ckj

OXFORD

Leading European Nephrology

Clinical Kidney Journal, 2016, vol. 9, no. 1, 82–89

doi: 10.1093/ckj/sfv114
Advance Access Publication Date: 10 November 2015
Original Article

ORIGINAL ARTICLE

Drug-induced Fanconi syndrome associated with fumaric acid esters treatment for psoriasis: a case series

Deepak M.W. Balak[1], Jan Nico Bouwes Bavinck[2], Aiko P.J. de Vries[3], Jenny Hartman[4], Hendrik A. Martino Neumann[1], Robert Zietse[5], and Hok Bing Thio[1]

[1]Department of Dermatology, Erasmus Medical Center, Rotterdam, The Netherlands, [2]Department of Dermatology, Leiden University Medical Center, Leiden, The Netherlands, [3]Division of Nephrology, Department of Medicine, Leiden University Medical Center, Leiden, The Netherlands, [4]Netherlands Pharmacovigilance Centre Lareb, 's-Hertogenbosch, The Netherlands, and [5]Division of Nephrology and Transplantation, Department of Internal Medicine, Erasmus Medical Center, Rotterdam, The Netherlands

Correspondence to: Deepak M.W. Balak; E-mail: d.balak@erasmusmc.nl; balak.dmw@gmail.com

Abstract

Background: Fumaric acid esters (FAEs), an oral immunomodulating treatment for psoriasis and multiple sclerosis, have been anecdotally associated with proximal renal tubular dysfunction due to a drug-induced Fanconi syndrome. Few data are available on clinical outcomes of FAE-induced Fanconi syndrome.

Methods: Descriptive case series with two cases of Fanconi syndrome associated with FAE treatment diagnosed at two Dutch university nephrology departments, three cases reported at the Dutch and German national pharmacovigilance databases and six previously reported cases.

Results: All 11 cases involved female patients with psoriasis. The median age at the time of onset was 38 years [interquartile range (IQR) 37–46]. Patients received long-term FAEs treatment with a median treatment duration of 60 months (IQR 28–111). Laboratory tests were typically significant for low serum levels of phosphate and uric acid, while urinalysis showed glycosuria and proteinuria. Eight (73%) patients had developed a hypophosphataemic osteomalacia and three (27%) had pathological bone fractures. All patients discontinued FAEs, while four (36%) patients were treated with supplementation of phosphate and/or vitamin D. Five (45%) patients had persisting symptoms despite FAEs discontinuation.

Conclusions: FAEs treatment can cause drug-induced Fanconi syndrome, but the association has been reported infrequently. Female patients with psoriasis treated long term with FAEs seem to be particularly at risk. Physicians treating patients with FAEs should be vigilant and monitor for the potential occurrence of Fanconi syndrome. Measurement of the urinary albumin:total protein ratio is a suggested screening tool for tubular proteinuria in Fanconi syndrome.

Key words: fumarates, hypophosphataemia, osteomalacia, proteinuria, proximal tubular dysfunction

Received: August 31, 2015. **Accepted:** October 12, 2015

Clinical Kidney Journal

Introduction

Fumaric acid esters (FAEs) are small molecules with immunomodulating effects that have been used as an oral treatment for psoriasis for four decades [1]. Since 1994, FAEs are an approved treatment for psoriasis in Germany. The licensed FAE formulation Fumaderm® (Biogen Idec, Ismaning, Germany) is a mixture of dimethylfumarate and monoethylfumarate salts [2]. Currently, Fumaderm is one of the most commonly used first-line systemic treatments in Germany [3]. In other countries, FAEs are increasingly used as an unlicensed treatment for psoriasis. The European S3 guidelines recommend FAEs as a treatment for moderate-to-severe psoriasis on the basis of their positive efficacy and safety profile [4]. The U.S. Food and Drug Administration and the European Medicines Agency approved an FAE formulation containing dimethylfumarate (Tecfidera®; Biogen Idec, Cambridge, MA, USA) as a treatment for multiple sclerosis in 2013 and 2014, respectively [5].

FAEs have been anecdotally linked to renal adverse events, such as acute kidney injury and Fanconi syndrome (FS) [6–9]. FS is defined by a generalized dysfunction of the proximal renal tubules, which can lead to an impaired resorption of glucose, amino acids and phosphate. A complication of FS is osteomalacia, which can lead to bone fractures and bone pain [10]. Several drugs can induce FS, such as tenofovir, ifosfamide, aminoglycoside antibiotics and FAEs (see Table 1) [7, 10]. There have been only a limited number of cases described of FS associated with FAEs. Consequently, few data are available on the clinical presentation and treatment of FAE-induced FS.

