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Drug survival of fumaric acid esters for psoriasis: a retrospective study

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Summary

Background Fumaric acid esters (FAEs) have been used for over 30 years in the management of psoriasis.
Objectives To determine drug survival of FAEs in patients with psoriasis, treatment-limiting adverse drug events and the range of effective drug doses.
Methods A retrospective, single-centre study assessing all patients commenced on FAEs between October 2003 and July 2012. Demographic data, length of treatment, reasons for discontinuation of FAEs, side-effects and range of doses were recorded.
Results Two hundred and forty-nine patients [160 (64%) male] were included. The mean age at which FAEs were commenced was 44·5 years (range 17–82 years). The mean length of treatment was 28 months (range 1 week to 106 months). In patients who were commenced on FAEs ≥ 4 years before inclusion in this study, the 4-year drug survival was 60% (64/107). FAEs were discontinued in 146/249 patients (59%); this was due to lack of efficacy in 59/146 (40%) and gastrointestinal upset in 39/146 (27%). A very low dose of FAEs (< 240 mg daily) was successful in maintaining control of psoriasis in 26 (10%) patients. The mean treatment duration of these patients was 64 months (range 32–106 months).
Conclusions Fumaric acid esters have a 4-year drug survival rate of 60%, which compares favourably with reported 4-year survival rates of 40% for etanercept and adalimumab and 70% for infliximab. Longer drug survival is more likely in the significant subgroup of patients in whom a very low dose of FAEs is sufficient to control disease. The reasons for this are unclear.

What's already known about this topic?

- Fumaric acid esters (FAEs) are an effective and generally well-tolerated treatment for psoriasis.
- Common side-effects that limit tolerance of therapy include gastrointestinal upset and flushing.

What does this study add?

- FAEs have a 4-year drug survival of 60%, which compares favourably with biologic therapies.
- Discontinuation of treatment with FAEs is highest during the first year of therapy.
- A significant subset of patients responds to a low dose of FAEs.

Fumaric acid esters (FAEs) have been used widely for over 30 years in the management of psoriasis. Schweckendiek[1] first reported the beneficial effects of FAEs in 1959. Since 1994, FAEs have been available commercially in Germany (Fumedica GmbH, Herne, Germany; now owned by Biogen Idec, Inc.), licensed under the name of Fumaderm®.[2] Fumaderm contains a mixture of dimethylfumarate (DMF) with calcium, magnesium and zinc salts of monoethylfumarate (MEF). DMF is

rapidly metabolized to monomethylfumarate (MMF), which, together with DMF, is regarded as the main bioactive metabolite.[3] Treatment with DMF and/or MMF produces a beneficial shift towards T helper 2-like cytokine secretion associated with a reduction in peripheral lymphocytes, primarily T cells,[4] and inhibits the proliferation of epidermal keratinocytes in patients with psoriasis.[5]

Guidelines recommend a gradual increase in FAE dosage to ensure patient tolerability and optimal efficacy.[3] Patients start on one tablet daily of a low-strength Fumaderm Initial® formulation (30 mg DMF, 75 mg MEF as calcium, magnesium and zinc salts), increasing over the following 8 weeks to a maximum of six tablets daily, taken in the form of full-strength Fumaderm (120 mg DMF; 95 mg MEF as calcium, magnesium and zinc salts) as a divided dose of two tablets three times daily.[3]

Studies, including one from this centre,[6] have shown FAEs to be efficacious and safe to use for patients with psoriasis.[7–11] In a multicentre, retrospective study from Germany[7] looking at 984 patients taking FAEs, significant clinical improvement as measured by Physician's Global Assessment was noted in 67% after 6 months, 78% after 24 months and 82% after 36 months of treatment. A prospective study carried out in the U.K. reported on 80 patients with severe recalcitrant psoriasis treated with FAEs. Twenty per cent of patients achieved a 50% improvement in Psoriasis Area Severity Index (PASI-50), 8% PASI-75 and 4% PASI-90 on an intention-to-treat analysis at 4 months, with an overall reduction in PASI from $13{\cdot}9 \pm 9{\cdot}0$ to $11{\cdot}3 \pm 9{\cdot}2$ ($P < 0{\cdot}001$).[8] However, FAEs remain unlicensed in many European countries, including Ireland and the U.K.

Drug survival is an overall measurement of the effectiveness of a treatment. Factors such as side-effects and clinical efficacy play important roles in ensuring treatment continuity.

The aim of this study was to determine the drug survival of FAEs in patients with psoriasis, treatment-limiting adverse drug events and the range of effective drug doses.

