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CLINICAL REPORT

Factors Associated with Drug Survival of Methotrexate and Acitretin in Patients with Psoriasis

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Drug survival has recently become an important clinical issue in psoriasis. However, there has been little research into factors associated with drug survival of methotrexate and acitretin. The aim of this study was to investigate factors associated with drug survival of methotrexate and acitretin treatment for psoriasis. Survival analysis was performed in patients who received methotrexate or acitretin for the treatment of psoriasis, drawn from the Clalit Health Services database. Investigated factors included demographic variables, obesity, metabolic syndrome, psoriatic arthritis, administration route and folic acid supplementation. Among 6,256 patients, factors associated with treatment drop-out were: younger age ($p<0.001$) and psoriatic arthritis (acitretin $p<0.001$). For methotrexate, metabolic syndrome ($p=0.033$), intramuscular administration route of injection ($p<0.001$) and lack of folic acid supplementation ($p<0.001$) were associated with treatment drop-out. In patients with psoriasis, some ancillary factors may modify the drug survival of acitretin and methotrexate. ***Key words: psoriasis; drug survival; traditional systemic agents; folic acid; methotrexate; acitretin.***

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The use of traditional systemic agents, such as methotrexate or oral retinoids, for patients with psoriasis is well established (1). In recent years, drug survival has become a focus of interest in clinical research on psoriasis. Drug survival is defined as the time period of treatment with a certain drug until its cessation. In the case of chronic diseases, such as psoriasis, drug survival is directly affected by the patient's adherence and compliance (2). Adherence to treatment is associated with treatment effectiveness, side-effects, and patients' satisfaction with the treatment (3). The degree of extent of adherence is one of the most important factors determining the cost-effectiveness of a therapy (4, 5). Although drug survival correlates well with adherence to treatment, these terms are not synonymous. While adherence to a treatment regimen is generally defined as the extent to which patients take medications as prescribed by their healthcare providers, drug survival reflects the length of time a certain drug was in use for a patient, or in other words "survived". Evaluation of drug survival in patients with psoriasis and identification of the factors that affect drug survival are important for clinical practice.

Suboptimal adherence is identified as a major obstacle in psoriasis management. A review of data from 29 clinical trials shows that only 21–66% of patients with psoriasis are classified as adherent (6). Various factors, such as significant stigmatization of the drug, and profound emotional, social, and physical effects on patients' quality of life have a great impact on patients' adherence to treatment (7–10). In contrast to drug survival, adherence to systemic agents in psoriasis has been investigated over the past years (11–14).

The purpose of the present study was to investigate factors associated with drug survival for methotrexate and acitretin in patients with psoriasis using the medical database of Clalit Health Services (CHS).

MATERIAL AND METHODS

CHS is the largest public healthcare provider organization in Israel, serving a population of approximately 4,200,000 enrollees. Clalit's database is a comprehensive computerized database with continuous real-time input from pharmaceutical, medical and administrative operating systems. The database was started in 1998 for facilitation of epidemiological studies, such as the current analysis, and includes 95,899 patients with psoriasis.

Information was extracted for all patients with psoriasis diagnosed by a dermatologist and treated with methotrexate or acitretin from January 2002 to the end of March 2013. Included in the study were patients with at least 2 consecutive pharmacy acquisitions per patient, within a timeframe of a minimum of 7 days and a maximum of 6 months between the 2 prescriptions. Patients who were treated with any biologic agent during the study observation period were excluded. A follow-up was conducted for 60 months following enrollment for each patient, or until the end of December 2013. The extracted information included sex, age, socioeconomic status,

presence of concomitant psoriatic arthritis diagnosed by a rheumatologist and the metabolic syndrome. The metabolic syndrome was defined as diabetes with the presence of at least 2 of the following: diagnosis of hyperlipidaemia, hypertension (systolic blood pressure > 140 mmHg or diastolic blood pressure > 90 mmHg), or obesity (body mass index > 30), according to the World Health Organization (WHO) 1999 criteria (15). The extracted data regarding methotrexate were the use of folic acid supplementation and the route of drug administration: oral (PO) or intramuscular (IM).