Table 1. Overview of drugs that can cause drug-induced FS [7, 10]

Drug	Class of drug	Indications
Adefovir	Antiviral	Hepatitis B
Aminoglycosides, e.g. gentamicin, tobramycin, amikacin	Antibiotic	Bacterial infections
Aspirin	Cyclooxygenase inhibitor	Pain, fever
Azacitidine	Cytostatic	Types of cancer
Carboplatin	Cytostatic	Types of cancer
Cidofovir	Antiviral	Cytomegalovirus retinitis
Cisplatin	Cytostatic	Types of cancer
Deferasirox	Iron chelator	Chronic iron overload
Didanosine	Antiviral	HIV
FAEs, e.g. dimethyl fumarate	Immunomodulator	Psoriasis, multiple sclerosis
Ifosfamide	Cytostatic	Types of cancer
Imatinib mesylate	Tyrosine kinase inhibitor	Leukaemia
Mercaptopurine	Cytostatic	Leukaemia
Ranitidine	Histamine antagonist	Gastroesophageal reflux, peptic ulcer disease
Streptozocin	Cytostatic	Types of cancer
Suramin	Antiparasitic	Trypanosomiasis, onchocerciasis
Tenofovir	Antiviral	HIV, hepatitis B
Tetracyclines, e.g. tetracycline	Antibiotic	Bacterial infections, acne
Valproic acid	Anticonvulsant	Epilepsy, bipolar disorder, migraine

Here, we assessed clinical and treatment outcomes of drug-induced FS associated with FAEs treatment.

Materials and methods

This is a descriptive case series of FAE-associated FS in patients with psoriasis. We described two new cases that were diagnosed at our department. We reviewed clinical features, laboratory findings and treatment outcomes. Measurements of serum levels of substances such as phosphate, calcium and 1,25-dihydroxyvitamin D were performed according to standard operating procedures at the Department of Clinical Chemistry. Additional testing to exclude the differential diagnoses of FS involved genetic testing or radiologic evaluation.

We searched for additional cases in pharmacovigilance databases of the Netherlands Pharmacovigilance Centre Lareb and the German Federal Institute for Drugs and Medical Devices [Bundesinstitut für Arzneimittel und Medizinprodukte (BfArM)] up to August 2015. We chose these two national pharmacovigilance databases given that FAEs are extensively used in these countries [3, 11]. In addition, Medline and Embase databases were searched up to August 2015 for published cases.

We used descriptive statistical methods to analyse data.

Results

Case characteristics

We included a total of 11 patients who developed FS during treatment with FAEs. Two cases were diagnosed at the nephrology department of two Dutch university medical centres, three cases were identified in German and Dutch pharmacovigilance databases and six case reports were found through a literature search. The clinical characteristics of the cases are presented in Table 2. All cases involved female patients with psoriasis. The median age at the time of onset of FS was 38 years [interquartile range (IQR) 37–46]. The median treatment duration with FAEs was 60 months (IQR 28–111) and the median daily FAEs dosage was 840 mg (IQR 720–1290). Data on body mass were available for four patients [median 20.9 kg/m^2 (IQR 20.3–23.6)].

In most cases, patients did not exhibit any symptoms. The most frequently reported presenting symptoms of FS were generalized weakness (27%), myalgia (27%) and arthralgia (27%) (see Table 3). Laboratory tests often displayed low serum levels of phosphate (73%), high alkaline phosphatase (45%) and low uric acid (45%). Urinalysis typically showed glycosuria (73%), proteinuria (64%), aminoaciduria (27%) and phosphaturia (27%). Diagnosis of FS was based on laboratory test results. Five (45%) patients were diagnosed with a hypophosphataemic osteomalacia, of whom three (27%) patients suffered from multiple pathological bone fractures. FAEs treatment was discontinued in almost all cases; two reports did not describe whether FAEs were discontinued. Four (36%) patients were treated with supplementation of phosphate and three (27%) with vitamin D supplementation. Complete improvement was reported in four (36%) patients, partial improvement in one (9%) patient and there were five (45%) patients who had no improvement. In one (9%) case, the symptoms of FS recurred twice upon rechallenges with FAEs [12].

