Retention rate of systemic drugs in patients with chronic plaque psoriasis

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Summary

Introduction. **The retention rate (RR) is the proportion of patients who maintain the same drug in a given time period, and it is a tool for evaluating the effectiveness and safety of treatments.**
Objective. **Estimate the RR of systemic drugs in real-life patients with chronic plaque psoriasis.**
Methods. **Retrospective evaluation of 392 adult patients with psoriasis who received a systemic drug, including methotrexate (n=158), cyclosporine (n=35), acitretin (n=24), infliximab (n=61), etanercept (n=76) and adalimumab (n=38). RR was evaluated using the Kaplan-Meier survival data analysis in which the event was drug discontinuation due to inefficacy or intolerance with log-rank tests. Cox proportional-hazards regression model was also estimated.**
Results. **The RR at 24 and 30 months (but not at 12 months) for TNF-α blockers was higher than methotrexate, cyclosporine and acitretin (p<0.001). Main cause of drug discontinuation was intolerance. No differences in RR were detected among TNF-α blockers. In multivariate analysis the predictors of early drug discontinuation were having received any conventional drugs versus any TNF-α blockers, higher body mass index (HR 1.91, 95% C.I. 1.68-2.1; p=0.008) and having previously been treated with more than three systemic drugs (HR 1.37, 95% C.I. 1.10-1.79; p=0.032).**
Conclusions. **RR of TNF-α blockers was higher than conventional drugs. Discontinuation of conventional drugs was mostly due to intolerance. RR of systemic drugs was negatively influenced by obesity and by history of previous drug failure.**

KEY WORDS: methotrexate; cyclosporine; acitretin; infliximab; etanercept; adalimumab; retention rates; chronic plaque psoriasis; psoriatic arthritis.

Introduction

Systemic drugs for the treatment of chronic plaque psoriasis include conventional and biological therapies (1). They differ significantly for the mechanism of action, the efficacy/safety profile and the adherence of patients (2). Adherence to treatment is an overall marker of treatment success, and it can be influenced by different factors including the effectiveness and tolerability of the drug, patient preferences, the severity of psoriasis and the presence of comorbidities (2). Adherence can be estimated by the retention rate (RR) which is the proportion of patients who maintain the same treatment in an established period of time (3). There are no studies comparing RR between conventional and biological drugs used in chronic plaque psoriasis. Long-term and safe disease control is a fundamental drug attribute, and has important implications. Initiating a therapy with a drug which is prematurely discontinued strongly affects the "perceived control" of the disease and may also increase the overall cost of therapy (4, 5).
The primary objective of this study was to evaluate RR of systemic drugs including methotrexate (MTX), cyclosporine (CsA), acitretin (ACI), infliximab (IFX), etanercept (ETA) and adalimumab (ADA) in a cohort of patients with chronic plaque psoriasis in daily practice.

Patients and methods

This was a retrospective observational study, involving a consecutive series of 392 adult patients with chronic plaque psoriasis receiving a systemic drug from July 2007 to July 2011. They were all adults patients admitted to the Division of Dermatology at the University Hospital of Verona. The inclusion criteria for patients were age older than 18, having chronic plaque psoriasis (i.e. lasting at least six months) treated with a systemic therapy. Diagnosis of psoriasis was clinical and disease severity was assessed using the Psoriasis Area and Severity Index (PASI). The systemic drugs considered in this analysis included MTX, CsA, ACI, IFX, ETA and ADA. These drugs were administered in accordance