Patients and methods

This single-centre, retrospective study identified patients taking FAEs by searching the departmental systemic medication database. This agent was first prescribed in the department in October 2003. Two hundred and forty-nine patients were commenced on FAEs between October 2003 and July 2012. A single patient was commenced on FAEs in 2000 by a centre in Germany and treatment was continued in our centre following transfer of care in 2004. Patients attended the department for clinical assessment, blood monitoring (full blood count, liver and renal profiles) and urinalysis at least every 12 weeks. Their medical notes were reviewed.

Patient demographic factors, previous treatments for psoriasis and age at which FAEs were commenced were recorded. The duration of treatment with FAEs was also recorded and the 4-year drug survival rate was calculated by identifying the percentage of patients still taking FAEs at least 4 years after commencement of therapy. Other factors, such as patient comorbidities (including psoriatic arthritis), body mass index (BMI), smoking status, PASI and Dermatology Life Quality Index, were recorded where documented in the medical notes. All side-effects observed following commencement of FAEs, reasons for discontinuation of therapy and maintenance doses required for disease control were noted.

Results

Patient characteristics

Of the 249 patients included in the study, 160 (64%) were male. Their baseline characteristics are outlined in Table 1. The majority had received previous phototherapy/photochemotherapy (205/249, 82%) with the maximum recommended treatment reached in 26/205 (13%) patients (200 lifetime exposures). FAEs were the first systemic agent used in

Table 1 Baseline characteristics of patients commenced on fumaric acid esters (FAEs)

	No. (%)
Male, n (%)	160 (64)
Age at which FAEs were commenced (years)	44·5; range 17–82
Previous phototherapy/photochemotherapy[a]	205 (82)
Previous treatment with systemic agents	100 (40)
Methotrexate	62
Ciclosporin	27
Acitretin	23
Adalimumab	6
Hydroxyurea	5
FAEs[b]	4
Etanercept	4
Infliximab	2
Comorbidities	
Psoriatic arthritis	25 (10)
Hypertension	50 (20)
Dyslipidaemia	48 (19)
Diabetes mellitus	17 (7)
Ischaemic heart disease	9 (4)
Liver disease	5 (2)
Cerebrovascular disease	4 (2)
Mean weight (kg) recorded in 245 patients	87·1; range 45–142
Mean BMI (kg m^{-2})[c]	29·5; range 19·7–42·3
Smokers	71 (29)
Mean PASI recorded in 146 patients	9·2; range 0–22·2
Mean DLQI recorded in 53 patients	13·4; range 0–27

BMI, body mass index; PASI, psoriasis area and severity index; DLQI, Dermatology Life Quality Index. [a]Narrowband ultraviolet B or psoralen/ultraviolet A. [b]Fumaric acid esters (FAEs) were used in other centres and had been discontinued prior to attendance at St Vincent's University Hospital, Dublin. [c]Recorded in 56 patients.

149/249 (60%). The mean number of systemic medications that patients required prior to FAEs was 1·3. Details of the previous systemic therapies used are outlined in Table 1. The mean age at commencement of FAEs was 44·5 years (±13·8; range 17–82 years). Thirteen (5%) patients took FAEs in combination with other systemic drugs: ciclosporin (four), acitretin (three), infliximab (three), etanercept (two) and adalimumab (one).

The baseline PASI was recorded in 146/249 (59%) patients, with a mean of 9·2 (range 0–22·2). One patient, who was treated with FAEs in order to switch treatment from ciclosporin, had a pretreatment PASI of 0. Coexisting psoriatic arthritis was documented in 25/249 (10%), with 12/25 (48%) necessitating a change from FAE therapy due to poorly controlled arthritis to either etanercept (five), methotrexate (two), adalimumab (two), infliximab (two) or ustekinumab (one).

Drug survival and side-effects of fumaric acid esters

The mean duration of treatment with FAEs was 28 months (range 1 week to 106 months). The range of treatment duration is illustrated in Figure 1. Fifty-one patients (21%) had been taking FAEs for more than 50 months without serious adverse effects at the time of inclusion in this study. The 4-year drug survival rate for FAEs in patients commenced on treatment at least 4 years prior to inclusion in this study was 60% (64/107, Fig. 2).

Of the 249 patients commenced on FAEs, 146 discontinued treatment (59%). The main reasons included lack of drug efficacy (40%, 59/146), gastrointestinal upset (27%, 39/146), intolerable hot flushes (3%, five of 146) and failure to attend follow-up (4%, six of 146). All the reasons for discontinuation of FAEs are listed in Table 2. Discontinuation of therapy was commonest in the first year after commencement of therapy (89/146, 61%), mostly because of gastrointestinal side-effects (33/89, 37%) and lack of drug efficacy (38/89, 43%) (Fig. 3).