Below, we describe detailed information on clinical features and outcomes of the novel FS cases.

New cases of FAE-associated FS

A 37-year-old female patient with plaque psoriasis developed FS during FAE treatment (patient no. 7; see Tables 2 and 4). This

Table 2. Overview of reported cases of drug-induced FS associated with FAEs treatment in patients with psoriasis

Patient no.	Reference (year)	Sex	Age (years)	Body weight, height, BMI	FAE treatment duration (months)	FAE dosage per day	Complaints	Laboratory deviations	Osteomalacia	Therapy	Outcome
1	Fliegner and Spiegel [12] (1992)	F	46	NR	16	1736 mg[a] (960 mg DMF + 776 mg MEF)	Arthralgia, myalgia, difficulties with walking, immobility	*Serum*: low phosphate, low uric acid, increased alkaline phosphatase *Urine*: glycosuria, proteinuria	Yes	FAE discontinuation. Oral phosphate and vitamin D3 supplementation	Complete improvement. Recurrence after re-treatment with FAEs
2	Haviv *et al.* [13] (1999)	F	48	47 kg, 152 cm, 20.3	12	NR	Generalized weakness, dyspnoea	*Serum*: increased alkaline phosphatase, low phosphate, increased PTH, vitamin B12 deficiency, low total calcium *Urine*: glycosuria, aminoaciduria, phosphaturia, uric aciduria	Yes	FAE discontinuation. Oral phosphate supplementation	Improvement of the respiratory capacity
3	Raschka and Koch [6] (1999)	F	38	57 kg, 168 cm, 20.2	60	840 mg[a]	Fatigue, weakness, polydipsia	*Serum*: low uric acid, low phosphate *Urine*: proteinuria, glycosuria	No	FAE discontinuation. Oral phosphate supplementation	No improvement within 6 months
4	Schilling and Schopf [14] (1999)	F	35	NR	~36	Max. 1290 mg[b] (720 DMF + 570 MEF)	Pain in feet, myalgia	*Serum*: increased alkaline phosphatase, low phosphate, low uric acid *Urine*: glycosuria, proteinuria, hypercalciuria	Yes	FAEs discontinuation	Complete improvement within 8 months
5	Warzecha *et al.* [15] (2001)	F	48	NR	~120	NR	Multiple pathological bone fractures, myalgia	*Serum*: increased alkaline phosphatase, low phosphate, low vitamin D3 *Urine*: proteinuria, aminoaciduria, glycosuria	Yes	FAEs discontinuation. Oral vitamin D3 supplementation	Complete improvement within 3 months
6	Reid *et al.* [16] (2013)	F	37	NR	25	720 mg	Generalized weakness and pain in her feet, multiple pathologic bone fractures	*Serum*: increased serum alkaline phosphatase, low phosphate, low uric acid, low potassium *Urine*: proteinuria, glycosuria, aminoaciduria, hypercalciuria	Yes	FAEs discontinuation	Complete improvement within 4 weeks

Table 2. Continued

Patient no.	Reference (year)	Sex	Age (years)	Body weight, height, BMI	FAE treatment duration (months)	FAE dosage per day	Complaints	Laboratory deviations	Osteomalacia	Therapy	Outcome
7	This report	F	37	65 kg, 174 cm, 21.5	180	120–480 mg DMF[b]	None	*Serum*: low phosphate, low uric acid, low PTH *Urine*: Proteinuria, glycosuria, hypercalciuria, phosphaturia	No	FAEs discontinuation	No improvement
8	This report	F	40	NR	84	720 mg DMF	None	*Serum*: low phosphate, low calcium, increased PTH, low bicarbonate, low vitamin B12 *Urine*: proteinuria, glycosuria, phosphaturia	No	FAEs discontinuation	Partial improvement
9	This report (Lareb)	F	31	83 kg, 167 cm, 29.8	60	NR	Spontaneous bone fracture	NR	Yes	FAEs discontinuation. Phosphate and vitamin D supplementation	No improvement
10	This report (BfArM)	F	45–49	NR	120	NR	NR	NR	Yes	NR	No improvement
11	This report (BfArM)	F	29–35	NR	NR	NR	NR	NR	Yes	NR	NR

DMF, dimethylfumate; F, female; FAEs, fumaric acid esters; M, male; MEF, monoethylfumarate; NR, not reported; BMI, body mass index.
[a]Unlicensed FAE formulation containing dimethylfumarate plus monoethylfumarate salts.
[b]Licensed German FAE formulation containing dimethylfumarate plus monoethylfumarate salts (Fumaderm).

