Switch of psoriasis therapy from a fumaric acid ester mixture to dimethyl fumarate monotherapy: Results of a prospective study

Sandra Falkvoll, Sascha Gerdes, Ulrich Mrowietz
Psoriasis Center, Department of Dermatology, University Medical Center Schleswig-Holstein, Campus Kiel, Germany

Introduction
Fumaric acid esters (FAEs) are widely used for systemic therapy of moderate-to-severe psoriasis in Germany, with a prescription rate of more than 50%. Fumaric acid esters are also used frequently in the Netherlands, United Kingdom, and Ireland for first-line treatment [1, 2]. Until recently, a mixture of four different fumaric acid esters including the main active compound dimethyl fumarate (DMF, Fumaderm®) was only authorized in Germany. Since 2017, a product containing DMF alone (Skilarence®) has been authorized in Europe and is now available outside Germany as well.

The advantages of the DMF product are that the only active substance it contains is DMF, flexible dosing is possible using the 30 mg and 120 mg tablets, and the DMF product is cheaper than the FAE mixture in Germany. The only requirement for safety monitoring is ensuring that laboratory parameters are within the normal range every three months. Switching from the FAE mixture to the DMF product therefore seems reasonable.

There are no data yet as to whether a direct switch from the FAE mixture to the DMF product can be performed without a washout period. A prospective study was performed to address this issue. Patients who were stable under treatment with the FAE mixture were asked to switch to the DMF product. Patients were asked about tolerability and other treatment-related parameters at the first follow-up visit after switching.

Methods
This prospective observational trial was approved by the Ethics Committee of the University of Kiel (AZ: D553/17). Patients who were treated with the FAE mixture and
presented at the outpatient service of the Kiel Psoriasis Center for routine safety monitoring were asked to participate, and written informed consent was obtained before they entered the study. Patients whose psoriasis had improved and who could tolerate treatment with the FAE mixture were recruited.

Treatment with the FAE mixture was switched to the DMF product without any interruption on the basis of the current DMF dose in the FAE mixture. Patients were then scheduled for the next regular check-up three months later.

To assess psoriasis severity, we used the PASI (psoriasis area and severity index). When presenting for their first check-up after switching, patients were handed a questionnaire to investigate their views about tolerability and efficacy and to provide a global judgment of the switch.

Results

A total of 40 patients (24 male, 16 female) were prospectively and consecutively recruited to the study and underwent a check-up after switching treatments.

The age of adult patients ranged from 18 to 74 years with a mean age of 46 years. One patient was 13 years old and received treatment off-label. Table 1 shows the demographics of the patients and the DMF dose at the time of switching from the FAE mixture to the DMF product. Most patients were treated with a daily DMF dose between 120 mg and 480 mg, and had previously been treated with the FAE mixture for one to five years (Figure 1).

In general, the patients regarded the outcome of the switch to the DMF product as neutral or positive (18 positive, 18 neutral, 4 negative). Efficacy as assessed with the PASI was equal or better in 34/37 patients, while 3/37 had a higher PASI severity after switching (Figure 2). A PASI estimate was not available at one of the visits in 3/40 patients.

According to regulatory requirements, both drug products have a similar formulation. Therefore, adverse drug effects such as gastrointestinal (GI) complaints should not differ in symptoms or intensity. The majority of patients (27/40) did not experience any difference in GI complaints after switching from the FAE mixture to the DMF product. Gastrointestinal tolerability was judged as better for the DMF product by 7/40 patients and worse by 2/40 patients. No GI complaints were reported with either drug product by 4/40 patients. Flushing was unchanged in 24/40 patients, 8/40 reported less flushing and 6/40 reported more flushing. Flushing did not occur with either drug product in 2/40 patients.

Regarding the question of overall tolerability, 28/40 patients reported similar tolerability, 8/40 reported better tolerability with the DMF product and 4/40 said that tolerability was worse after switching. In answer to the question about skin status in general, 27/40 patients reported that it was unchanged after switching from the FAE mixture to the DMF product, patients, 7/40 reported that it was better and 6/40 said it was worse.