Proteinuria was found frequently on urinalysis (170/249, 68%), with 20 (12%) patients having persistent proteinuria (positive in at least three consecutive specimens, 12 weeks apart). Four (2%) patients developed an increased creatinine level, which required cessation of FAEs in one patient. Subsequent to the completion of this study, one further patient discontinued FAE therapy due to development of Fanconi syndrome.[12] Lymphopenia ($< 1{\cdot}0 \times 10^9$ cells L^{-1}) was

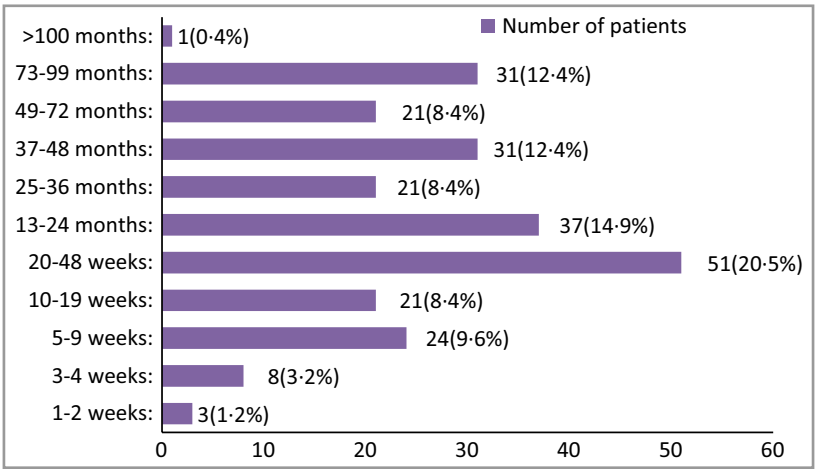

Fig 1. Length of treatment with fumaric acid esters.

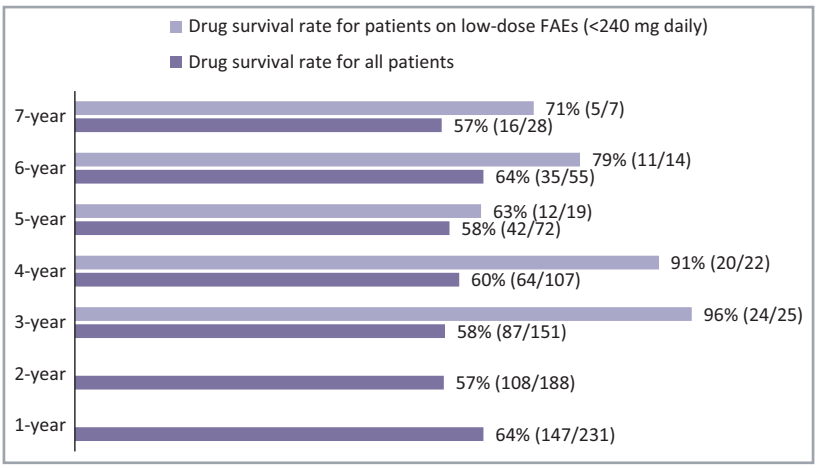

Fig 2. Drug survival rates for fumaric acid esters (FAEs).

Table 2 Reasons for discontinuation of treatment with fumaric acid esters

	No. (%) (n = 146)
Lack of efficacy	59 (40)
Gastrointestinal upset	39 (27)
Lymphopenia	16 (6)
Failure to attend follow-up	6 (4)
Intolerable hot flushes	5 (3)
Others	
Commenced biologic agent for other illness	7 (5)
Planning for family	2 (2)
Psoriasis clear	2 (2)
Headache	2 (2)
Died from treatment-unrelated causes[a]	2 (2)
Acute tubular necrosis	1 (1)
Collapse	1 (1)
Pancytopenia	1 (1)
Recurrence of malignancy	1 (1)
Infection[b]	1 (1)
Cryptogenic pneumonitis	1 (1)

[a]Decompensated alcoholic liver disease and ischaemic heart disease; [b]perianal abscess.

another common side-effect of therapy, observed in 133 patients (53%), necessitating cessation in 16/249 (6%) due to persistent counts of $< 0{\cdot}5 \times 10^9$ cells L^{-1}. No patients with persistent lymphopenia developed significant sequelae.