Table 3. Overview of characteristics of drug-induced FS observed in cases associated with FAE treatment for psoriasis ($n = 11$)

Characteristics	Frequency in cases linked to FAEs
Subjective symptoms	
Myalgia	3
Generalized weakness	3
Arthralgia/pain in feet	3
Fatigue	1
Polydipsia	1
Immobility	1
Dyspnoea	1
Laboratory abnormalities	
Low phosphate	8
High alkaline phosphatase	5
Low uric acid	5
High PTH	2
Low vitamin B12	2
Low calcium	2
Low potassium	1
Low vitamin D3	1
Low bicarbonate	1
Low PTH	1
Urine analysis abnormalities	
Glycosuria	8
Proteinuria	7
Aminoaciduria	3
Hypercalciuria	3
Phosphaturia	3
Uric aciduria	1
Complications	
Osteomalacia	8
Pathological bone fractures	3

Table 4. Laboratory data characteristics from the two new cases of drug-induced FS associated with FAE treatment

Characteristics (reference values)	Patient no. 7	Patient no. 8
Serum		
eGFR (>60 mL/min/1.73 m^2)	>60	63
Creatinine (49–90 μmol/L)	74	87
Uric acid (0.14–0.34 mmol/L)	0.09	NA
Phosphate (0.90–1.50 mmol/L)	0.86	0.58
1,25-Dihydroxyvitamin D3 (38–183 pmol/L)	259	69
25-Hydroxyvitamin D3 (50–250 nmol/L)	161	71
PTH (1.4–7.3 pmol/L)	0.7	9.1
PTH-like peptide	Negative	NA
Alkaline phosphatase (0–97 U/L)	43	NA
Calcium (2.20–2.65 mmol/L)	2.50	2.16
Bicarbonate (21.0–27.0 mmol/L)	26	19.9
HbA1c (26–42 mmol/mol)	32	NA
Glucose (4–6.1 mmol/L)	NA	4.8
Urine		
Proteinuria (dipstick)	Positive (2+)	Positive (1+)
Proteinuria (g protein/24 h)	0.86	0.38
Glycosuria	Positive (1+)	Positive (3+)
Hypercalciuria (mmol/L)	4.5	NA
Creatinine (mmol/L)	5.1	4.7
Phosphate (mmol/L)	16	9.6
Fractional phosphate excretion	22%	31%
Fractional uric acid excretion	>73%	NA

eGFR, estimated glomerular filtration rate; NA, not available.

patient had a history of psoriasis from the age of 20 years and had been previously treated with phototherapy and topical treatments. She had been treated with oral FAEs for 15 years and had only temporarily stopped FAEs during pregnancy. Her medical history was remarkable for two miscarriages, migraine and recurrent urinary tract infections. She used FAEs (Fumaderm) 215 mg dimethylfumarate once per day, rizatriptan 5 mg as needed, an ethinylestradiol/gestodene contraceptive and calcipotriol/betamethasone dipropionate ointment as needed. She had no history of drug use known to cause drug-induced FS. The psoriasis was well controlled with FAEs and there were no adverse events. Routine urinalyses throughout FAE treatment indicated persisting proteinuria and glycosuria, therefore she was referred to the nephrology department for further analysis. Additional laboratory testing showed a hypophosphataemia (serum phosphate 0.86 mmol/L, RR 0.90–1.50) with a normal serum creatinine level (74 μmol/L, RR 49–90) and a normal estimated glomerular filtration rate (eGFR) >60 mL/min/1.73 m^2 (see Table 3). The fractional phosphate excretion was 22%, suggesting renal phosphate wasting. There was also a low serum level of uric acid of 0.09 mmol/L (RR 0.14–0.34); the fractional uric acid excretion was >73%. Further urinalysis revealed a tubular proteinuria (0.86 g protein/24 h). There was also glycosuria (1+ glucose on dipstick) in the face of a normal glycated haemoglobin level of 32 mmol/mol Hb (RR 20–42). She also had hypercalciuria and nephrolithiasis. Her serum calcium level was normal. The parathyroid hormone (PTH) level was decreased (0.7 pmol/L, RR 1.4–7.3) and PTH-like peptide was not present. Differential diagnoses as Dent's disease and sarcoidosis were excluded by genetic mutation testing and by chest radiograph evaluation, respectively. The findings in this case were consistent with a drug-induced FS. However, although unlikely, a new genetic entity cannot be excluded. FAE treatment was subsequently discontinued. However, the laboratory and urine abnormalities persisted.