Demographic data and patient characteristics at baseline were collected. Continuous variables were compared using *t*-test and dichotomous variables were compared using Pearson's χ^2 test. Treatment periods for acitretin and methotrexate were calculated as the time to cessation event (in months). A cessation event was defined as treatment replacement or termination, whereas death, end of eligibility, or end of follow-up period were defined as censorship. For each participant, the first treatment interval was included in the study. Survival analysis for the drug was performed using the Kaplan–Meier analysis with stratification by log-rank test for the following variables: sex, age (above or below 50 years), route of drug administration (for methotrexate), folic acid supplementation (for methotrexate), socio-economic status (low, medium, or high), and coexistence of obesity, metabolic syndrome, or psoriatic arthritis. Cox proportional hazard regression model was used to identify predictive factors for drop-out, including, age, sex, socio-economic class, route of drug administration, folic acid supplementation, and coexistence of obesity, metabolic syndrome, or psoriatic arthritis. A significance level of 0.05 was used. The study was conducted in the wider framework of investigation of the quality of care in CHS and in accordance with the principles of the Declaration of Helsinki and approved by the CHS Ethics Review Committee. Statistical analysis was performed using the SPSS package, version 20 (SPSS Inc., Chicago, IL, USA).

RESULTS

The study included 2,632 patients treated with methotrexate and 3,624 patients treated with acitretin. A total of 9,598 patient-years were analysed. Demographic data, general data, and patient characteristics are presented in Table I. There were more female patients and patients of older age in the methotrexate group. The methotrexate group comprised patients of higher socioeconomic status with greater prevalence of obesity, metabolic syndrome, and psoriatic arthritis compared with the patients treated with acitretin.

The mean drug survival duration of the entire study population was 25.6 ± 0.3 months, with a median of 17 ± 0.5 months. There were no significant differences in survival duration between methotrexate and acitretin.

Drug survival was analysed using the Kaplan–Meier method for each systemic treatment (Fig. 1). Survival rates for the first 5 years of follow-up for each treatment are shown in Table II. Log-rank test results describing the association between each categorical variable and drug survival are shown in Table III. Factors associated with longer drug survival were: age above 50 years in both methotrexate and acitretin groups ($p < 0.001$); absence of psoriatic arthritis in the acitretin group ($p < 0.001$); presence of metabolic syndrome, oral route of administration, and folic acid supplementation in the methotrexate group ($p < 0.001$). In a multivariate analysis, young age at baseline was significantly associated with higher hazard ratio for treatment termination in both methotrexate and acitretin groups (Table IV). The presence of psoriatic arthritis was associated with higher risk for treatment termination in the acitretin

Table I. *Characteristics of the study population*

	Methotrexate (n = 2,632)	Acitretin (n = 3,624)	p-value
Age, years, mean (SD)	52.4 (16.4)	51.1 (15.9)	< 0.05
Age > 50 years, *n* (%)	1,521 (58)	1,993 (55)	NS
Male, *n* (%)	1,136 (43)	2,287 (63)	
Female, *n* (%)	1,496 (57)	1,337 (37)	< 0.05
Socio-economic status			
Not defined, *n* (%)	40 (1.5)	44 (1.2)	NS
Low, *n* (%)	780 (29.6)	1,368 (37.8)	< 0.05
Intermediate, *n* (%)	1,186 (45)	1,535 (42.4)	< 0.05
High, *n* (%)	626 (23.8)	677 (18.7)	< 0.05
Patients with obesity, *n* (%)	765 (29)	933 (25.7)	< 0.05
Patients with:			
Metabolic syndrome, *n* (%)	492 (18.7)	599 (16.5)	< 0.05
Psoriatic arthritis, *n* (%)	574 (21.8)	107 (3)	< 0.05
Folic acid suppl., *n* (%)	2,105 (79.9)	Not relevant	
Route of administration			
Oral, *n* (%)	2,354 (89)	3,624 (100)	
Intramuscular, *n* (%)	94 (3.6)	Not relevant	
Survival time in months			
Mean (SE)	25.9 (0.47)	25.5 (0.5)	
Median (SE)	18 (0.72)	16 (0.73)	NS
Total years follow-up	5,258.3	4,340.1	

SD: standard deviation; NS: not significant; SE: standard error.

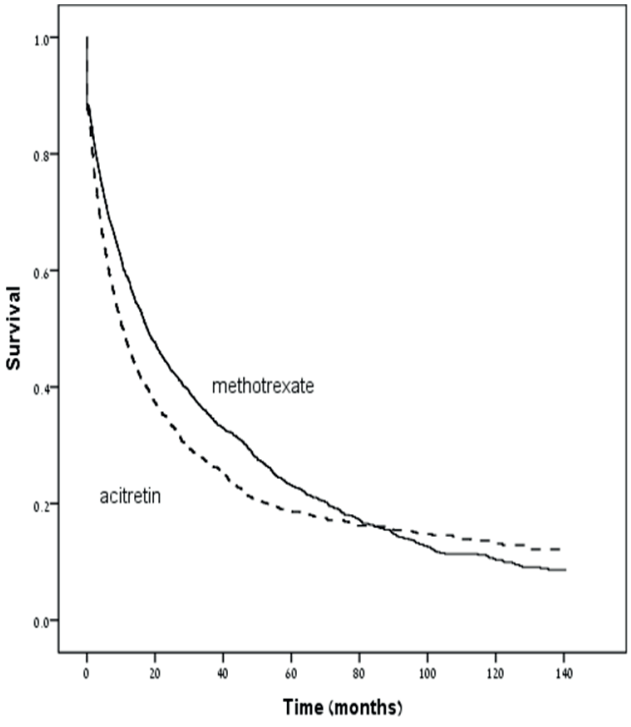

Fig. 1. Cumulative survival of methotrexate and acitretin during 140 months of follow-up.

