

Treatment of patients with psoriasis resulting from a review of previously unmet needs, with particular reference to the new line of treatment with dimethyl fumarate (DMF): experts' recommendations

DOI:10.7365/JHPOR.2019.2.1

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Keywords:

psoriasis, sequential therapy, dimethyl fumarate

How to cite this article?

Owezarek W, Niewiedziol M, Kalinowska A, Pruszek C, Narbutt J. Treatment of patients with psoriasis resulting from a review of previously unmet needs, with particular reference to the new line of treatment with dimethyl fumarate (DMF): experts' recommendations. *J Health Policy Outcomes Res* [Internet]. 2019 [cited YYYY Mon DD];2. Available from: <https://www.jhpor.com/article/2225-treatment-of-patients-with-psoriasis-resulting-from-a-review-of-previously-unmet-needs-with-particular-reference-to-the-new-line-of-treatment-with-dimethyl-fumarate-dmf-experts-recommendations> DOI: 10.7365/JHPOR.2019.2.1

contributed: 2019-05-20
final review: 2019-06-14
published: 2019-08-11

Abstract

Psoriasis has a significant impact on patients' physical and mental state. Their quality of life is often impaired. What is more, despite the involvement of a significant number and type of health care services and significant financial outlays, psoriasis patients in Poland are treated suboptimally and non-cost-effectively (large percentage – 11.1% – of hospitalizations because of psoriasis, the longest hospitalization of patients with psoriasis among other dermatological patients – 8.6 days, treatment outside their administrative region – 58.1% of hospitalized patients). Psoriasis management is based on a sequential therapy. Biological treatment is available only to a limited group of patients with the most severe disease, what indicates the desirability of widening prescription-based systemic treatments that could be used prior to biological treatment. This would increase the possibility of treatment individualization by all dermatologists. In order to achieve optimal treatment results, patients should be offered to be treated with several treatment lines because it is not known which drug will be effective in their case. Dimethyl fumarate (DMF) is the one of new drugs, that meets the criteria for an additional systemic treatment option, prior to biological treatment. DMF therapy is associated with significant health benefits, which include improving the quality of life and lengthening the time with an adequate response to treatment. This therapy allows the patients to obtain greater benefits from treatment and to prolong the time without symptoms of the disease (symptoms-free).

Introduction

It is estimated that in Poland the total number of patients with psoriasis in all stages ranges between 800,000 and 1,000,000. In 2014 there were 64,500 new cases^[1], and 182,000 patients looked for medical help. In total 530,000 medical advices were provided for patients with psoriasis and 15,400 hospitalizations were recorded (94% of patients in ambulatory setting). Only 2% of patients were hospitalized and did not continue their therapy in ambulatory conditions.^[2]

Four percent of Polish patients were treated in outpatient and inpatient care in 2014.^[2] The average hospitalization duration was 89.9 patient-days^[3] (average length of stay for one psoriasis patient was 8.6 days)^[1,2]

The average age of a patient hospitalized because of psoriasis is 49.33 years; patients over 65 years of age account for 17.14% and patients over 80 years of age - 2.35%. The majority of hospitalized patients were female (44.93%). Overall, 8.4% of patients with psoriasis were treated in a hospital outside their voivodeship region; 58.1% - outside their administrative region (powiat), but in their voivodeship, and 33.5% of patients in their administrative region (powiat).^[1]

Methods

The aim of this article is to review a current knowledge of psoriasis treatment methods, with particular emphasis on the need of additional systemic treatment option, that allows the patients to prolong the time without symptoms of the disease.

Thus, the most important facts about psoriasis were presented and guidelines were described, wherein the treatment options currently available in Poland and options for extending the treatment sequence were outlined. Dimethyl fumarate may be a new therapeutic option, which responds to the unmet needs of both dermatologists and patients, therefore the metaanalysis results for these drugs were presented, based on literature review.