A second case of FAE-associated FS involved a 40-year-old female patient who had plaque psoriasis since the age of 8 years (patient no. 8; see Tables 2 and 4). Her medical history was remarkable for hypercholesterolaemia and recurrent vaginal yeast infections, and she was recently diagnosed with a vitamin B12 deficiency. Her medication use included atorvastatin 10 mg once daily, fluconazole 150 mg as needed and vitamin B12 injections. There was no prior use of drugs linked to drug-induced FS. She had previously been treated with topical psoriasis treatments and phototherapy. In May 2008, she started FAE treatment 215 mg three to six times per day. Her psoriasis was well controlled and she reported no adverse events. She had used FAEs continuously for 7 years. Routine urinalysis showed persisting proteinuria, and therefore she was referred to the nephrology department. Additional testing was significant for hypophosphataemia (serum phosphate 0.58 mmol/L, RR 0.80–1.40), hypocalcaemia (serum calcium 2.16 mmol/L, RR 2.20–2.65), an increased PTH level of 9.1 pmol/L (RR 1.4–7.3) and a slightly decreased serum bicarbonate level of 19.9 mmol/L (RR 21.0–27.0) (see Table 3). The fractional phosphate excretion was 30.6%, which is in line with renal phosphate wasting. The serum creatinine level was within the normal range (87 μmol/L, RR 55–90), as was the eGFR of 63 mL/min/1.73 m^2 (RR >60). Urinalysis was significant for glycosuria (3+ glucose on dipstick) and tubular proteinuria (0.38 g protein/L). Based on these findings, a diagnosis of

FAE-induced FS was made. It is likely that the patient's vitamin B12 deficiency is part of FS, considering that vitamin B12 is taken up at the proximal renal tubule [17]. Pernicious anaemia as an alternative reason for the vitamin B12 deficiency was excluded, as antibodies to intrinsic factor were not present. Vitamin D is also taken up in the proximal tubule [17], but in this case serum 1,25-dihydroxyvitamin D was within normal limits (69 pmol/L, RR 38–183). Following the diagnosis of FS, FAEs were stopped. There was partial improvement of the symptoms with normalization of serum phosphate levels and proteinuria.

Cases reported in Dutch and German national pharmacovigilance databases

One case of FS linked to FAEs was reported to Lareb. This case involved a 31-year-old female psoriasis patient. Her medical history was remarkable for endometriosis, and she used celecoxib and a lynestrenol contraceptive. She had been treated with FAEs for 5 years (dosage not reported). She developed FS with severe osteomalacia. She had no symptoms except for a spontaneous bone fracture. FAE treatment was discontinued and the patient was treated with supplementation of phosphate and vitamin D. The patient did not recover and became wheelchair dependent.

Two cases of FS were reported by BfArM. A female patient between 45 and 49 years of age was reported with FS. She had been treated since 1989 with Fumaderm (dosage not reported) and topical fumaric acid. In 1999, she developed FS, from which she did not recover. She also developed osteomalacia, which led to a pathologic fracture. The second case involved a female psoriasis patient between 29 and 35 years of age who had been treated with Fumaderm (dosage not reported) since 1995. She was reported with FS (year of onset not reported) with a complete recovery. She was diagnosed in 1998 with osteomalacia.

Discussion

FS is a renal disorder that is characterized by proximal tubular dysfunction, which can lead to inappropriate urinary losses of phosphate, glucose, bicarbonate and amino acids. Here, we report 11 psoriasis patients who developed an FAE-induced FS. Presenting symptoms of FS included generalized weakness and myalgia. Laboratory tests typically showed low serum levels of phosphate and uric acid and a proximal tubular acidosis, while urinalysis showed glycosuria and proteinuria. Eight (73%) patients had hypophosphataemic osteomalacia and five (45%) patients had persisting symptoms despite FAE discontinuation.