Figure 1 Number of patients related to the duration of continuous FAE therapy that they received before switching from the FAE mixture to the DMF product (n = 40).
Table 1 Demographic characteristics of patients before switching from the FAE mixture to the DMF product, including the daily dose of DMF at the time of switching. One patient received a dose of DMF of 120 mg every third day; the calculated daily dose was 40 mg.

| Pat. No. | m/f | *FDPso | Age | **DMF | Start DMF | Duration of FAE-mixture therapy (months) | Comorbidity | Comedication | Smoking | Alcohol | ***Previous therapies |
|----------|-----|--------|-----|-------|-----------|-----------------------------------------|-------------|--------------|---------|---------|----------------------|
| 1        | m   | 1984   | 44  | 120   | 01/2017   | 11                                      | Rosacea     | None         | Yes     | Yes     | CS, CS+D3             |
| 2        | m   | Unknown| 33  | 720   | 02/2017   | 9                                       | None        | None         | Unknown | No      | CS, (UVB)             |
| 3        | m   | 1984   | 57  | 240   | 2009      | 108                                     | None        | None         | Unknown | No      | CS, D3               |
| 4        | m   | 1995   | 67  | 120   | 2009      | 84                                      | Hypertension, muscle pain, coronary artery disease, disc prolapse, Ramipril, aspirin, nitroglycerine, ibuprofen | Yes         | No           | CS, CS+D3, dithranol |
| 5        | m   | 2001   | 35  | 240   | 12/2015   | 27                                      | Upper airway syndrome, sleep apnea | None         | Yes           | Yes     | CS, (UVB)             |
| 6        | m   | 1989   | 56  | 600   | 1996      | 84                                      | None        | None         | Yes     | No      | CS, MTX, PUVA         |
| 7        | m   | 1995   | 53  | 480   | 03/2012   | 68                                      | None        | None         | Yes     | Yes     | None                 |
| 8        | f   | 2011   | 61  | 360   | 03/2017   | 8                                       | None        | None         | Yes     | Yes     | CS, CS+D3             |
| 9        | m   | 2013   | 49  | 120   | 01/2014   | 45                                      | Recurrent tonsillitis, asthma | Pantoprazole, inhaled steroids | Yes     | Yes     | CS                   |
| 10       | m   | 2000   | 57  | 480   | 12/2014   | 37                                      | Hypercholesterolemia, hypertension, | Simvastatin, diltiazem | No      | Yes     | CS, D3               |
| 11       | f   | 1995   | 49  | 480   | 07/2015   | 30                                      | None        | L-thyroxine | Unknown | No      | CS, CS+D3, UVB        |
| 12       | f   | 1997   | 52  | 240   | 01/2017   | 11                                      | None        | None         | Yes     | Yes     | PUVA                 |
| 13       | f   | 1988   | 62  | 720   | 07/2008   | 115                                     | Reflux esophagitis | Pantoprazole | Yes     | No      | Dithranol            |
| 14       | f   | 2009   | 42  | 120   | 07/2013   | 51                                      | None        | Pantoprazole | Yes     | No      | PUVA                 |
| 15       | m   | 2007   | 43  | 360   | 06/2016   | 17                                      | None        | None         | Yes     | No      | CS, UVB               |
| 16       | f   | 1987   | 44  | 60    | 11/2015   | 23                                      | None        | None         | Unknown | No      | PUVA, CS             |
| 17       | f   | 2010   | 13  | 30    | 07/2013   | 54                                      | None        | None         | No      | No      | None                 |
| 18       | m   | 1999   | 38  | 240   | 12/2014   | 36                                      | None        | None         | Unknown | Yes     | CS, D3, UVB           |

