The Role of Fumaric Acid and Derivatives in the Management of Psoriasis

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ABSTRACT

Psoriasis is a multi-system, chronic, inflammatory disorder with increased morbidity and mortality. Current treatment modalities involve topical agents, systemic agents including biologics and phototherapy. Owing to the chronicity of the disease, long term therapy is much needed and options have to be evaluated in terms of efficacy and safety profile. Fumaric acid esters have been widely in use for the treatment of psoriasis in Germany as a licensed drug for more than 2 decades. FAE have various immunomodulatory, anti-inflammatory, and anti-oxidative properties that have caused it to be a possible emerging treatment modality for patients suffering from the disease. Due to the success in treatment, though unlicensed, it is being used in several other European countries. To date, 10 randomized controlled trials and 38 observational studies have evaluated FAE in a combined total of 5,003 patients. The efficacy and safety profile of FAE is favorable. About 50%–70% of patients achieve at least 75% improvement in psoriasis severity after 16 weeks of treatment. The safety profile of FAEs was marked and studied. Intolerable gastrointestinal complaints and flushing led to early treatment withdrawal in 6-40%. However these gradually improve after 3 months of treatment. Lymphocytopenia, eosinophilia, increased liver enzymes, and proteinuria were commonly observed, but rarely resulted in disruption in treatment. Studies with long-term data are much needed for further assessment. The 2009 European evidence-based S3-guidelines on psoriasis treatment recommend FAE and suggest it as a first-line systemic treatment for moderate-to-severe plaque psoriasis. This review is aimed to give an overview of the role of FAE treatment in the management of psoriasis.

INTRODUCTION

Psoriasis is a noncontagious, multisystem, multifactorial inflammatory disorder usually involving the skin of the elbows, knees, scalp, lumbosacral areas, inter-gluteal clefts, and glans penis. In up to 30% of the patients, joints may also be affected. With a prevalence of 1–3 % worldwide psoriasis belongs to the most frequent chronic, relapsing inflammatory skin diseases1. The onset of the disease may be seen typically between the ages of 20-30. There is no variation in the prevalence of psoriasis between male and females11.

It is associated with impairments in health related quality of life even in mild cases, and excess mortality in severe cases3. Approximately 15–20% of patients have extensive skin involvement or severe disease requiring systemic therapy. Psoriasis has been associated with multiple comorbidities including cardiovascular disease, the metabolic syndrome, cancer, gastrointestinal disease, and chronic obstructive pulmonary disease (COPD). Further, psoriasis patients often suffer from depression, and more frequently smoke and drink alcohol to excess, which may negatively compound the health status of these patients4. Patients with severe psoriasis have a 50% increased risk of mortality as compared to patients with milder psoriasis5.

Involvement of the immune system in psoriasis was first indicated in early studies that identified complex infiltrates of leukocytes involved in both innate and adaptive immunity in psoriatic skin12. This confirmed the hypothesis that psoriasis is a chronic inflammatory condition as a result of persistent stimulation of T cells by immunogens of epidermal origin12.Besides T cells, the role of antigen-presenting cells, keratinocytes, Langerhans' cell, macrophages, natural killer cells, an array of Th1 type cytokines, certain growth factors like vascular endothelial growth factor (VEGF) keratinocyte growth factor (KGF) and others have been suggested to play a key role in pathogenesis of psoriasis. However, the exact mechanism is not understood fully.

About 90 % of psoriasis patients have chronic plaque-type psoriasis (psoriasis vulgaris), which is the most common form of psoriasis and is characterized by oval or irregularly shaped, red, sharply demarcated, raised plaques covered by silvery scales. Other forms include flexural psoriasis, which are described by erythematous plaques located in the skin creases; guttate psoriasis, in which multiple small plaques are found, predominantly on the trunk; generalized pustular psoriasis, involving multiple skin pustules; and erythrodermic psoriasis covering nearly most of the skin surface. Due to the high morbidity and increased mortality associated with moderate to severe psoriasis, long term effective treatment that is both safe and affordable need to be established.