Results

3.1 Psoriasis severity classification

Severity of psoriasis is scored according to BSA (Body Surface Area) and PASI (Psoriasis Area and Severity Index) scales. BSA is used to estimate the percentage of skin affected by lesions and may range from 0 to 100%. One percent corresponds to one hand (from wrist to finger-

tips). PASI is a scale that evaluates the severity of psoriasis including parameters such as erythema, infiltration, thickness of the scales and the percentage of the affected skin area. PASI score ranges from 0 to 72. Depending on BSA and PASI scores, psoriasis may be classified as mild ($BSA < 3\%$, $PASI < 7$), moderate ($3\% \leq BSA \leq 10\%$, $7 \leq PASI \leq 12$) or severe ($BSA > 10\%$, $PASI > 12$). According to Mrowietz, $PASI > 10$ or $BSA > 10$ and DLQI (Dermatology Life Quality Index) > 10 defines moderate-to-severe psoriasis, while $PASI \leq 10$, $BSA \leq 10$ and $DLQI \leq 10$ – mild disease[4]. However, European consensus and Polish Dermatological Society consider every case with $PASI > 10$ and/or $BSA > 10\%$ (objective disease severity) as moderate-to-severe plaque psoriasis. Psoriasis with severe course also includes all cases of generalized pustular psoriasis (regardless of the extent of the disease) and erythrodermic psoriasis (psoriatic erythroderma). The PASI index is also used to assess the effectiveness of psoriasis treatment. PASI score is also used to assess the effectiveness of psoriasis treatment.^[5,6]

Due to significant impact of the psoriasis on patients' mental state of, the quality of life is often measured. DLQI is commonly used for this purpose.

In the PTD recommendations, experts stated that because there is not enough data to clearly distinguish between moderate and severe psoriasis, all drugs which based on SmPC are indicated for the treatment of severe psoriasis can be used in patients who meet the criteria for moderate to severe psoriasis, i.e. $PASI > 10$. This applies to conventional prescription drugs, contrary to patients qualified for biological therapies.^[7]

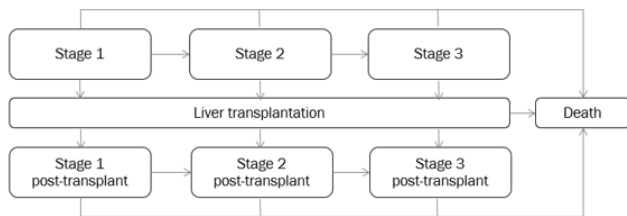


Figure 1. Psoriasis severity classification according to Polish Dermatological Society[7]

3.2. Psoriasis treatment

Psoriasis management is based on a sequential therapy. As with other types of therapy, the addition of another treatment line allows for longer remission of the disease. The choice of method should take into account the severity of the disease, the impact of the disease on physical, mental and social health, the coexistence of psoriatic arthritis or other comorbidities.

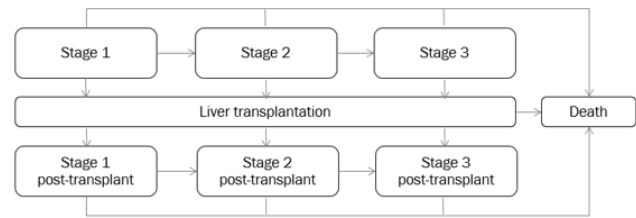


Figure 2. Sequential therapy of plaque psoriasis

Mild psoriasis should be treated with topical therapies, which is usually long-term and requires systematic application of medicine.

According to the recommendations of PTD experts, moderate-to-severe psoriasis therapy cannot be based solely on the application of topical preparations. It is advisable to combine treatment with at least phototherapy, or patients should receive general treatment[6]. Conventional systemic therapy is recommended by NICE for all psoriasis levels of severity, provided that:

- cannot be controlled with topical therapy,
- it has a significant impact on physical, psychological or social well-being,
- meets one or more of the following conditions:
 1. psoriasis is extensive (for example, more than 10% of body surface area affected or a PASI score of more than 10) or
 2. psoriasis is localized and associated with significant functional impairment and/or high levels of distress (for example severe nail disease or involvement at high-impact sites) or
 3. phototherapy has been ineffective, cannot be used or has resulted in rapid relapse (rapid relapse is defined as greater than 50% of baseline disease severity within 3 months)[8].