Continued
| Pat. No. | Sex | Age | **DMF | Start DMF | Duration of FAE-mixture therapy (months) | Comorbidity | Comedication | Smoking | Alcohol | ***Previous therapies |
|---------|-----|-----|-------|----------|------------------------------------------|-------------|--------------|---------|---------|---------------------|
| 19      | m   | 47  | 240   | 09/2014  | 40                                       | Hypothyroidism | L-thyroxine | Yes     | Yes     | D3, CS+D3           |
| 20      | m   | 74  | 240   | 07/2017  | 7                                        | Prostate cancer, COPD, hypothyroidism, osteoporosis, ventricular cardiac arrhythmia | Alendronic acid, levothyroxine, omeprazole, aspirin, flecainide, atorvastatin, sotalol, budesonide, tiotropium, ipratropium, salbutamol, n-butylscopolamine, oxaceprol | Yes     | Yes     | UVB                 |
| 21      | f   | 26  | 480   | 01/2016  | 23                                       | Hypothyroidism, hypersomnia | L-thyroxine, bupropion | No      | No      | PUVA                |
| 22      | m   | 63  | 360   | 11/2016  | 13                                       | Tremor       | Propranolol | Yes     | Yes     | PUVA                |
| 23      | f   | 61  | 60    | 07/2015  | 28                                       | Lung emphysema | None | Yes     | No      | CS+D3, UVB          |
| 24      | m   | 34  | 360   | 01/2014  | 47                                       | None         | None | Yes     | Yes     | CS, D3, CS+D3, PUVA |
| 25      | m   | 37  | 240   | 10/2014  | 39                                       | None         | Unknown | Yes     | No      | None                |
| 26      | f   | 26  | 240   | 10/2016  | 14                                       | Migraine-like headache | Metamizole | Yes     | No      | None                |
| 27      | m   | 46  | 240   | 07/2015  | 28                                       | Dilated cardiomyopathy, complete left atrial block, single coronary occlusion, hypertension, adiposity, hyperlipoproteinemia | Aspirin, metoprolol, ramipril, torsemide, eplerenone, simvastatin | Yes     | No      | CS, CS+D3, MTX, golimumab, PUVA |
| 28      | m   | 47  | 120   | 03/2016  | 19                                       | None         | None | Yes     | Yes     | CS, D3              |
| 29      | m   | 54  | 480   | 03/2017  | 8                                        | Hypertension, depressive mood disorder | Amlodipine, St. John's wort | Yes     | Yes     | CS, UVB             |
| 30      | f   | 25  | 30    | 11/2011  | 72                                       | None         | None | Unknown | No      | CS                  |
| 31      | m   | 30  | 480   | 03/2012  | 68                                       | None         | None | Yes     | Yes     | None                |
Table 1 Continued.

| Pat. No. | m/f | *FDPso | Age | **DMF Start DMF | Duration of FAE-mixture therapy (months) | Comorbidity | Comedication | Smoking | Alcohol | ***Previous therapies |
|----------|-----|---------|-----|-----------------|------------------------------------------|-------------|--------------|---------|---------|-----------------------|
| 32       | f   | 1958    | 69  | 360             | 1997                                     | 48          | None         | Candesartan | Unknown | No        | CS                    |
| 33       | m   | 1973    | 54  | 240             | 09/2011                                  | 74          | Hypertension, hypercholesterolemia | Atorvastatin, minoxidil, spironolactone, nebivolol, candesartan, doxazosin | No      | No       | D3, PUVA              |
| 34       | f   | 1965    | 59  | 720             | 2009                                     | 60          | Radicular pain syndrome           | None      | Yes      | No        | None                  |
| 35       | f   | 2006    | 70  | 360             | 02/2017                                  | 9           | Type 2 diabetes, hyperlipidemia, hypercholesterolemia, coronary artery disease, disc prolapse | Insulin, aspirin, atorvastatin, diclofenac, nitroglycerine | No      | No       | CS, CS+D3              |
| 36       | f   | 2012    | 27  | 40              | 04/2014                                  | 42          | None         | None      | No       | No        | Systemic steroid       |
| 37       | m   | 2008    | 30  | Unknown         | 08/2017                                  | 3           | Asthma, adiposity, alopecia areata universalis | None      | No       | Yes       | MTX, systemic steroid, CS |
| 38       | m   | 2003    | 39  | 720             | 04/2017                                  | 6           | Kyphosis, scoliosis               | None      | No       | Yes       | CS, D3                |
| 39       | m   | 2012    | 18  | 720             | 05/2017                                  | 5           | None         | None      | Unknown  | No        | CS                    |
| 40       | f   | 2005    | 24  | 360             | 11/2016                                  | 12          | Vitiligo      | None      | No       | No        | UVB                   |