The reported cases of FAE-associated FS share several phenotypical similarities. All cases involved females. Sex differences in renal proximal tubular function and in the expression of organic anion receptors have been described and such differences could underlie differential risks for male and female patients to develop FAE-associated FS [18, 19]. However, we cannot exclude selective reporting due to the relatively small sample size described in our case series. Whether there is a predominance for females to develop FS remains to be determined. Furthermore, all patients reported with FS were treated long term with FAEs. The median duration of FAEs treatment was 60 months (IQR 28–111). The five cases that were published in the 1990s were linked to the use of unlicensed FAEs formulations with dimethylfumarate and monoethylfumarate salts. Moreover, the doses of FAEs applied in these cases exceeded the maximum daily dose of 1290 mg that is recommended in current psoriasis guidelines [4]. However, several of the patients were treated with lower dosages of FAEs and still developed FS (see Table 2). Therefore, a clear correlation between FAE dosage and proximal tubular dysfunction cannot be made. Higher doses of FAEs per body weight has been proposed as a potential factor in the nephrotoxicity of FAEs [9]. The body mass index (BMI) was reported for only four cases, with a median BMI for these cases of 20.9 kg/m^2 (IQR 20.3–23.6). More data are needed to identify risk factors for the development of FS during FAEs treatment.

Limitations of our study are the relatively small sample size and the fact that causality between FAEs and drug-induced FS cannot be proven in this data set. In addition, the data available for some cases were incomplete for findings of proximal tubular dysfunction. Also, some cases had limited data on alternative causes of FS or use of prior and concomitant drugs that are known to result in drug-induced FS. Two recent epidemiological studies have shown an independent association between moderate-to-severe psoriasis and an increased risk for glomerulonephritis or chronic kidney disease [20, 21]. Psoriasis itself does not seem to be associated with FS.

The incidence of FAE-associated FS has not been studied. In randomized controlled trials that evaluated FAEs treatment in psoriasis patients, no renal toxicity was reported [4]. This could be due to the relatively short follow-up period in these trials. Long-term observational studies have not indicated an increased risk for nephrotoxicity during continuous FAE treatment [22, 23]. FS could be underdiagnosed, especially mild forms of proximal tubular dysfunction, given that proteinuria is a recognized and common adverse event of FAEs [24]. Up to 30% of patients display proteinuria [25]. On the other hand, FAE-induced proteinuria is typically transient, even with continued FAE treatment [4].

The current psoriasis guidelines recommend regular urinalysis during FAEs, but there is no consensus on the optimal frequency. The 2009 European S3 guidelines on psoriasis treatment recommend monitoring serum creatinine and urine sediment every 4 weeks [4]. In the 2011 German psoriasis guidelines, it is advised to monitor serum creatinine and urine status every 4 weeks for the first 4 months of treatment, followed by once every 8 weeks [26]. Urinalysis is typically performed with a urine dipstick, but this method is sensitive for albumin and probably not reliable for detection of tubular proteinuria [27]. Tubular dysfunction leads to increased urinary levels of proteins other than albumin, such as β2-microglobulin. Haring *et al*. [9] assessed the use of β2-microglobulin in urine as a marker for proximal tubular damage during FAEs treatment in psoriasis patients. Urinary β2-microglobulin was increased in 3 of 23 patients receiving FAEs, which normalized upon discontinuation of the FAEs. β2-microglobulin does not seem to be a sensitive marker, which may be due to the collection method. β2-microglobulin is not stable in acid urine and is only measurable after alkalinization of the urine. A new method is measurement of the urinary albumin:total protein ratio, which is an inexpensive and simple screening test. If albumin constitutes <40% of the total protein in urine, this is a good indication for tubular proteinuria [28]. In our data set, we had no data available on the urinary albumin:total protein ratio. Use of the urinary albumin:total protein ratio as a screening test for tubular proteinuria needs to be tested and validated for FAEs-induced FS.

FAEs are increasingly being used, also for conditions other than psoriasis [29]. An FAE formulation containing dimethylfumarate (Tecfidera®, Biogen Idec) was approved for the treatment of multiple sclerosis in 2013. Although the FAEs formulation and the dosage schedule are different than those used in the treatment of psoriasis, the safety profile of this FAE formulation

seems similar to that of FAE treatment in psoriasis. There have been no reports of proximal tubular dysfunction with dimethylfumarate in multiple sclerosis patients [30, 31].

