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Use of fumaric acid derivatives (FADs) in Italian reference centres for psoriasis

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Abstract

BACKGROUND: Several therapies are available for psoriasis, including in some countries oral fumaric acid derivatives (FADs). Even if FADs are not available in the Italian market, they can be prescribed and reimbursed by the National Health Service, on request from the treating physician, when considered as a valuable option in selected patient.

METHODS: We performed a retrospective analysis of the PsoReal registry data, restricted to adult psoriatic patients enrolled between 2009 and 2017. Demographic and clinical data were collected together with information on systemic therapies prescribed for psoriasis, drug shifts and adverse effects. We focused our analysis on FADs compared with other systemic drugs.

RESULTS: From the registry data, a total of 17,064 patients were extracted, and 11,592 patients (67.9%), fulfilled inclusion criteria. The majority of them had chronic plaque psoriasis, the mean disease duration was 17.1 ± 12.6 years, and the mean PASI was 17.8 ± 10.9, with 51.5% presenting a moderate Ps (PASI between 10 and 20). A total of 36 patients (0.3%) were treated by FADs. The average treatment duration of conventional (9.0 ± 10.0 months) and biological agents (13.7 ± 11.6 months) was lower compared to the duration of FADs (28.1 ± 20.1, p-value<0.001). FADs were used at an average dosage of 361.0 ± 146.3 mg/day and FADs treated patients displayed an overall lower healthcare cost compared with other drugs.

CONCLUSIONS: The current study confirms previous European data about efficacy and safety of FADs, and suggests a decrease of healthcare costs for FADs treated patients as compared to other treatments.

Key words: psoriasis, fumaric acid, safety, adverse effects, hospitalization

Introduction

Psoriasis (Ps) is a chronic, inflammatory, immune-mediated skin disorder affecting approximately 2-3% of the general population in Europe [1-3]. It can occur at any time of life; however, it is estimated that 75% of cases occur before 46 years of age [4], with a peak at age 20-30 years [5-7]. Current European guidelines on Ps consider phototherapy and systemic non-biological agents such as cyclosporine, methotrexate, acitretin or fumaric acid derivatives (FADs) as a suitable option for the first line treatment of moderate-to-severe plaque psoriasis [6]. Despite existing guidelines, a wide variability in clinical practice across Europe has been described in the literature [8,9].

FADs are chemical compounds derived from an isomeric unsaturated dicarboxylic acid, the fumaric acid [10], that have been used in the treatment of Ps in selected mostly German speaking European countries for over 30 years. The major current hypothesis of the pharmacodynamic effect of FADs is based on the concept that DMF and MMF influence pro-inflammatory signal transduction pathways through modulation of the intracellular redox system [11]. Through this and other activities, FADs modulate a variety of events involved in the exaggerated immune response in Ps.

Available clinical studies on FADs suggest that up to 50% of patients with Ps achieve at least 75% reduction of their baseline psoriasis area and severity index (PASI) after 12-16 weeks of treatment [10,12]. One major advantage of FADs is their good retention and safety during long-term treatment. In long-term studies, 50-70% of the patients experience improvements of ≥70% after 1 year of therapy [11-15]. Most of these studies were conducted in Germany and the use of FADs for the treatment of Ps in other countries is still sparse and inconsistent and remains to be explored. Even if FADs are not present in the Italian market, they can be prescribed and reimbursed by the National Health System when considered by the treating physician as a suitable option in selected patients[16-19].

The primary objective of this study was to describe the characteristics of patients undergoing systemic treatment for Ps, with special attention to FADs use, analysing data from the PsoReal registry in Italy. Secondary objectives included the description of the frequencies and reasons for suspending treatments or switching to other agents as well as healthcare resource utilization.

Material and methods

This was a retrospective analysis of a cohort of patients recruited within the PsoReal registry in Italy. PsoReal is a continuation of the Psocare experience[10], that ended in September 2009. It includes both new patients undergoing systemic treatments for Ps, observed in a group of 18 referral centers for Ps in Lombardy and Piedmonts, and an update on previous patients recruited in the Psocare

registry until the time of data extraction (April 2017), in an extended group of 155 centers. The study was approved by the Ethics Committees of the participating centers.