Psoriasis vulgaris may be solely diagnosed alone on the clinical appearance of the lesions. Auspitz's sign (i.e. numerous fine bleeding points after psoriatic scale is removed) may be elicited in scaly plaques. Involvement of predilection sites and the presence of nail psoriasis further help contribute to the diagnosis. At times, confirmation of a clinical diagnosis may require histological examination of biopsies that are taken from the characteristic lesions. In order to assess the severity of psoriasis which plays a most important aspect in the judicial use of systemic treatment modalities, several scoring systems have been developed. These have been based on the following factors: extent of disease, the location of lesions, the degree of inflammation, the responsiveness to treatment, and the impact on quality of life.

The Psoriasis Area and Severity Index (PASI) developed by Fredriksson and Pettersson in 1978 may be considered as the 'gold standard' in clinical trials6. This is usually presented as a percentage response rate; e.g., PASI 50, PASI 75 etc. PASI 75, for example, signifies the percentage (or number) of patients who have achieved a 75% or more reduction in their PASI score from baseline. According to the European S3 Guidelines on the systemic treatment of psoriasis vulgaris, moderate to severe disease is defines as PASI>107. Other tools include Physicians Global Assessment of disease severity (PGA), and body surface area (BSA). Quality of life indices include Impact of Psoriasis on health related quality of life (HRQoL) and Dermatology Life Quality Index (DLQI), commonly evaluated by questionnaires.

While topical therapy alone may be indicated for mild psoriasis, systemic agents, biologics and phototherapy are other treatment modalities usually reserved for moderate to severed disease. But the latter may be accompanied with the risk of significant side effects.

Topical corticosteroids remain the mainstay for topical psoriasis treatment8. They exhibit anti-inflammatory, anti-proliferative, and immunosuppressive actions. However, due to increased risk of side effects with chronic topical use of steroids, close monitoring by the clinician is required for long durations9.

Ultraviolet irradiation is one of the safer and beneficial treatment options for moderate to severe psoriasis. It may act via anti-proliferative effects and anti-inflammatory effects. But consideration must be given to the risk of developing actinic damage, premature skin ageing and potential carcinogenic effects.

In 2008 and 2009, the American Academy of Dermatology published guidelines for the management of psoriasis with systemic therapies14,15. Traditional systemic therapies continue to play an important role in the treatment of psoriasis with their oral route of administration and low cost (compared with biologics) making them an important treatment option in the appropriate patient14. In 2015, an update to the European S3-Guidelines on the systemic treatment of psoriasis was published7. Different options for systemic therapy include methotrexate, cyclosporine, apremilast and biologic agents. Retinoids (both topical and oral) may also be used as part of treatment. Side effects like gastrointestinal intolerance, hepatic damage and marrow suppression (methotrexate) or renal damage (cyclosporine) can be predicted with the use of such drugs. Retinoids are also known to cause dry eye, blepharitis, corneal opacities, cataracts, and decreased night vision. They are also contraindicated during pregnancy and conception and may cause hypertriglyceridemia10.

The British Association of Dermatologists has also published guidelines for the use of systemic biologic therapies for the treatment of psoriasis and psoriatic arthritis16. Psoriasis factors that determine the need for biologics intervention include the goal of therapy (e.g. Physician's Global Assessment (PGA) of clear or nearly clear), disease phenotype and pattern of activity, disease severity and impact, the presence of psoriatic arthritis (in consultation with an adult or pediatric rheumatologist) and outcomes of previous treatments for psoriasis16. Examples of biologic therapies include etanercept, infliximab, adalimumab, ustekinumab, secukinumab, ixekizumab, brodalumab, and guselkumab.A meta-analysis was done that evaluated randomized trials with treatment durations of at least 24 weeks to compare the efficacy amongst the various long term systemic therapies17. Evidence was found to support infliximab, secukinumab, and ustekinumab as the most effective long-term therapies. Conversely, it is noted that all TNF-alpha inhibitors have the possibility to activate latent infections such as tuberculosis, and increased rates of infection have been seen in patients with rheumatoid arthritis treated with etanercept, infliximab, and adalimumab. Additionally, risk for herpes zoster may be increased in patients receiving combination therapy with methotrexate.