If a significant decrease in the quality of life (expressed as a result >10 points according to DLQI score) persists longer than 3 months, even with PASI and BSA indicators that objectively assess the disease severity <10 points, it can be considered that such a patient suffers from moderate psoriasis, which according to these recommendations should be treated at least with phototherapy or systemically.^[9]

According to patients' opinion (focus survey, own data), topical treatment in professionally active patients significantly impairs the quality of life and hinders professional activation.

Biological therapy – available as drug programs in Poland – in moderate-to-severe plaque psoriasis is dedicated for patients who:

- do not respond adequately do to conventional systemic therapy (in 2-3 months assessment),
- do not tolerate or have contraindications to conventional systemic therapy.

The biological therapy is appropriate for patients, who did not achieve the improvement as a result of **at least 2 different** conventional therapies before qualification to drug program. In case of 6-18 years old patients, this criterion applies to **at least one conventional therapy**.

3.3 Overview of current treatment options in patients with psoriasis

In the first stage of psoriasis treatment, keratolytic preparations should be used. We usually use prescription formulas or dermocosmetics available in pharmacies containing salicylic acid, sulfur and urea. These preparations in monotherapy are not effective, but it is possible to use them together with anti-inflammatory drugs, e.g. glucocorticosteroids. In the next stage of therapy, drugs with an inhibitory effect on the number of cell divisions and reducing inflammation are recommended.^[7]

The most widely used topical preparations include dithranol, glucocorticoids and vitamin D3 derivatives, also in combination with glucocorticoids. Secondly, coal tar and vitamin A derivatives are recommended. Due to poor cosmetic properties, dithranol and coal tar are most often used in hospital conditions.^[7]

Phototherapy is an established first-line treatment for moderate-to-severe psoriasis. It uses either UVA 311 nm radiation or a wide UVA band in combination with psoralens (so-called PUVA). The possibility of using this method of treatment is mainly limited by low availability for patients (a small number of facilities equipped with lamps). Additionally, physicians report inappropriate phototherapy tariff, so the use of this method is certainly too rare (only 27% visits in outpatient care involved it).

3.3.1. Systemic treatment of moderate-to-severe psoriasis

Acitretin has no immunosuppressive activity. In plaque psoriasis patients this drug is often combined with phototherapy (Re-PUVA method). Due to teratogenic effect, women in reproductive age are obliged to use strict contraceptive agents during the treatment and for 3 years thereafter). Patient who take acitretin also must not donate blood for at least 1 years after stopping treatment. It is necessary to control blood morphology, liver enzymes and lipid profile. Women should take a pregnancy test every month. Acitretin is not indicated in patients with severe liver and renal failure, severe hyperlipidemia (especially hypertriglyceridemia), alcohol abuse or taking drugs that may interact with acitretin. Clinical evidence has shown that acitretin monotherapy is less effective than other conventional drugs. PASI 75 response was achieved in 23% patients treated with 50 mg/kg acitretin for 8 weeks. The best effects are observed in patients with generalized forms of pustular psoriasis (84% of patients achieve complete remission).^[6]

Cyclosporin has a documented therapeutic efficacy in psoriasis based on the results of clinical trials. According to recommendations, treatment period is 3-4 months, and in special cases – maximum 2 years. Cyclosporin is highly effective – in 84th (on average) day of treatment, 80% of patient with severe psoriasis achieved clinical improvement for more than 75%. PASI score 50% reduction was observed on average after about 4-6 weeks of CyA treatment, while maximum efficacy is achieved after about 5-12 weeks. The advantage of cyclosporin is its rapid action, however, clinical observations also indicate a rapid relapse after treatment discontinuation. A special target group is therefore patients who are particularly advised to rapidly achieve clinical improvement. Some dermatologists describe cyclosporin therapy as rescue treatment.^[6]