Study population

The study population will include all adult patients (18 years or older) with a confirmed diagnosis of chronic plaque Ps and with available follow-up information who started a conventional systemic or biological treatment for Ps including cyclosporine, methotrexate, acitretin, FADs, etanercept, infliximab, adalimumab and ustekinumab. Patients with a specific diagnosis of psoriasis arthritis (PsA) and without signs of Ps were excluded from this study. FADs treated patients usually reported contraindications to treatment with other conventional or biological agents.

Collected data

Data were collected through an electronic web based form system built with internal quality controls and security systems, including patients anonymisation, confidentiality checks and automatic regular backups. For the purpose of the study, a selection of available variables was analyzed. This included at baseline: patient's demographics and personal habits, anthropometric measures, history of comorbidities including PsA, Ps characteristics and associated subtypes, severity of Ps as assed by PASI score, previous and current systemic treatment for Ps and their dosages, diagnostic and laboratory tests performed.

Follow-up information included: an update of patient's comorbidities, Ps subtypes and PsA, systemic drugs taken during the follow-up period as well as any suspension and reasons for it, PASI score assessment, hospitalizations, new diagnostic and laboratory tests performed.

Statistical analysis

For descriptive purposes data were presented as means and standard deviations (SD) or number with percentages, for continuous and categorical variables respectively. For analysis purposes, continuous data were also categorized by using clinical relevant thresholds as cutoff points. Differences between continuous variables were assessed by means of Mann-Whitney U test, while Pearson's X^2 test with Yates' correction for continuity was used to assess differences between categorical variables. The log-rank test was used to assess differences between treatments discontinuation rates. All tests were considered statistically significant at p-value <0.05. Analyses were carried out by using Matlab v.7.8 (The MathWorks Inc., Natick, MA, US).

Results

Overall 17,064 patients were included in the registry, corresponding to 0.034% of the Italian adult population (2016 EUROSTAT census data). Of these, a total of 11,592 patients (67.9%), fulfilling inclusion criteria, were considered in the study. 66.8% of the patients were males, with a mean age of 48.7 ± 14.3 years (Table 1). Most patients were overweight or obese (64.0%), with a mean BMI of 27.1 ± 5.0 kg/m^2. 39.4% of patients were current smokers and the most frequent comorbidities were presence of PsA (25.5%), high blood pressure (25.1%) and type II diabetes (7.2%).

Characteristics of patients with chronic plaque Ps at entry in the study are shown in Table 2. The mean duration of Ps since diagnosis was 17.1 ± 12.6 years. Guttate Ps subtype was present in 4.4% of patients, while erythrodermic and pustular Ps in 3.0% and 2.6% respectively. Most of patients had scalp (73.8%) and nails (38.0%) involvement. The mean PASI was 17.8 ± 10.9, with most of patients (51.5%) presenting a moderate Ps (PASI between 10 and 20).

The overall use and duration of treatments for Ps during a maximum of 5 years period from baseline is reported in Table 3. The most frequent conventional drugs prescribed were cyclosporine (27.5%), methotrexate (20.7%) and retinoids (15.8%), while the most used biological drugs were etanercept (36.0%) and infliximab (12.6%). The average duration of conventional drugs (9.0 ± 10.0 months) was significantly lower than the mean duration of biological agents (13.7 ± 11.6, p-value<0.001). Nevertheless the average duration of FADs (28.1 ± 20.1) was significantly higher than both other conventional and biological drugs (p-value<0.001).

During the exposure period FADs were used at an average dosage of 361.0 ± 146.3 mg/dd, corresponding to 3 caps of 120 mg per day.

Reasons for discontinuation of main and secondary systemic treatments prescribed at baseline are shown in Table 4. Overall the discontinuation rate of FADs was lower compared to the average rate of other conventional or biological drugs (p-value<0.001). In particular 3 patients (12%) with FADs prescribed at baseline stopped the treatment because of side effects or contraindications.

Regarding the use of health care resources during the exposure period (Table 5), the number of hospitalizations for Ps was similar among patients with FADs and other drugs prescription, while among main diagnostic tests performed the number of Quantiferon tests for tuberculosis was significantly lower in patients using FADs compared to other drugs (p-value<0.001).