*FDPso: Time point of first psoriasis diagnosis.
**DMF: Corresponding dose of DMF in the FAE mixture at the time of switching.
***Previous psoriasis treatments. CS: topical steroids, CS+D3: fixed topical combination of steroid and vitamin D3 analog; D3: topical vitamin D3 analogs; MTX: methotrexate; UVB: broad or narrow-band UVB; PUVA: psoralen + UVA.
Discussion

Therapy of systemic psoriasis with FAE has a long tradition in Germany and also in the Netherlands. In Germany, a mixture of DMF and three salts of ethyl hydrogen fumarate (Fumaderm®) has been authorized since 1994; the FAE mixture has been made up in compounding pharmacies in the Netherlands. Scientific evidence has shown that DMF is the active ingredient in the FAE mixture, and acts as a prodrug for the main DMF metabolite (monomethyl fumarate; MMF) after oral administration [3]. In fact, the first DMF product was registered earlier for the treatment of relapsing-remitting multiple sclerosis (Tecfidera®). Since fall 2017, another DMF product has been approved for oral first-line therapy of moderate-to-severe plaque psoriasis (Skilarence®) [4].

The extent of gastrointestinal symptoms and flushing depends on the formulation of the DMF-containing drugs. Due to regulatory requirements, the FAE mixture and the DMF product have similar formulations. Consistent with this, the results of our observational study showed that the majority of our patients did not observe any difference after switching from the FAE mixture to the same dose of DMF. This was also shown for flushing, although there is little evidence that flushing depends on the details of the formulation.

Omitting the three salts of ethyl hydrogen fumarate from the FAE mixture did not result in any change in the tolerability or efficacy of the DMF product. As stated in a recent review, there is no scientific evidence that ethyl hydrogen fumarate salts have a pharmacological effect in psoriasis [5]. Most of the patients in our study had already been treated with the FAE mixture for one to five years, and 22.5 % were long-term users, having taken the drug for 5 to 10 years. The patients investigated in the study were clinical responders to FAE and were able to tolerate potential adverse effect such as GI complaints and flushing. The unexpectedly high proportion of patients who regarded the switch from the FAE mixture to the DMF product as positive may be due in part to the fact that recommended intervals between check-ups are three months with the DMF product instead of one month with the FAE mixture.

In conclusion, the results of this study show that psoriasis patients can switch from the traditional FAE mixture to the same dose of DMF with similar clinical relief but without any washout period.

Acknowledgement

We are indebted to Birgit Dethlefs for her great help in coordinating the study.

Conflicts of interest

Ulrich Mrowietz was advisor, study coordinator or participant and has received funding from all companies who market or develop fumaric acid ester compounds for psoriasis (Almirall, Biogen, Forward Pharma, Dr. Reddy’s and Xenoport). Sandra Falkvoll and Sascha Gerdes have no conflicts of interest to disclose.
Correspondence to

Ulrich Mrowietz, MD
Psoriasis Center
Department of Dermatology
University Medical Center Schleswig-Holstein, Campus Kiel
Rosalind-Franklin-Strasse 7
24105 Kiel, Germany
E-mail: umrowietz@dermatology.uni-kiel.de

References

1. Nast A, Amelunxen L, Augustin M et al. S3 Guideline for the treatment of psoriasis vulgaris, update - Short version part 1 – Systemic treatment. J Dtsch Dermatol Ges 2018; 16(5): 645–69.

2. Nast A, Gisondi P, Ormerod AD et al. European S3-Guidelines on the systemic treatment of psoriasis vulgaris–Update 2015–Short version–EDF in cooperation with EADV and IPC. J Eur Acad Dermatol Venereol 2015; 29(12): 2277–94.

3. Mrowietz U, Morrison PJ, Suhrkamp I et al. The pharmacokinetics of fumaric acid esters reveal their in vivo effects. Trends Pharmacol Sci 2018; 39(1): 1–12.

4. Blair HA. Dimethyl fumarate: A review in moderate to severe plaque psoriasis. Drugs 2018; 78(1): 123–30.

5. Landeck L, Asadullah K, Amasuno A et al. Dimethyl fumarate (DMF) vs. monoethyl fumarate (MEF) salts for the treatment of plaque psoriasis: a review of clinical data. Arch Dermatol Res 2018; 310(6): 475–83.