The majority of patients in whom FAEs had to be discontinued went on to require further systemic treatment (132/146, 90%). The mean number of systemic medications used after discontinuation of FAEs was 2·2 (Fig. 4). The majority of patients (90/146, 62%) required biologic therapy following discontinuation of FAEs for control of their psoriasis (Fig. 5).

Range of effective doses of fumaric acid esters

Seventy-nine (32%) patients were on the maximum dosage of FAEs (240 mg three times daily) at the time of inclusion in this study. The mean dose of FAEs taken by patients was 415 mg daily. A low dose of FAEs (< 240 mg daily) was successful in maintaining control of psoriasis in 26 (10%) patients. The mean treatment duration in this group was 64 months (range 32–106 months). The 7-year drug survival for this subgroup was 71% (five of seven). The 6-year, 5-year, 4-year and 3-year drug survival rates were 78% (11/14), 63% (12/19), 91% (20/22) and 96% (24/25), respectively (Fig. 2).

Discussion

This large retrospective, single-centre study shows that FAEs have an excellent 4-year survival of 60%. This 4-year drug survival compares favourably with that of biologic agents. Gniadecki *et al.*[13] reported 4-year drug survival of 70% for infliximab and of 40% for both etanercept and adalimumab. FAEs are effective even in moderate-to-severe psoriasis, with the mean PASI in this group prior to treatment of 9·2 (in those in whom it was recorded) and 40% having had treatment with at least one other systemic agent prior to FAEs.

There are several factors that influence the choice of FAEs as first-line systemic therapy for patients attending our clinics. Although we have incomplete data on alcohol consumption in this study, given the limitations of retrospective chart review, a previous study from this centre found that alcohol misuse is a common problem, with 32% of patients drinking hazardously.[14] We recognize that methotrexate is not an option for patients who do not wish to discontinue or minimize alcohol consumption. In Ireland, FAEs are cheaper than the commonly used biologic treatments, costing approximately €6300 per patient per year (mean dose of 415 mg daily). In contrast, etanercept and adalimumab each cost in excess of €25 000 per patient per year.

The side-effects of FAEs are common and predictable.[7,15,16] Gastrointestinal upset and flushing usually occur within the first 6 months and decrease or subside after prolonged and uninterrupted use.[16] Forty-seven per cent (68/146) of the patients in this group discontinued FAEs due to side-effects, the majority due to gastrointestinal upset (39/146),

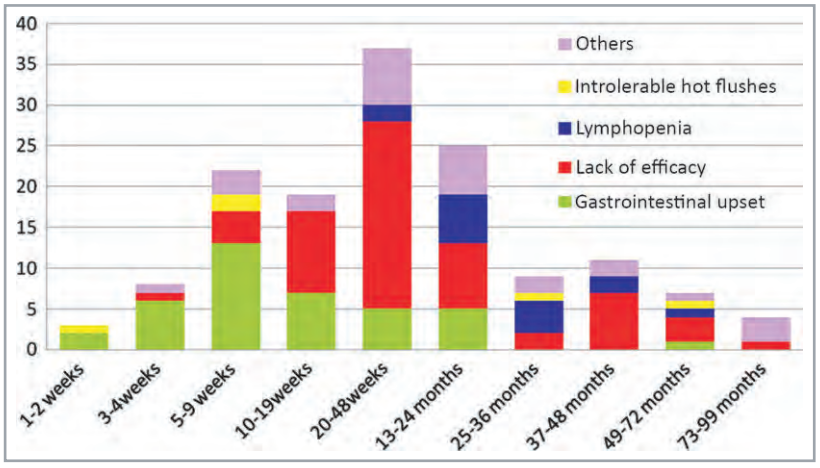

Fig 3. Reasons for discontinuation of fumaric acid esters according to length of treatment.

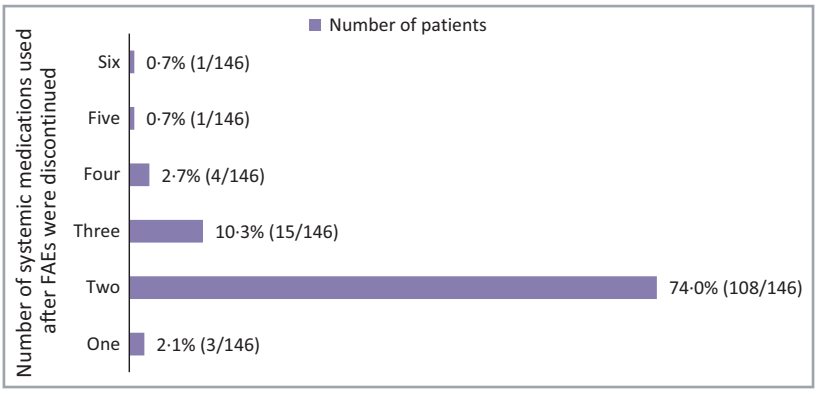

Fig 4. Number of systemic medications used after fumaric acid esters (FAEs) were discontinued; 5% (seven of 146) stayed on topical treatments; 3% (five of 146) were lost to follow-up; 1% (two of 146) died from unrelated causes.