Table II. *Five-year drug-survival of methotrexate and acitretin*

Survival period (years)	Methotrexate, % ($n=2632$)	Acitretin, % ($n=3624$)	Total study group, % ($n=6256$)
1	59.3	55.7	57.2
2	41.4	40.8	41.1
3	32.1	32.3	32.2
4	25.6	25.5	25.5
5	19.6	23	21.6

group. In the methotrexate group, concomitant metabolic syndrome, oral administration route, and folic acid supplementation were associated with lower risk for treatment termination.

In a multivariate analysis, which included the entire study population, the risk for treatment termination was reduced by 0.8% per year of age. There was no significant difference between the use of methotrexate and the use of acitretin with regards to drug survival (hazard ratio 0.951, 95% confidence interval 0.88–1.02 for methotrexate with acitretin as the reference).

DISCUSSION

The present study is based on a large sample of patients with psoriasis from the CHS database. The major observation is that drug survival of the traditional systemic agents for the treatment of psoriasis is low and diminishes gradually over time. Median drug survival of less than 20 months and approximately 20% after 5 years of observation found in the entire study population is lower than expected, compared with an adherence rate of 50% observed in general chronic conditions (based on World Health Organization observations) (16) or the 20–60% adherence reported in psoriasis specifically (6).

There were no significant differences between methotrexate and acitretin regarding their survival duration, yet it seems that the higher drop-out rates in the acitretin group occur during the first years of treatment, while after that initial adjustment period the retention rates of acitretin correspond with the retention rates of methotrexate, with a minor advantage for acitretin after 4 years (Fig. 1). A clinical explanation for that observation may be that the tolerance for acitretin is determined during the first months of treatment. In contrast to the safer long-term use of acitretin, the long-term use of methotrexate is less favourable, since the higher cumulative dosage of the drug involves higher cumulative hepatic risks (1). Young age was observed to be a risk factor for treatment termination in both methotrexate and acitretin groups ($p<0.01$). Higher drop-out rates observed in these young patients might be explained by earlier treatment termination due to concern for future morbidities (i.e. hyperlipidaemia, liver diseases), emergence of side-effects or intolerance, alteration in disease severity, or teratogenic properties of both drugs, promoting treatment discontinuation. Psoriatic arthritis was observed to be associated with treatment termination in the acitretin group ($p<0.01$). This observation

Table III. *Predictors of drug survival of methotrexate and acitretin*

	Methotrexate ($n=2,632$)			Acitretin ($n=3,624$)		
	Mean[a]	Median[a]	*p*-value	Mean[a]	Median[a]	*p*-value
Overall drug survival						
Age < 50 years	22.8	14	<0.001	22.7	13	<0.001
Age > 50 years	28.2	21		27.6	19	
Male	26.3	19	NS	24.9	16	NS
Female	25.7	17		26.5	16	
Obesity						
Yes	26.9	19	NS	25.3	15	NS
No	25.6	17		25.5	16	
Metabolic syndrome						
Yes	29.5	24	<0.001	26.9	15	NS
No	25.1	17		25.1	16	
Psoriatic arthritis						
Yes	25.9	18	NS	12.9	7	<0.001
No	25.9	17		25.9	17	
Route of administration						
Oral	25.9	18	<0.001			
Intramuscular	14.9	10				
Folic acid supplementation						
Yes	27.6	20	<0.001			
No	18.5	10				

[a]Data are presented in months.

Log-rank test results for the association between selected variables and drug survival.