The mechanisms leading to FAE-induced proximal tubular dysfunction in FS are not understood [7]. One potential mechanism involves FAE-induced glutathione depletion. FAEs are able to enter proximal tubular cells via the organic anion transporter (OAT1) [32] and deplete intracellular levels of glutathione levels [33], which can cause FS [9, 34]. Maleic acid, a *cis* isomer of fumaric acid, induces FS in rats through similar mechanisms of intracellular depletion of glutathione and adenosine triphosphate [35].

In conclusion, FS seems to be an infrequent adverse event of FAE treatment. Female patients treated long term with FAEs seem to be particularly at risk. Physicians treating patients with FAEs should be aware of and vigilant for proximal tubular dysfunction during FAEs treatment. Quantitative total protein measurement to calculate the albumin:total protein ratio is suggested as a screening test for tubular proteinuria.

Conflict of interest statement

None to declare. Results presented in this article have not been published previously in whole or part.

References

1. Mrowietz U, Asadullah K. Dimethylfumarate for psoriasis: more than a dietary curiosity. *Trends Mol Med* 2005; 11: 43–48
2. Rostami Yazdi M, Mrowietz U. Fumaric acid esters. *Clin Dermatol* 2008; 26: 522–526
3. Augustin M, Spehr C, Radtke MA *et al*. German psoriasis registry PsoBest: objectives, methodology and baseline data. *J Dtsch Dermatol Ges* 2014; 12: 48–57
4. Pathirana D, Ormerod AD, Saiag P *et al*. European S3-guidelines on the systemic treatment of psoriasis vulgaris. *J Eur Acad Dermatol Venereol* 2009; 23(Suppl 2): 1–70
5. Sheridan C. Second oral MS drug wins FDA nod. *Nat Biotechnol* 2013; 31: 373
6. Raschka C, Koch HJ. Longterm treatment of psoriasis using fumaric acid preparations can be associated with severe proximal tubular damage. *Hum Exp Toxicol* 1999; 18: 738–739
7. Izzedine H, Launay-Vacher V, Isnard-Bagnis C *et al*. Drug-induced Fanconi's syndrome. *Am J Kidney Dis* 2003; 41: 292–309
8. Roodnat JI, Christiaans MH, Nugteren-Huying WM *et al*. [Acute kidney insufficiency in patients treated with fumaric acid esters for psoriasis] Acute nierinsufficientie bij patienten behandeld met fumaarzuuresters wegens psoriasis. *Ned Tijdschr Geneeskd* 1989; 133: 2623–2626
9. Haring N, Mahr HS, Mundle M *et al*. Early detection of renal damage caused by fumaric acid ester therapy by determination of urinary beta2-microglobulin. *Br J Dermatol* 2011; 164: 648–651
10. Hall AM, Bass P, Unwin RJ. Drug-induced renal Fanconi syndrome. *QJM* 2014; 107: 261–269
11. Fallah Arani S, Balak DMW, Neumann HAM *et al*. Treatment of psoriasis with non-registered fumaric acid esters in the Netherlands: a nationwide survey among Dutch dermatologists. *J Eur Acad Dermatol Venereol* 2014; 28: 972–975
12. Fliegner L, Spiegel P. Osteomalacia as an obviously rare secondary effect of oral fumaric acid therapy. *Hautarzt* 1992; 43: 554–560
13. Haviv YS, Zimmerman M, Berkman N *et al*. Fumaric acid ester-induced diffuse renal tubular injury presenting as Fanconi syndrome and osteomalacia. *Clin Drug Investig* 1999; 17: 333–335
14. Schilling F, Schopf RE. Adult Debre-de Toni-Fanconi syndrome with osteomalacia, acquired through long-term psoriasis therapy with fumaric acid ester—and a contribution to malacic osteoarthropathy. *Aktuelle Rheumatol* 1999; 24: 174–179
15. Warzecha J, Runck A, Priepke E *et al*. [Multiple pathological fractures within the scope of DeToni-Debre-Fanconi syndrome after fumarate therapy in psoriasis] Multiple pathologische Frakturen im Rahmen eines DeToni-Debre-Fanconi-Syndroms nach Fumarattherapie bei Psoriasis. *Unfallchirurg* 2001; 104: 448–451