The most important adverse event of CyA is renal impairment, with a clinical symptom including increased blood pressure and creatinine blood level. however, if the therapy is well monitored (laboratory tests and blood pressure measurement), these symptoms are early diagnosed and prevention of further consequences is possible by lowering the drug dose or complete discontinuation. Cyclosporin is contraindicated in patients with renal failure, uncontrolled hypertension, severe infections, malignancies (active or in history) or simultaneous PUVA therapy.^[6]

Cyclosporin may be used in pregnant women, taking into consideration risk-benefit ratio, due to no teratogenic effect. However, pregnant women receiving CyA are at risk of premature delivery.^[6]

Cyclosporin interacts with numerous drugs that may increase or decrease its serum concentration. Therefore, before including this medicine, check all medicines that you are taking because of other comorbidities. Rapid therapeutic effect after the use of cyclosporin allows patients to return to normal life and take up professional work^[6]. Methotrexate is administered in weekly courses (usually every 7 days) most often in the oral form, but also as subcutaneous injections at a dose of 15-20 mg / week. Clinical efficacy is assessed after 3-4 months of treatment. In a meta-analysis of more than a dozen studies, it was shown that improvement in the PASI 75 range in the 12. or 16. week of therapy is obtained in 45.2% of patients. The most serious side effects of methotrexate are blood abnormalities (anemia, leukopenia, thrombocytopenia) and liver damage. In order to avoid them, laboratory monitoring should be carried out in accordance with the recommendations, initially every month, then every 3 months. The risk of liver damage increases significantly in patients with alcohol abuse, obesity, diabetes or viral hepatitis.^[6] Lack of cooperation between patient and physician excludes the possibility of continuing the therapy.^[6]

Pregnant or breast-feeding psoriatic patients should not receive methotrexate. Effective contraception must be used by men and women during treatment and for at least 3 months after^[6].

Methotrexate is absolutely contraindicated in patients with severe infections, impaired hepatic function, renal failure, alcohol abuse, marrow dysfunction, hematological diseases, immunity disorders, active peptic ulcer of the stomach and duodenum and significantly impaired lung function.^[6]

Methotrexate should be continued as long as clinical improvement is maintained and no adverse reactions occur.^[6]

3.3.2. Biologic drugs

Patients with moderate-to-severe plaque psoriasis are eligible for biological treatment, if they failed to respond conventional systemic therapies with methotrexate, ciclosporin, acitretin and/or PUVA, or have contraindications for conventional therapy, or are intolerant (adverse events occurred, that cause treatment discontinuation). Inclusion criteria are specified in drug program on the treatment of moderate-to-severe plaque psoriasis.

In Poland there are available tumor necrosis factor alfa (TNF-alfa) inhibitors, including infliximab, etanercept, adalimumab, as well as interleukin 12/23 (IL 12/23) inhibitors, like ustekinumab, and interleukin 17 (IL 17) inhibitors, like ixekizumab and secukinumab. The choice of the drug base on psoriasis severity, the presence or absence of joint involvement and patient's preferences regarding administration route (subcutaneous or intravenous, administration frequency).

Adalimumab is administered subcutaneously bimonthly and is indicated not only in adult patients, but also in children with psoriasis. Results from clinical trials show, that PASI 75 response at week 16. of treatment is achieved by 71% of patients, and at week 48.– 83%. Adalimumab has a good safety profile and is well tolerated by most patients.^[10]

Infliximab is the only biologic drug reimbursed in moderate-to-severe plaque psoriasis. It is administered intravenously. Literature shows, that PASI 75 response after 10 weeks of treatment is achieved by 80% of patients, and this effect is maintained until week 50. in 60% of them.^[11] As part of a two-year drug program in Poland for patients, for whom severity of psoriasis is assessed at PASI >10, biosimilar infliximab is available. Infliximab therapy is well tolerated and has a beneficial safety profile.