FUMARIC ACID ESTERS

The last two decades has seen the use of fumaric acid esters widely in the treatment of psoriasis vulgaris in Western Europe. It was first proposed in 1959 and became the most common systemic treatment for psoriasis in Germany. While they are approved for use in Europe, there is currently no FDA-approved use for psoriasis in the US18.

This treatment was empirically devised by the German chemist Schweckendiek and further developed by the German physician Schafer. Fumaric acid therapy is based on the following principles: (1) oral treatment with monoethyl and dimethyl esters of fumaric acid, (2) topical treatment with monoethylfumarate, and (3) a diet devoid of nuts, spices, wines, and distilled products of wine. Several clinical studies were conducted to determine the clinical efficacy of fumaric acid esters and the results revealed an anti-psoriatic effect in patients suffering from moderate to severe psoriasis19-21. In a randomized, double-blind, placebo-controlled clinical trial Altmeyer et al. showed improvement of psoriasis lesions in 70% of patients after 4 months of treatment21. In addition, a prospective multicenter study revealed a mean reduction in Psoriasis Area and Severity Index of 80% after 4 months23. Since psoriasis has a chronic nature, long-term clinical effectiveness and adverse effects summary are of major importance in the selection process of choosing the appropriate drug for the skin condition of the disease. Two studies done showed that FAE were also effective after a prolonged period of treatment of 2 and 3 years, respectively19,20. Studies with longer follow-up times are lacking.

Licensed preparations include Fumaderm Fumaderm Initial and Skilarence (dimethyl fumarate). Fumaderm contains a mixture of dimethylfumarate (DMF) with calcium, magnesium and zinc salts of ethylhydrogenfumarate. A standard dose protocol is recommended whereby the dose is gradually increased to improve tolerance. Individual dose adjustment is then made according to therapeutic response. The maximum dose was defined as a total amount of 1.2 g FAE/day (two high-strength tablets three times a day), representing 720 mg dimethylfumarate (DMF)22. During therapy full blood count,

liver enzymes, urine sediment and serum creatinine must be recorded.

Treatment with FAE would appear from the trials to be relatively safe in comparison with the risks known to be associated with other systemic treatments for psoriasis. Commonly reported side-effects of FAE are flushing and gastrointestinal disturbance. A modest reduction in peripheral lymphocyte count and an increase in eosinophils are also frequently observed but these haematological changes do not usually seem to cause serious clinical concern. Changes in liver enzymes and serum creatinine have only rarely been reported.

In the 2015 update of the European S3-guidelines, FAEs are recommended for the long-term treatment of psoriasis, but the recommendation is based on expert opinion only7. Hence, there are uncertainties on the suitability of FAEs as a psoriasis treatment. In this narrative review, the author is aimed at providing an overview of the role of fumaric acid and its derivatives in the management of psoriasis.

METHOD

This review involved a search of the PubMed database, Google scholar, and Cochrane library to answer clinical queries on the role of fumaric acid esters in the management of psoriasis of the English-language medical literature. The following search terms were used : 'psoriasis','fumaric acid esters', 'anti-psoriatic', fumarate', 'dimethylfumarate', 'fumaderm' and combinations of these terms. In addition, the references cited in these articles were looked up to obtain additional information. Regarding the role of FAE in the management of psoriasis, evidence was reviewed from meta-analyses, randomized controlled trials, and retrospective studies. A separate analysis of the data was carried out to present a summary of the pros and cons regarding the scope of FAE in the future of psoriasis treatment guidelines.

