a gradual increase in dosage according to the schedule depicted in Table 1. This schedule has been shown to improve gastrointestinal tolerance.^[4] In each patient, the final daily dosage needs to be adjusted according to the individual

response and the onset of adverse effects. One tablet of Fumaderm initial[®] appears to be a reasonable starting dose for a dose-escalation protocol. Dose escalation is continued until a satisfactory clinical response is reached and then the dosage is steadily reduced to an individual maintenance dose. The final dosage may range up to 1-2 g/d (6 tablets of Fumaderm[®]). Most patients treated with fumaric acids require two to four tablets of Fumaderm[®]. Dosage is neither related to body weight nor to the activity of the disease. Treatment may be discontinued abruptly as relapse or rebound phenomena do not occur.^[4]

RECOMMENDATIONS

Recommendations for follow-up investigations are given in Table 2. Treatment should be discontinued immediately when lymphocytes decrease below 500/ μ l or when serum creatinine levels increase above the normal range.^[4]

CONCOMITANT THERAPY

Currently, a combination of fumaric acids with systemic medication, i.e., cyclosporine or methotrexate is not recommended because of lack of experience. However, the additional use of calcipotriol administered topically has been shown to significantly increase the efficacy of FAE treatment with faster resolution of psoriatic lesions than with FAE monotherapy.^[9]

SIDE EFFECTS

Side effects of treatment with FAEs are summarized in Table 3. Adverse events during treatment with fumaric acids are

Table 1: Dosage schedule of fumaric acid esters used for patients with psoriasis

Week	Fumaderm [®] initial	Fumaderm [®]	Dosage of DMF
1	1-0-0		30 mg
2	1-0-1		60 mg
3	1-1-1		90 mg
4		1-0-0	120 mg
5		1-0-1	240 mg
6		1-1-1	360 mg
7		2-1-1	480 mg
8		2-1-2	600 mg
9		2-2-2	720 mg

Table 2: Monitoring blood and urine tests during therapy with fumaric esters

	Before treatment	Month 1-6 monthly	Month >6 bimonthly
Complete blood count	X	X	X
Liver function test	X	X	X
Creatinine	X	X	X
Urine analysis	X	X	X

Table 3: Side effects of fumaric acid esters

Most frequently	Gastrointestinal complaints, flushes
Frequent	Lymphopenia
Infrequent	Eosinophilia, proteinuria
Rare	ALAT increase, raised bilirubin increase

common and are reported in up to two thirds of all patients.^[5,27] The most common side effects are gastrointestinal symptoms such as abdominal pain, diarrhea, nausea and malaise. These signs and symptoms occur primarily within the first few weeks after initiation of treatment and within 90 minutes to six hours after oral intake of the drug. They last for several minutes up to half an hour and can be alleviated by intake of tablets with milk. Flushing of the skin is another common complaint, ranging from rapid sensation of heat to long-lasting facial redness. Improvement of the latter side effect has been seen on treatment with acetylsalicylic acid but this has not yet been confirmed scientifically. The adverse effects just mentioned are dose-dependent and they decrease in frequency during the course of the treatment.

Less commonly observed side effects are lymphocytopenia, leukocytopenia and elevated eosinophil counts. A decrease of lymphocytes below 500/mm³ should lead to dosage reduction or withdrawal of treatment. The eosinophilia is transient and usually observed between the fourth and tenth week of treatment.

Rarely, moderate elevations of liver enzymes and bilirubin have been observed. Proteinuria has been noted too, but it proved to be transient.^[4,37,38] An increased risk for infections has not been documented.

TERATOGENICITY/PREGNANCY/LACTATION

Toxicologic investigations have given no evidence that fumaric acids are teratogenic or mutagenic. Nevertheless, fumaric acids should be avoided in pregnancy or lactation because data for use in these conditions is limited.^[4,37,38]

DRUG INTERACTIONS

FAEs have no known metabolic interactions with other drugs. Concurrent use of fumaric acids with other drugs having side effects on kidney function should be avoided because of increased toxicity (e.g., methotrexate, cyclosporine, psoralen, immunosuppressive drugs and cytostatics).

Fumaric acids have been proven to be an effective therapy in patients with psoriasis even though the mechanisms of action are not completely understood. According to the

German S3-guidelines of psoriasis, evaluation of 13 studies has shown a proportion of 50-70% of patients who achieved PASI 75 improvement within four months of treatment and without any long-term toxicity, immunosuppressive effects or increased risk of infection or malignancy.^[4] Tolerance is limited by gastrointestinal side effects and flushing of the skin in about two thirds of the patients. These side effects are dose-dependent and decrease in frequency in the course of treatment. Monitoring of full blood cell count, liver and kidney function as well as urine analysis is necessary. Improvement of lesions of psoriasis on fumaric acids may be accelerated by combination with topical agents such as calcipotriol.

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