Etanercept is administered subcutaneously once or twice a week. This drug is also indicated in children at the age of 4 years or older. PASI 75 response is reported in 47%

patients after 12 weeks of therapy and in 59% of patients after 24 weeks. Based on literature it can be concluded, that the safety profile of etanercept is favorable and most patients tolerate treatment very well.^[12]

Among drugs reimbursed in the Polish Drug program, there is also ustekinumab – interleukin 12/23 inhibitor. This drug is highly effective in plaque psoriasis and has a good safety profile.^[6]

Ixekizumab and secukinumab represent two new molecules inhibiting interleukin 17, that are reimbursed in drug program for moderate-to-severe plaque psoriasis since 1st November 2018. The efficacy of these drugs was proved in many multicenter, randomized controlled trials, often including several thousand populations. They are characterized by high efficacy (over 80% of patients achieved PASI 75 response, and about 70% - PASI 90 response) and good safety profile. Objective results from clinical trials show higher of PASI 75 response rate for interleukin 17 inhibitors than for TNF-alfa inhibitors or interleukin 12/23 inhibitors. Long-term trials proved, that this high efficacy and beneficial safety profile are maintained during whole follow-up.^[13]

According to the European recommendations, the lowest effectiveness, allowing to state that a given therapy is effective should be at least PASI 75. If PASI 50 is achieved, we decide to maintain or change treatment based on the patient's needs and the DLQI index. With efficacy below the PASI 50 it is necessary to switch the therapy.

3.4. Unmet needs of patients with psoriasis

Large general population of psoriatic patients in Poland, as an opposite to small number of patients treated conventionally or biologically, indicate that there is significant need of new systemic therapies, available on prescription in pharmacy, and hence, broader access to treatment and reduction of patients migration to reference centers realizing drug programs.

Questionnaire survey of dermatologists (own research) shows, that they usually do not prescribe systemic drugs because of their doubts about therapy safety and lack of reimbursement. What is important, more than 90% of physicians report the need for new therapies other than biological drugs.

In turn, focus survey, carried out in the group of psoriatic patients (own research) showed that they complain about the lack of modern, still non-biological drugs, available on prescription. In addition, in the opinion of patients, the availability of drug programs is low and involves the need for therapy in reference centers, frequent trips and incurring additional indirect costs. The Polish Commis-

sioner for Citizens' Rights in his letter to the Minister of Health from 19.10.2017 also draws attention to the difficult situation of psoriasis patients and, based on the patients' representatives data, indicates, that there is a problem with the availability of new-generation treatment (including biological) and only 5% of the most severe patients receive biological treatment. In the Watch Health Care Foundation's report, concerning the moderate-to-severe psoriasis patients access to treatment, authors indicate following reasons for limited access to biologic treatment: hindered access to specialized institutions qualifying for biological treatment for patients not from larger urban centers, additional costs of transport for patients, and the lack of adequate knowledge of new therapeutic forms both among patients and physicians.^[14]

3.5. Review of dimethyl fumarate (DMF) trials

A new therapeutic option, which responds to the unmet needs of both dermatologists and patients in terms of the availability of innovative systemic non-biological medications in the treatment of plaque psoriasis, may be fumaric acid esters (FAEs), used for over 30 years in some European countries, i.e. Germany, Austria or the Netherlands. Dimethyl fumarate (DMF) seems to be particularly noteworthy, which is the first ester of fumaric acid authorized by EMA for use in the treatment of adult patients suffering from chronic plaque psoriasis of moderate-to-severe severity. This registration has resulted in the appearance of dimethyl fumarate (DMF) also in Poland. It should be used for treatment of patients with moderate-to-severe disease who are not considered for systemic treatment other than biological treatment

Systematic review of medical information databases was carried out to identify DMF trials. One randomized controlled trial – BRIDGE was found, which assessed efficacy and safety of DMF versus placebo^[15,16]

Results of BRIDGE trial show, that after 16 weeks of treatment, PASI 50, PASI 75 and PASI 90 responses were significantly more frequent in DMF group than in placebo group. Also reduction of disease activity, assessed by Physician's Global Assessment (PGA), was significantly more frequent in DMF group.