with the European guidelines for the treatment of chronic plaque psoriasis (6). In particular, ACI, MTX and CsA were used as first line treatment and selected after a complete evaluation of patients and disease characteristics including age, sex, disease severity and localization, presence of psoriatic arthritis (PsA), diagnosed according to the CASPAR criteria (7), cardio-metabolic comorbidities and desire to become pregnant. TNF-α blockers were prescribed only in those patients with contraindications, intolerance and/or who did not respond to conventional treatments. In patients treated sequentially with different drugs, each treatment course was analyzed independently. Thus, a given patient may have been analyzed several times. Regarding the doses of each treatment, ACI was administered orally 0.3-0.5 mg/Kg/day; MTX by intramuscular injection at the dose of 10-20 mg weekly followed by folic acid administration on the day after; CsA orally 3-5 mg/kg/day; IFX by intravenous infusion 5 mg/Kg at week 0, 2, 6 and every 8 weeks; ETA by subcutaneous injection 50 mg weekly, after the 12 weeks of induction with 50 mg twice a week and ADA by subcutaneous injection 40 mg every other week, after the loading dose of 80 mg. All the drugs were used according to label. In particular, dose adjustments for biological agents were not performed except for reducing in some patients the interval of IFX administration to 6 weeks, instead of 8. Causes of treatment interruption were classified as inefficacy (i.e. the patient did not reach and/or maintain the PASI 50 response) (8), or intolerance (any adverse events, emergence and/or worsening of adverse events likely imputable to the drug that contraindicated its maintenance). Other causes of treatment interruption including loss to follow up, patient's request to suspend the treatment were not included in this analysis. Age, sex, body mass index (BMI), smoking habit, duration and severity of psoriasis, previous systemic drugs and the presence of comorbidities including PsA, liver steatosis, hypertension, diabetes, dyslipidemia and metabolic syndrome were registered for each patient. BMI was calculated as weight in kilograms divided by height squared in meters. Current smokers were defined as participants who smoked cigarettes daily or who had stopped smoking <5 years before the enrolment in the study. Non smokers were participants who had smoked <5 to 10 packs of cigarettes during their lifetime or who had stopped smoking >5 years before the enrolment. Liver steatosis was diagnosed on the basis of characteristic ultrasonographic features, i.e., evidence of diffuse hyper-echogenicity of liver relative to kidneys, ultrasound beam attenuation and poor visualization of intra-hepatic structures (9). Patients were defined as having diabetes mellitus when fasting hyperglycemia was found or they were taking hypoglycemic medications or if a physician had ever told them that they had diabetes. Hypertension was diagnosed if patients were taking anti-hypertensive medications, reported being told by a physician that they had high blood pressure, or the average of three blood pressure readings was higher than 140/90 mm Hg. Dyslipidemia was diagnosed either if serum triglycerides were >1.7 mmol/L or total cholesterol >5.68 mmol/L. Metabolic syndrome was diagnosed in the presence of three or more criteria of the National Cholesterol Education Program's Adult Panel III (ATP III) (10). Venous blood was drawn in the morning after an overnight fast. Serum lipids were determined by standard laboratory procedures (DAX 96, Bayer Diagnostics, Milan, Italy). All subjects gave informed consent to the study.

Statistical analysis

Descriptive statistics were used for patients characteristics which were compared with two-way analysis of variance or chi-square test for continuous and categorical variables with a level of significance set at 5%. RR at month 12, 24 and 30 was evaluated using Kaplan Meier survival method. Person-years at risk were computed from the beginning of the systemic therapy to the interruption of treatment, end of study or loss to follow-up, whichever occurred first. The event for "global" RR was interruption of treatment due to inefficacy or toxicity, the event for "inefficacy" RR was interruption due to inefficacy (i.e. PASI 50 response was not reached and/or maintained by the patient), and the event for the "intolerance" RR was interruption due to intolerance (i.e. any adverse events likely imputable to the drug that contraindicated its maintenance). Other causes of interruption, and loss to follow-up were censored. All analyses were performed using the STATA software version 10.0 (StataCorp LP, College Station, TXUSA).