DISCUSSION

Fumaric acid esters (FAE) are chemical compounds derived from the unsaturated dicarbonic acid, fumaric acid. A white crystalline powder, fumaric acid plays an important role in the Kreb's Cycle. It is approved for the use of food addictive (usually as a flavoring agent in cakes and sweets) and is also used as an acidulant, due to its characteristic acid taste.

Esters of fumaric acid (FAEs), namely monoethyl fumarate (MEF), monomethyl fumarate (MMF), diethyl fumarate (DEF) and dimethyl fumarate (DMF) are potent chemicals currently in use for the treatment of psoriasis in various European countries like Germany, Switzerland and The Netherlands.

HISTORY:

The history of the clinical use of fumaric acid derivatives dates back to 1959, when the German chemist Walter Schweckendiek, who suffered from psoriasis, hypothesized that the disease might be caused, at least partly, by defects in the citric acid cycle. He proposed that the exogenous supplementation of fumaric acid might nullify these defects and reverse the pathological development24.Due to the gastrointestinal irritation accompanying the intake of oral fumaric acid, Schweckendiek , in his various self-experiments ,tried to prove his hypothesis by treating himself with fumaric acid derivatives with a higher efficacy and bioavailability than fumaric acid itself. Gastrointestinal (GI) irritant effects, however, could not fully be circumvented. Although Schweckendiek's original hypothesis regarding an anomalous citric acid cycle as the cause for psoriasis was never proven, patients suffering from the disease seemed to benefit from oral treatment with a mixture of different FAE with dimethyl fumarate (DMF) and monoethyl fumarate (MEF)-salts.

The 1970s saw new developments as the German general practitioner Gunther Schäfer standardized FAE treatment with oral and topical application of FAE in combination with a diet. Using this treatment regimen, Schäfer was able to report promising results in treating psoriasis patients with FAE.

However, these results couldn't be replicated by other German dermatologists and there were growing concerns on the safety of FAE as several cases were reported of acute renal toxicity in patients treated with FAE as well. This caused a disruption in the development of FAE for psoriasis treatment for nearly a decade. In the subsequent years that followed, under the influence of the psoriasis patient associations, FAE treatment became an object of interest to academic dermatologists25.

In the early 1990s, the first randomized, placebo-controlled trials that evaluated FAE in psoriasis were published, in which efficacious responses and a good safety profile were observed in patients with chronic plaque psoriasis21,26. 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 for more than two decades has been in used for systemic therapy of the disease. Since its official registration, Fumaderm has become the number one drug for the systemic therapy of psoriasis in Germany (approximately 66% of all prescriptions for systemic psoriasis therapy. In recent years, the effectiveness of FAEs has been proven in controlled clinical trials28,29.

MECHANISM OF ACTION

The mechanisms of action by which FAE improve pso¬riasis are not yet completely understood27. DMF is rapidly metabolized to monomethyl fumarate (MMF) which, together with DMF, is regarded as the main bioactive metabolite. The major 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 system21,23. 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-a, interleukin (IL)-8 and IL-1b.

Another proposed mechanism is that angiogenesis inhibition probably plays a role in the activity of dimethylfumarate. FAE are believed to act through various immunomodulating effects22. Experimental studies have described various

immunomodulatory, anti-inflammatory, and anti-oxidative properties of FAE as contributing causes.

RESULTS

RANDOMIZED CONTROLLED TRIALS:

FAE have been shown to be effective in improving moderate-to-severe plaque psoriasis in several RCTs. To date, there have been 10 RCTs in the period 1990- 2017 that evaluated FAE in psoriasis treatment with a total of 1183 patients.

Four trials compared FAEs to placebo, one trial compared two different FAE formulations to placebo, one trial compared FAEs to methrotrexate, one trial compared the combination of FAEs with narrow band UVB to FAEs monotherapy, one trial compared FAEs with an oral histamine antagonist to FAEs monotherapy, one trial compared combination of biologics with FAE to biologics (etanercept) monotherapy and one trial compared the combination of FAEs with topical calcipotriol to FAEs monotherapy. The characteristics of each RCT in terms of study design and sample populations are briefly summarized in table 1.