In patients undergoing DMF therapy, worsening of psoriatic lesions was significantly less frequently than in patients receiving placebo, evaluated 2 months after completion of treatment^[15]

DMF has also been effective in improving the quality of life assessed on the DLQI scale. The result obtained after 16 weeks of treatment was statistically significantly higher than for patients receiving the placebo in this study. It is also remarkable, that DLQI score reduction was on average 5.9 points in DMF group, what represents clinical significance.^[15]

The analysis of the affected body surface area (BSA) also showed higher DMF efficacy over 16 weeks compared to placebo.

Dimethyl fumarate, according to physicians and patients intention, could be used in patients unsuccessfully treated with systemic non-biological drugs. Because of lack of trials allowing to direct compare DMF with biological drug, a network meta-analysis was done. First, a systematic review was conducted, to identify trials for biologic drugs used in Poland, including: infliximab (INF), adalimumab (ADA), etanercept (ETA), ustekinumab (UST) and ixekizumab (IXE). When the procedure of meta-analysis was finished, secucinumab was not yet reimbursed nor the positive reimbursement recommendation existed, so this drug was not included in analysis. Almost 40 trials were identified, however, populations of patients slightly differed between them (were not fully homogenous, e.g. not all studies provided information on the number of previously used systemic therapies). What is more, some of patients in the included studies had previously used biological treatment (however, this population did not account for more than 20% of the study group).^[17]

Comparing DMF with biological drugs used in the B.47 Drug Program, i.e. with adalimumab, etanercept, infliximab, ustekinumab and iksekizumab as a network meta-analysis it was demonstrated that during DMF therapy PASI 50 and PASI 75 responses were recorded statistically more frequently than in patients receiving placebo. However, these measures were more frequently achieved by patients treated with biologic drugs than these treated by dimethyl fumarate. Analysis of PASI 90 response rate showed no significant differences between DMF and most of biologic drugs (ADA, UST, ETA). Only in comparisons with IXE and INF there was higher PASI 90 response rate for these groups than for DMF group.^[17]

The quality of life assessment showed that patients taking DMF achieved statistically significantly higher quality of life improvement (on DLQI scale) compared to patients receiving placebo. There was no statistically significant difference between DMF and ETA at low dose. Other biological agents have been shown to be more effective than DMF in this aspect.^[17]

The results of Kolbach 1992 experimental study indicate that the longer the period of treatment with fumaric acid esters, the higher the PASI 75 response rate. In this study, the percentage of patients who received a PASI 75 response increased from approximately 40% in 3-6 months to approximately 77% in 18-24 months in the DMF monotherapy group and from approximately 53% in 3-6 months to approximately 80% during 18-24 months in the group of patients who received FAE, i.e. mixtures of fumaric acid esters.^[17,18]

Similarly, the increase of the PASI response rate along with treatment duration was demonstrated on the basis of Wain

2010 prospective observational study. In this study, for the maximum follow-up period of 60 months, the PASI 50 and PASI 75 response rates were respectively approximately 67 % and approximately 33%. PASI 90 response rate in the 48 months follow-up was approximately 33%.^[17,19]

Based on prospective observational studies, it was shown that after 6 and 12 months of therapy with fumaric acid esters, the quality of life of patients improved statistically significantly. It is important that the difference regarding the initial value is greater than 5 points for both treatment periods, and therefore these results are also clinically relevant.^[17]