Results

Study population

Three hundred and ninety-two patients were included in the study (Table 1). Two hundred and sixty-three (67.1%) were males and 129 (32.9%) females; mean age at baseline was 55.2 years±13.9 SD (median 56, range 25-84), but patients receiving CsA and ADA were younger (p=0.0001). Mean BMI was 27.7 Kg/m^2 ± 4.8 SD (median 26.6 range 17.6-40.4). Mean PASI score at baseline was 8.1±8.6 SD (median 6, range 0-40), with patients treated with ACI had a lower PASI score compared to patients treated with other drugs. Mean duration of psoriasis was 19.9 years±13.0 SD (median 18, range 2-60). PsA was diagnosed in 186/392 (47.5%) patients: 125 (31.9%) patients had peripheral arthritis, 5 (1.3%) axial arthritis, 54 (13.8 %) mixed arthritis (peripheral and axial) and 2 (0.5%) arthritis mutilans. Mean duration of PsA was 9.7 years±8.0 SD (median 7, range 1-46). As expected, patients treated with ACI or CsA had lower prevalence of PsA. Proportion of patients who were obese or smokers, or with hepatic steatosis, diabetes, dyslipidemia or metabolic syndrome were similar among the different treatment groups. In contrast, patients treated with CsA had a lower prevalence of arterial hypertension. Concomitant MTX was administered to 53 of 175 (30.2%) patients receiving TNF-α blockers. Two hundred and thirty patients (58.9%) had been previously treated with another drug that had not been effective: 94 (24.0%) had received one course of therapy, 96 (24.5%) two courses of therapy and 40 (10.2%) three courses of therapy. In the analysis of the RR, all the patients treated with a TNF-α blocker were grouped together and were compared with patients receiving conventional drugs.

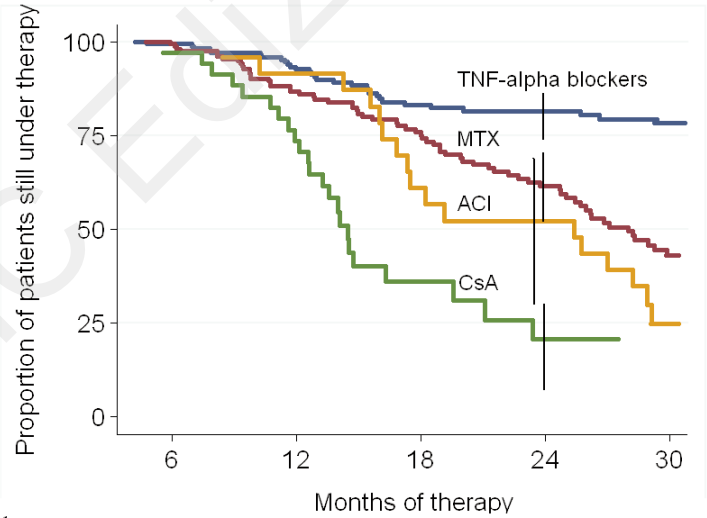
Table 1 - Characteristics of the study population.