Discussion

This study presents the largest Italian experience on FADs therapy in psoriasis. Our data confirm that FADs treatment is associated with a longer survival compared with other drugs, with a limited rate of severe adverse reactions and reduced healthcare costs. The main limitation of our study is the small number of patients treated by FADs and the probable high selection of these patients due

to the lack of availability of the drug in the Italian market. Patient selection was probably based, at least partly, on their lack of eligibility to other conventional or biological agents, and to patient preference. Unfortunately, we did not collect data on the patient preference and attitude to specific therapies.

In spite of the observation that lack of efficacy was the most common reason for FADs discontinuation, FADs treated patients globally displayed the longest survival, 28 weeks on average, comparable only with ustekinumab (20 weeks). Psoriasis is a chronic disease and patients often need therapeutic shifts. The present study suggests that FADs should be an interesting strategy to reduce those treatment shifts.

In spite of a high rate of minor side effects, such as gastrointestinal discomfort or flushing [20,21], major side effects leading to discontinuation of treatment occurred rarely in our series. To reduce early withdrawal due to side effects, slow increase in dosage or transitory dose tapering, could be considered. Lymphocytopenia and eosinophilia are common but rarely relevant reactions [13]. In our FADs treated patients three patients displayed side effects leading to discontinuation, namely 2 gastrointestinal discomfort and 1 lymphocytopenia. No other reported side effect in a 5 year follow up was reported. A recent Cochrane meta-analysis of systemic pharmacological treatments in psoriasis concluded that uncertainties exist regarding the rate of severe side effects during FADs treatment[19]. Another systematic review showed that FADs had five times greater rates of gastrointestinal side effects compared with placebo [22]. In the KIDS FUTURE study 127 children and adolescents underwent FADs treatment. A total of 25.43% had gastrointestinal side effects, but only 11.8% had to discontinue the therapy due to side effects [23].

Our study globally displayed a lower rate of instrumental tests (chest radiogram) and laboratory examinations (namely tuberculosis test) in patients undergoing FADs as compared with other drugs. Such data indicate that the drug may be cost-effective in term of consumption of healthcare resources. However, due to the limited number of patients treated, such data should be taken cautiously.

In conclusion, our study, even if based on a limited number of FADs treated patients in Italy, adds supportive data on the efficacy and safety of FADs. Future studies should consider longer-term follow-up of FADs and larger number of patients [24,25].

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Table 1 - General characteristics, personal habits and main comorbidities of patients included in the study

		n=11,592	%
Gender	Male	7739	66.8
	Female	3853	33.2
Age (years)	*Mean, SD*	*48.7*	*14.3*
	18-44	4672	40.3
	45-64	5198	44.8
	65+	1722	14.9
BMI (kg/m^2)	*Mean, SD*	*27.1*	*5.0*
	<20.0	449	4.0
	20.0 - 24.9	3583	32.0
	25.0 - 29.9	4651	41.5
	30.0+	2528	22.5
Smoking habits	No	4565	40.2
	Yes	4471	39.4
	Ex	2310	20.4
Main comorbidities	High blood pressure	2909	25.1
	Chronic Bronchitis/emphysema	84	0.7
	Type II diabetes	832	7.2
	Psoriatic arthritis	2957	25.5

BMI: body mass index

Table 2 - Characteristics of patients with chronic plaque psoriasis at entry in the study

		n	%
Duration of Ps since diagnosis (years)	*Mean, SD*	*17.1*	*12.6*
	<10	3597	32.0
	10 - 19	3367	30.0
	20+	4263	38.0
Associated Ps subtypes	Erythrodermic	347	3.0
	Guttate	512	4.4
	Pustular	304	2.6
Involvement of specific sites	Nails	4357	38.0
	Flexural	2778	24.2
	Scalp	8472	73.8
PASI	*Mean, SD*	*17.8*	*10.9*
	<10	1546	18.5
	10-20	4298	51.5
	>20	2508	30.0

PASI: psoriasis area and severity index, Ps: psoriasis

Table 3 - Overall use and duration of treatments for psoriasis during a maximum of 5 years period from baseline