16. Reid C, Holian J, Kane D *et al*. De Toni-Fanconi syndrome secondary to fumaric acid esters. *Br J Dermatol* 2013; 169: 24
17. Birn H. The kidney in vitamin B12 and folate homeostasis: characterization of receptors for tubular uptake of vitamins and carrier proteins. *Am J Physiol Renal Physiol* 2006; 291: F22–F36
18. Sharma N, Li L, Ecelbarger CM. Sex differences in renal and metabolic responses to a high-fructose diet in mice. *Am J Physiol Renal Physiol* 2015; 308: F400–F410
19. Sekine T, Miyazaki H, Endou H. Molecular physiology of renal organic anion transporters. *Am J Physiol Renal Physiol* 2006; 290: F251–F261
20. Wan J, Wang S, Haynes K *et al*. Risk of moderate to advanced kidney disease in patients with psoriasis: population based cohort study. *BMJ* 2013; 347: f5961
21. Chiu HY, Huang HL, Li CH *et al*. Increased risk of glomerulonephritis and chronic kidney disease in relation to the severity of psoriasis, concomitant medication, and comorbidity: a nationwide population-based cohort study. *Br J Dermatol* 2015; 173: 146–154
22. Reich K, Thaci D, Mrowietz U *et al*. Efficacy and safety of fumaric acid esters in the long-term treatment of psoriasis—a retrospective study (FUTURE). *J Dtsch Dermatol Ges* 2009; 7: 603–611
23. Hoefnagel JJ, Thio HB, Willemze R *et al*. Long-term safety aspects of systemic therapy with fumaric acid esters in severe psoriasis. *Br J Dermatol* 2003; 149: 363–369
24. Ogilvie S, Lewis Jones S, Dawe R *et al*. Proteinuria with fumaric acid ester treatment for psoriasis. *Clin Exp Dermatol* 2011; 36: 632–634
25. Balak DM, Fallah-Arani S, Venema CM *et al*. Addition of an oral histamine antagonist to reduce adverse events associated with fumaric acid esters in the treatment of psoriasis: a randomized double-blind placebo-controlled trial. *Br J Dermatol* 2015; 172: 754–759
26. Nast A, Boehncke WH, Mrowietz U *et al*. German S3-guidelines on the treatment of psoriasis vulgaris (short version). *Arch Dermatol Res* 2012; 304: 87–113
27. Sise ME, Hirsch JS, Canetta PA *et al*. Nonalbumin proteinuria predominates in biopsy-proven tenofovir nephrotoxicity. *AIDS* 2015; 29: 941–946
28. Smith ER, Cai MM, McMahon LP *et al*. The value of simultaneous measurements of urinary albumin and total protein in proteinuric patients. *Nephrol Dial Transplant* 2012; 27: 1534–1541
29. Meissner M, Valesky EM, Kippenberger S *et al*. Dimethyl fumarate—only an anti-psoriatic medication? *J Dtsch Dermatol Ges* 2012; 10: 793–801
30. Fox RJ, Miller DH, Phillips JT *et al*. Placebo-controlled phase 3 study of oral BG-12 or glatiramer in multiple sclerosis. *N Engl J Med* 2012; 367: 1087–1097
31. Gold R, Kappos L, Arnold DL *et al*. Placebo-controlled phase 3 study of oral BG-12 for relapsing multiple sclerosis. *N Engl J Med* 2012; 367: 1098–1107

32. Kaler G, Truong DM, Khandelwal A *et al*. Structural variation governs substrate specificity for organic anion transporter (OAT) homologs. Potential remote sensing by OAT family members. *J Biol Chem* 2007; 282: 23841–23853
33. Ghoreschi K, Bruck J, Kellerer C *et al*. Fumarates improve psoriasis and multiple sclerosis by inducing type II dendritic cells. *J Exp Med* 2011; 208: 2291–2303
34. Abraham P, Ramamoorthy H, Isaac B. Depletion of the cellular antioxidant system contributes to tenofovir disoproxil fumarate-induced mitochondrial damage and increased oxido-nitrosative stress in the kidney. *J Biomed Sci* 2013; 20: 61
35. Zager RA, Johnson AC, Naito M *et al*. Maleate nephrotoxicity: mechanisms of injury and correlates with ischemic/hypoxic tubular cell death. *Am J Physiol Renal Physiol* 2008; 294: F187–F197

Clinical Kidney Journal
ckj