There was considerable clinical heterogeneity among the RCTs in the efficacy outcomes, time of efficacy assessment and used FAE formulations. The most frequently used outcomes were changes in PASI and BSA. Treatment duration varied from 12 to 24 weeks. Most of the studies used Fumaderm for the treatment of the patients rather than other FAE formulations. Sample sizes of the RCTs were in the range of 27 to 671. On the whole, 1183 patients were included in the studies. Majority of the patients were treated for moderate to ever plaque psoriasis. One RCT included patients with psoriatic arthritis30.

The largest randomized, placebo controlled trial was a German phase III, double-blind, non-inferiority trial conducted to assess the efficacy and safety of a new formulation of DMF (LAS41008), compared with placebo and Fumaderm® for 16 weeks. In total, 671 patients were randomized and 33% treated with LAS41008 were 'clear' or 'almost clear' in the PGA at week 16, compared with 13•0% receiving placebo (P< 0•0001; LAS41008 superiority vs. placebo) and 37•4% receiving Fumaderm®. The placebo controlled RCT in psoriatic arthritis found remarkable improvement in skin lesions, but only modest improvement in arthritis30.

In another placebo-controlled RCT which was a Dutch study published in 1990, 39 psoriasis patients were randomized to receive FAE (Fumaderm), octyl fumarate, or placebo26. In contrast to the octyl fumarate and placebo groups, the psoriasis improved significantly in patients treated with Fumaderm with a 68% reduction in body surface affected from 21% to 6.7%. Adding a topical vitamin D analogue calcipotriol resulted in greater and faster improvement of psoriatic lesions compared wot FAE's monotherapy. In contrast, etanercept in combination with FAE did not yield statistically significant results.

Adding a 6-week course of narrow-band UVB to FAE both accelerates and augments the therapeutic response during the early phase of treatment and increases quality of life in patients with moderate-to-severe plaque psoriasis31. This was seen in the RCT done with 30 patients who were randomized to either monotherapy with FAE (n=16) or a combination of FAE with NB UVB (n=14). The mean reduction in PASI after 6 weeks was significantly greater with the combination treatment (p=0.016). Only one RCT reported improvements in health related quality of life following FAEs treatment29. Mean improvement rates in psoriasis severity of 42%–76% were reported after FAE treatment in the other three RCT's.

OBSERVATIONAL STUDIES:

There have been 38 observational studies published in the period 1987–2017 (Table 2) with a total of 3820 patients. Considerable clinical heterogeneity was seen among the various studies with regard to FAE formulations and treatment duration.

Most of the studies were prospective, single center studies. There were 3 prospective multiple center studies23,32,33. Two cross-sectional studies were included, while the rest were case series.

Patients with moderate to severe plaque psoriasis were mainly included in majority of the case studies. Due to the uncontrolled nature of the studies, quality of the studies was low. Two studies evaluated FAEs in patients with mild plaque psoriasis. A few studies even included patients with other sub types like guttate or palmoplantar psoriasis. Adults constituted most of the patient pool, except for 2 studies that included pediatric psoriasis patients34,35. Treatment duration varied from 1 month to 14 years. 19 studies were of long-term FAEs treatment from 1 year up to 14 years. Sample size ranged from 6 to 984. Measures of effectiveness outcomes varied among the studies. PASI, OGA and global psoriasis severity assessments were used.

The largest observational study was a retrospective, mul¬ticenter study published in 2009.15 In this cross-sectional study among 984 psoriasis patients treated with Fumaderm, a large proportion (82%) had a marked or clear improvement after 36 months of treatment36.

Improvements in patient- reported quality of life was seen in several studies32,37. The effectiveness of results of FAEs assessed in pediatric patients were similar to the results reported in adults34,35.