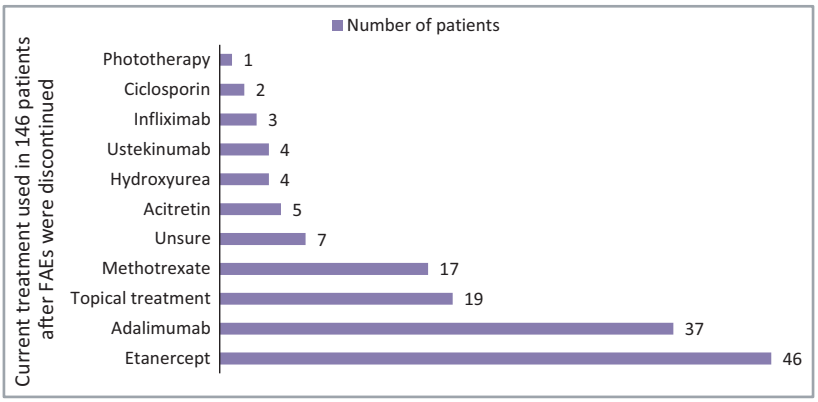

Fig 5. Treatment being used at the time of inclusion in the study in patients after fumaric acid esters (FAEs) were discontinued.

lymphopenia (16/146) and hot flushes (five of 146). Studies from Dutch and German populations reported that relatively similar percentages of patients developed adverse events: 73% in the Dutch study and 69% in the German study.[16,17] A lower proportion of patients in these studies discontinued FAE therapy because of adverse events: 23% in the Dutch study and 7% in the German study,[17] compared with our study (47%). The German prospective, multicentre study also reported that no significant morbidity or serious side-effects resulted from treatment with FAEs. From our experience, proteinuria and lymphopenia were usually reversible once the dose of FAEs was reduced, and rarely necessitated discontinuation of therapy. This is similar to the findings of other studies.[15,18] One patient developed Fanconi syndrome subsequent to our study period, but otherwise we are not aware of any patients developing significant sequelae from therapy with FAEs. In those in whom FAEs had to be discontinued, most required at least two sequential systemic medications to control their psoriasis by July 2012. We can hypothesize that our group of patients probably had more severe psoriasis, particularly as this is a tertiary referral centre for psoriasis. It would be interesting to see whether any particular subgroup of patients develops adverse events from FAEs, for example related to alcohol intake, BMI or smoking habit. However, our study did not measure alcohol intake among the patients, and also relatively few patients had their BMI recorded (56/249). Among those who had their smoking status recorded (71/249), very few had numbers of cigarettes recorded (which could range from one cigarette every 2 weeks to 40 cigarettes every day). We suggest that a prospective study is needed to evaluate this relationship.

A consensus from German experts stated that FAEs should not be used in combination with other systemic medications due to lack of clinical evidence.[3] Thirteen of our patients (5%) safely used FAEs in combination with other systemic or biologic agents. One retrospective study from the U.K. demonstrated that when FAEs were used in combination with other systemic agents, the doses of more toxic drugs could be reduced in 70% of patients without loss of disease control.[19]

The guidelines on the use of FAEs recommend a maximum dosage of 720 mg daily.[3] Previous studies have found that the majority of patients who respond well to FAEs require the maximum recommended dose and those who fail to respond to treatment are on lower doses of FAEs.[8,20] In this study we identified an interesting subgroup of 26 patients on a very low dose of FAEs (< 240 mg daily) with well-controlled psoriasis. Attempts were made to discontinue FAEs in this subgroup of patients, but these attempts resulted in a flare-up of psoriasis. Longer drug survival is more likely in this subgroup of patients. Further work is required to elucidate reasons for a well-maintained therapeutic response in this subgroup.

Notwithstanding the limitations of this retrospective study, we have demonstrated that FAEs are a safe and effective therapeutic option for patients with even severe psoriasis and have excellent drug survival.

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