Long-term safety assessment has been carried out for an observation period of a maximum of 14 years. Based on the included studies, no deaths or serious adverse events or adverse reactions have been reported. Adverse events and adverse reactions were reported in 60-70% of patients. The most common disorders were: reddening, diarrhea, abdominal contractions/pains, lymphopenia, leukopenia, eosinophilia and proteinuria (including transient proteinuria).^[17]

3.6. Suggested place of dimethyl fumarate in psoriasis therapy

The introduction of dimethyl fumarate in the clinical practice of moderate-to-severe plaque psoriasis treatment is not intended to replace any of the currently used drugs, but to add the treatment option to a current treatment scheme, thus respond to the unmet need of patients by prolonging the therapeutic sequence. This approach would only be a change in the current therapeutic regimen, as sequential therapy is already used in Poland - it is about treatment with biological drugs of patients who have been previously treated at least two methods of classical systemic therapy.

The results of the cost-utility analysis (CUA) comparing the treatment with dimethyl fumarate prior to biological therapy (FAE/ DMF → biological therapy) with biological therapy alone indicate that by using DMF patients gain 0.06 quality-adjusted life year, with relatively low costs. The incremental cost-utility ratio, which determines the profitability of such a clinical approach, is well below the threshold defined as 3 x GDP/capita, thus indicating a high cost-effectiveness (profitability of the indicated treatment sequence).^[20]

Dimethyl fumarate treatment is associated with significant health benefits, which include improving the quality of life and prolongation of time with an adequate response to treatment. DMF therapy will allow patients to obtain greater benefits from treatment, expressed in the QALY parameter, i.e. quality adjusted life years. The inclusion

of dimethyl fumarate in the treatment sequence of adult patients with moderate-to-severe plaque psoriasis will contribute to the introduction of a new standard of therapeutic treatment for plaque psoriasis, and longer patients' response time. This treatment will therefore contribute to improving the health-related quality of life of patients.

Eight hundred eighty five patients are currently participating in the drug program. There are 493 patients actively treated, i.e. receiving the drug, and 392 patients during the treatment interruption. Taking into account the number of patients with plaque psoriasis in Poland, about 2,500 patients should be biologically treated. Conventional treatment is used by about 15,000 of patients. This is a group requiring systemic treatment. These patients will be referred to the drug program^[21,22,23]

Dimethyl fumarate treatment would be started in patients qualified for plaque psoriasis drug program (there would be a delay in the initiation of biological treatment in these patients), as well as patients treated systemically previously, and still fulfilling the inclusion criteria for biologic therapy. In the opinion of the Agency for Health Technology Assessment and Tariff System, there would be approximately 1,200 such patients.^[24]

Conclusions and recommendations

1. Patients with psoriasis, despite the involvement of a significant number and type of health care services and significant financial outlays, are treated suboptimally and non-cost-effectively (large percentage – 11.1% – of hospitalizations because of psoriasis, the longest hospitalization of patients with psoriasis among other dermatological patients – 8.6 days, treatment outside their administrative region – 58.1% of hospitalized patients).
2. Biological treatment is available only to a limited group of patients with the most severe disease, what indicates the desirability of widening prescription-based systemic treatments that could be used prior to biological treatment. This would increase the possibility of treatment individualization by all dermatologists.
3. In order to achieve optimal treatment results (defined as PASI 90 and PASI 100 response), patients should be offered to be treated with several treatment lines because it is not known which drug will be effective in their case.
4. Dimethyl fumarate (DMF) meets the criteria for an additional systemic treatment option, prior to biological treatment. DMF therapy is associated with significant health benefits, which include improving the quality of life and lengthening the time with an

adequate response to treatment. This therapy allows the patients to obtain greater benefits from treatment and to prolong the time without symptoms of the disease (symptoms-free).

5. The suggested place for DMF in moderate-to-severe plaque psoriasis sequential therapy is the treatment of patients for whom no other systemic treatment than biologic drugs is considered.

CONFLICT OF INTERESTS

The publication was prepared at the request of Almirall Sp. z o. o. who financed the work. The authors declared no other type of conflict of interest.

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