Furthermore, there were no major adverse events observed during FAE treatment. The other observational studies also reported favorable effec¬tiveness and safety outcomes of FAE treatment. The results of these studies cannot be easily pooled given that there is heterogeneity in FAE formulations, treatment duration, and treatment outcomes. Over all Mean reductions in PASI ranged from 13% to 86% after 3-4 months of treatment. PASI-75 responses from the studies ranged from 8% to 33%.

SIDE EFFECTS PROFILE

Most common side effects that were reported were gastrointestinal symptoms and skin flushing. According to European guidelines, GI adverse effects may occur in upto 60%

of psoriasis patients treated with FAEs, predominantly in the initial few weeks of therapy7.

Skin flushing via cutaneous vasodilatation is the second most common adverse event affecting almost 55% of patients receiving FAE treatment40. In the RCTs up to100% of the patients complained of GI symptoms. About 8 to 39% of patients discontinued FAEs treatment due to adverse events, most probably due to intolerable GI symptoms or flushing.

In one study done in 2016 with 33 patients treated with combination therapy with fumarates, no discontinuation was seen due to adverse effects and an acceptable tolerability up to 48 weeks was seen. An adjusted dose of up to 215 mg 4 times a day was used instead of the commonly used maximum dose of 6 tablets a day to combat the increased incidence of side effects. Leucopenia and/or lymphopenia, was not recorded in any of the patients during the 1-year course of the study either39.

Another study carried out in 2015 with 671 patients treated with new formulations of FAE showed that Adverse events were more frequent in the LAS41008 and Fumaderm® groups compared with placebo; however, most were considered 'mild' in severity, mainly comprising gastrointestinal disorders (62.7% and 63.3%, respectively), and flushing (18.3% and 16.3%, respectively)38.

These symptoms are extremely common and gradually decrease over time after the first 3 months. If therapy is started at a lower dose and gradually increased over a period of time and given along with food, side effects maybe better tolerated39. Once remission has been attained, the dose may be decreased to a lower maintenance dose to maintain clinical response while minimizing the risk of side effect.

Skin flushing has been mainly attributed to activated HCA2 expressed on epidermal Langerhans cells and selectively induced by cyclooxygenase-1 (COX-1), while another proposed mechanism involves HCA2 expressed on keratinocytes and COX-2. Mechanisms for the GI complaints include DMF-induced allergic contact mucositis of the gastrointesti¬nal tract and FAE-triggered release of tumor necrosis factor alpha (TNF-α) as various possible causes.

LABORATORY ALTERATIONS:

Leukocytopenia, lymphocytopenia, elevated liver enzymes and eosinophilia have been observed during therapy with FAEs. Data from case series suggest that FAE-induced lymphopenia is usually mild, can be managed with dose adjustments, and reverts upon treatment discontinuation4. As a resultant of severe lymphopenia, the risk of rare opportunistic infections may be increased. Progressive multifocal leukoencephalopathy (PML) has been linked to the use of Fumaderm® for psoriasis since 1994. Other cases have included patients treated with Psorinova (FAE combination) for psoriasis and with Tecfidera (DMF) for multiple sclerosis28. To minimize the risk of PML and other malignancy like squamous cell carcinoma, the EMA recommended that a complete blood count be performed at the start of treatment and suggested that in patients with abnormal baseline lymphocyte counts, treatment should not be started. Blood counts must be monitored every 4 weeks. It is recommended to reduce the treatment dosage if lymphocyte counts decrease below 0.7 x 109 cells/L and to stop the treatment dose if lymphocyte counts do not increase a month after dose reduction, or if they fall below 0.5 x 109 cells/l7.

At present, there is no high level of evidence to suggest an increased risk of malignancy or infections when treated with FAE, However, the possibility for such adverse vents must not be overlooked due to the potential immunosuppression.