		Patients' use		Treatment duration (moths)	
		n	%	Mean	SD
Conventional drugs	*Overall*	*6676*	*57.6*	*9.0*	*10.0*
	Retinoids	1829	15.8	6.6	7.1
	Phototherapy	545	4.7	5.9	7.4
	Methotrexate	2404	20.7	8.9	9.1
	FADs*	36	0.3	28.1	20.1
	Cyclosporine	3190	27.5	7.0	7.4
Biological drugs	*Overall*	*7216*	*62.2*	*13.7*	*11.6*
	Etanercept	4172	36.0	11.5	10.5
	Infliximab	1466	12.6	12.7	10.2
	Adalimumab	1120	9.7	8.1	9.7
	Ustekinumab	40	0.3	20.9	19.9
	Others	1981	17.1	11.1	9.4

FADs: fumaric acid derivatives

* The mean treatment duration is significantly higher than the average duration in patients undergoing other conventional or biological drugs (p-value<0.001, Mann-Whitney U test).

Table 4 - Reasons for discontinuation of main and secondary systemic treatments prescribed at baseline

	Treatment suspension	
	n	%
Retinoids (n=1375)	***987***	***71.8***
Lack or loss of efficacy/inefficacy	145	10.5
Remission	169	12.3
Side effects/contraindications	139	10.1
Pregnancy or intention to become pregnant	0	0.0
Patient's request	68	4.9
Other	199	14.5
Missing/unknown	267	19.4
Methotrexate (n=1405)	***803***	***57.2***
Lack or loss of efficacy/inefficacy	130	9.3
Remission	93	6.6
Side effects/contraindications	140	10.0
Pregnancy or intention to become pregnant	1	0.1
Patient's request	84	6.0
Other	128	9.1
Missing/unknown	227	16.2
FADs (n=25)*	***10***	***40.0***
Lack or loss of efficacy/inefficacy	4	16.0
Remission	2	8.0
Side effects/contraindications	3	12.0
Pregnancy or intention to become pregnant	0	0.0
Patient's request	1	4.0
Other	0	0.0
Missing/unknown	0	0.0
Cyclosporine (n=2541)	***1739***	***68.4***
Lack or loss of efficacy/inefficacy	209	8.2
Remission	350	13.8
Side effects/contraindications	233	9.2
Pregnancy or intention to become pregnant	4	0.2
Patient's request	133	5.2
Other	312	12.3
Missing/unknown	498	19.6
Etanercept (n=3263)	***2004***	***61.4***
Lack or loss of efficacy/inefficacy	236	7.2
Remission	425	13.0
Side effects/contraindications	175	5.4
Pregnancy or intention to become pregnant	3	0.1
Patient's request	126	3.9
Other	442	13.5
Missing/unknown	597	18.3
Infliximab (n=983)	***392***	***39.9***

	Treatment suspension	
	n	%
Lack or loss of efficacy/inefficacy	97	9.9
Remission	11	1.1
Side effects/contraindications	88	9.0
Pregnancy or intention to become pregnant	1	0.1
Patient's request	21	2.1
Other	39	4.0
Missing/unknown	135	13.7
Adalimumab (n=517)	***166***	***32.1***
Lack or loss of efficacy/inefficacy	38	7.4
Remission	12	2.3
Side effects/contraindications	24	4.6
Pregnancy or intention to become pregnant	2	0.4
Patient's request	11	2.1
Other	35	6.8
Missing/unknown	44	8.5

FADs: fumaric acid derivatives

* The suspension rate is significantly lower than the average rate in patients undergoing other conventional or biological drugs (p-value<0.001, log-rank test)

Table 5 - Description of number and percentage of patients using each health care resource during a maximum of 5 years period from baseline

		Overall		FADs		Other drugs		P-value*
		n	%	n	%	n	%	
Hospitalizations for psoriasis	0	11105	95.8	33	91.7	11072	95.8	0.38
	1	348	3.0	3	8.3	345	3.0	
	2+	139	1.2	0	0.0	139	1.2	
*Diagnostic tests^*								
Laboratory tests (serology for hepatitis and tuberculosis)	0	5407	46.6	29	80.6	5378	46.5	<0.001
	1	5314	45.8	4	11.1	5310	46.0	
	2+	871	7.5	3	8.3	868	7.5	
Radiologic examinations	0	5268	45.9	5	50.0	5263	45.9	0.11
	1	5276	46.0	2	20.0	5274	46.0	
	2+	932	8.1	3	30.0	929	8.1	

FADs: fumaric acid derivatives

* Pearson's X^2 test with Yates' correction for continuity

^ Connected with the prescription