Table IV. *Cox proportional hazard model for treatment drop-out of methotrexate and acitretin*

Exposure	Hazard ratio	95% CI	*p*-value
Methotrexate			
1 Age, per year	0.99	0.9–0.99	<0.001
2 Female sex (Ref.)	1	–	NS
Male sex	0.96	0.88–1.06	
3 Socioeconomic class, low (Ref.)	1	–	–
Socioeconomic class, medium	0.94	0.85–1.05	NS
Socioeconomic class, high	0.98	0.86–1.11	NS
4 Patients without psoriatic arthritis (Ref.)	1	–	NS
Patients with psoriatic arthritis	1.03	0.93–1.16	
5 Patients without metabolic syndrome (Ref.)	1	–	0.033
Patients with metabolic syndrome	0.87	0.76–0.99	
6 No folic acid supplementation (Ref.)	1	–	<0.001
Folic acid supplementation	0.64	0.57–0.72	
7 Oral administration (PO) (Ref.)	1	–	<0.001
Intramuscular administration	1.68	1.32–2.13	
Acitretin			
1 Age, per year	0.992	0.9–0.99	<0.001
2 Female sex (Ref.)	1	–	NS
Male sex	1.017	0.92–1.13	
3 Socioeconomic class, low (Ref.)	1	–	–
Socioeconomic class, medium	1.066	0.96–1.19	NS
Socioeconomic class, high	1.025	0.89–1.17	NS
4 Patients without psoriatic arthritis (Ref.)	1	–	<0.001
Patients with psoriatic arthritis	1.979	1.59–2.46	
5 Patients without metabolic syndrome (Ref.)	1	–	NS
Patients with metabolic syndrome	1.001	0.88–1.14	

is not surprising, and has good clinical explanation, as acitretin is not the systemic drug of choice for treatment of patients with psoriatic arthritis. Therefore, emergence of articular disease following the diagnosis of cutaneous psoriasis may have led to treatment switch or termination in patients who initially were treated with acitretin. Apparently, psoriatic arthritis has much more influence on drug survival in the case of acitretin treatment than methotrexate treatment, since it was not observed to be a significant factor in the methotrexate group. In the methotrexate group, folic acid supplementation, oral administration route, and concomitant metabolic syndrome were associated with significantly lower risk for treatment drop-out ($p < 0.01$). Folic acid supplement of the methotrexate regimen is known for its ameliorating effect on methotrexate adverse effects, and the current observation emphasizes its importance. The inconvenience of the IM administration route may explain its inferiority compared with the oral administration route.

Although there is abundant literature on studies regarding adherence to treatment in psoriasis, drug survival is a relatively newly discussed issue, with only a few studies referring to this term, all of which exclusively address biologic agents (17–20). Most of the studies regarding adherence to traditional systemic agents in psoriasis were not based on large patient populations nor did they have a long duration of follow-up. Nevertheless, current studies suggest that adherence is a major clinical issue in psoriasis management and the biggest downfall of the current treatment.

The present study is based on computerized drug dispensing data, from which drug survival rates are extracted. This is a widely accepted measure in adherence investigations. Adherence can be tested by many different methods, as reported in the literature. More conveniently, many investigators examine adherence using a patient self-report scale (12, 14, 16, 21) or pharmacy prescription refill records. Other methods considered as the gold standard, but not frequently used, are medication weight, pill counting (22–25), and the Medication Event Monitoring System (MEMS) method, by which opening and closing of a medication bottle cap are electronically monitored (22–24, 26). Recently, Woolf et al. (27) demonstrated that methotrexate consumption can be followed by the presence of methotrexate polyglutamate levels. Studies comparing the different types of methods show that self-reporting measures tend to overestimate adherence compared with medication weights and MEMS (25, 26), yet pharmacy prescription refill records or medication administration were not reported to be inferior and are considered as an evidence-based method to follow adherence (12, 28–30).

Our study is based on a large cohort with real-time data and a total of almost 10,000 patient-years, however, the reasons for treatment termination could not be analysed. Nevertheless, the authors feel that the advent of biological therapies has shortened the mean treatment duration with more traditional agents in recent years. Patient demand for cleaner, more efficient drugs with better side-effect profiles and, from the physicians' perspective, the possibility of better compliance, more complete clearance and fewer adverse events, may have led to lowering of the threshold for switching from methotrexate or acitretin to biologic agent. Therefore, the mean treatment survival of more traditional agents might have reduced greatly, compared with 20 years ago when other treatment alternatives did not exist. Since the Psoriasis Area and Severity Index (PASI) is not available in the CHS database its inclusion as a possible factor influencing drug survival was not possible. Despite these limitations, the present study sheds light on important data regarding drop-out rates of systemic treatments for psoriasis.

In conclusion, this study demonstrates that drug survival of methotrexate and acitretin in patients with psoriasis is relatively low. To increase drug survival of methotrexate, we recommend the use of folic acid supplementation.

Conflicts of interest. ADC serve as consultants to Abbvie, Agis, BMZ, Dexcel Pharma, Dexxon, Etwal, Glaxo, Janssen, Leo, Lev Bar, Medison, Neopharm, Novartis, Perrigo, Pfizer, Rafa, Roche, Schering-plough, Serono, Taro, Tetrapharm, Teva and Trima. ADC received research grants from Novartis. All other authors declare no conflicts of interest.

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