NEPHROTOXICITY

Proteinuria seems to be associated with dose levels of FAE. In most cases, proteinuria is fully reversible following dosage reduction or treatment discontinuation. Acute renal insufficiency in patients treated with FAE was seen in the earlier studies carried out in the 1980s. But this was most likely due to exposure to too high doses of FAE (more than the maximum daily dosage of 720 mg of DMF currently used). Data from RCTs and long-term observational studies so far have not shown an increased risk for acute nephrotoxicity during FAE treatment23,37,40.

Less frequent occurring adverse events during FAE treat¬ment are fatigue, headache, pruritus, and edema of the lower extremities. A summary of the related adverse events can be seen in table 3.

TREATMENT DISCONTINUATION DUE TO ADVERSE EFFECTS

Most common adverse effects that led to treatment discontinuation were gastrointestinal symptoms and flushing symptoms. In the randomized trials, the proportion of patients who suffered with adverse effects was high, ranging from 69% to 92%. Eight to 39% of patients discontinued FAEs treatment mostly due to intolerable gastrointestinal or flushing complaints.

In the observational studies, 45% to 87% of patients had experienced common adverse effects out of which 6%-47% discontinued FAEs treatment. Changes in laboratory tests during FAE therapy are usually mild in severity and transitory, such that treatment discontinuation may not be mandatory36.

On the question of safety of long-term therapy with FAEs, few studies have reported that there is no increased risk of infections, malignancies or any other serious adverse effects as a result of long-term treatment FAE treatment. One study treated patients with FAE for 10-14 years and no serious adverse events were reported40. There were few studies that specifically evaluated long-term treatment with FAEs. The available data indicated no increased risk for infections, malignancies, or other serious adverse events associated with long-term FAE treatment. In a small, retrospective single center study among patients treated with FAE continuously for up to 10 to 14 years, no serious adverse events or malignancies were observed53. Similar safety results were reported in a large, German study among nearly 1000 patients treated with FAE for a mean duration of 3.5 years.

ROLE OF FAE IN OTHER DISEASES:

FAE are also being used in the treatment of diseases other

than psoriasis. Inflammatory and granulomatous skin diseases, like sarcoidosis, cheilitis granulomatosa, granuloma annulare, necrobiosis lipoidica, and lupus erythematosus have been benefitted from the use of FAE.

Another example is multiple sclerosis, for which FAE became approved by the FDA and the European Medicines Agency in 2013 for the treatment of relapsing forms of multiple sclerosis.

Additionally, FAE are also being considered for various other diseases, including Huntington disease, myocardial infarction, and asthma.

Table 3: Commonly reported adverse events associated with FAE treatment in psoriasis

Gastrointestinal complaints
Skin flushing
Pruritus
Headache
Fatigue
Lower extremity edema
Malaise
Lymphocytopenia
Increase in liver enzymes
Eosinophilia
Proteinuria
Leukocytopenia
Increase in creatinine

CONCLUSION

Though the development of FAE didn't pass through the usual drug phase development, fumaric acid esters have come a long way in the treatment of psoriasis in countries like Germany. For more than 2 decades they have been in use and patients have been treated with great success due its immunomodulating, anti-inflammatory, anti-oxidative, and anti-proliferative effects.

10 RCTs and 38 observational studies have evaluated FAE in a combined total number of 5,003 patients. About 50%–70% achieved around 75% improvement in PASI following 12 to 16 weeks of treatment. Adverse effects linked with the same have been reported in more than 80% of patients, however, they were of only mild severity. Lymphocytopenia, eosinophilia, and proteinuria are com¬monly observed during FAE treatment, but rarely call for treat¬ment discontinuation. All laboratory values must be monitored regularly. No serious adverse effects have been recorded with long-term FAEs therapy.

In conclusion, though the quality of the currently available evidence is low, FAEs may be considered a potential systematic treatment for moderate to severe plaque psoriasis. Further studies involving newer formulations and comparing FAEs to other systemic treatments with higher level of evidence could be undertaken so as to confirm the future possibility of an FDA approved use in the treatment of psoriasis and hence widening the treatment options for the same.

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