	MTX N=158 (40.3%)	CsA N=35 (8.9%)	ACI N=24 (6.1%)	IFX N=61 (15.6%)	ETA N=76 (19.4%)	ADA N=38 (9.7%)	p
Sex							
Females	58 (36.7%)	11 (31.4%)	6 (25.0%)	23 (27.7%)	23 (30.3%)	8 (21.0%)	
Males	100 (63.3%)	24 (68.6%)	18 (75.0%)	38 (62.3%)	53 (69.7%)	30 (79.0%)	0.432
Age, yrs (mean ± SD)	58.3 ±14.3	49.2 ± 12.5	58.3 ± 16.1	52.0 ± 11.8	56.2 ± 13.5	49.7 ± 12.1	
Median (range)	60 (26-87)	48 (25-46)	61 (25-81)	52 (26-80)	56 (10-87)	49 (29-73)	0.000
BMI (Kg/m^2) (mean ± SD)	26.9 ± 4.8	26.8 ±4.8	26.1 ± 3.1	27.0 ± 4.4	28.1 ± 5.2	28.4 ± 5.9	
Median (range)	26.6 (17.3-40.1)	27.3 (17.0-40.0)	25.9 (20.8-32.1)	26.5 (17.6-38.3)	26.7(17.5-41.4)	26.8 (19.2-40.6)	0.721
PASI (mean ± SD)	7.5 ± 7.4	8.7 ± 8.6	4.9 ± 5.7	11.2 ±10.6	8.4 ± 9.2	7.1 ± 5.8	
Median (range)	6.1 (0-32)	5 (0-33)	4 (0-25)	7 (0-46)	6.5 (0-58.5)	6 (0-30)	0.050
Duration of Psoriasis (yrs) (mean ± SD)	19.1 ± 13.3	18.5 ± 11.8	17.2 ± 13.6	20.5 ± 11.8	23.1 ± 14.2	16.5 ± 10.5	
Median (range)	17 (3-55)	17 (4-54)	14 (3-55)	18 (1-61)	21 (2-61)	17 (2-49)	0.119
Presence of PsA	63 (39.9%)	9 (25.7%)	3 (12.5%)	40 (65.7%)	52 (68.4%)	19 (50.0%)	0.000
Duration of PsA (yrs) (mean ± SD)	9.3 ± 9.1	8.3 ±7.6	NA	10.1 ± 6.0	10.6 ± 9.1	7.9 ± 4.3	
Median (range)	6 (1-46)	4 (3-20)		9 (1-25)	9 (2-49)	7 (2-19)	0.425
Smoking habit	40 (25.3%)	10 (28.6%)	6 (25%)	9 (14.8%)	15 (19.7%)	10 (26.3%)	0.569
Liver Steatosis	69 (43.7%)	20 (57.14%)	7 (29.2%)	32 (52.5%)	43 (56.6%)	15 (39.5%)	0.094
Obesity	34 (21.5%)	7 (20.0%)	3 (12.5%)	18 (29.5%)	27 (35.5%)	13 (34.2%)	0.076
Hypertension	69 (43.7%)	6 (17.1%)	9 (37.5%)	33 (54.1%)	44 (57.9%)	19 (50.0%)	0.002
Diabetes	24 (15.2%)	5 (14.3%)	3 (12.5%)	5 (8.2%)	12 (15.8%)	9 (23.7%)	0.523
Dyslipidemia	61 (38.6%)	10 (28.6%)	7 (29.2%)	14 (23.0%)	27 (35.5%)	11 (29.0%)	0.356
Metabolic syndrome	20 (12.7%)	4 (11.4%)	3 (12.5%)	8 (13.1%)	17 (22.4%)	10 (26.3%)	0.192
Previous systemic therapies							
None	123 (77.9%)	17 (48.7%)	2 (40.0%)	4 (6.6%)	6 (8.1%)	1 (2.6%)	
1	31(19.6%)	9 (25.7%)	2 (40.0%)	14 (22.9%)	19 (25.7%)	14 (36.8%)	
2	4 (2.5%)	8 (22.9%)	0 (0.0%)	35 (57.4%)	34 (45.9%)	12 (31.6%)	
3	0 (0.0%)	1 (2.9%)	1 (20.0%)	8 (13.1%)	15 (20.3%)	11 (28.9%)	0.000
N. of patients receiving MTX plus TNF α blockers	N.A.	N.A	N.A.	10 (16.3%)	10 (13.2%)	8 (21.0%)	0.000

Global retention rate

The study population contributed with a total of 743.4 person-years. Mean duration of follow-up was 25.1 months ± 13.0 SD (median 22 months, range 6 months-4.7 years), but it was significantly shorter for patients receiving CsA (mean 15.7 months ± 7.5 SD, median 13; range 5 months-3 years). Interruption of treatment was observed in 159/392 (40.6%) patients; of these 16.3% stopped treatment due to intolerance, and 21.7% due to inefficacy, whereas the others were still retaining the drug at the end of the study.

Global RR of TNF-α blockers at month 24 and 30 was significantly higher compared to any conventional drugs (Figure 1). In particular, the proportion of patients still retaining the TNF-α blockers at month 24 was 81.4% (± 3.2 SE) compared to MTX (61.5% ± 4.3), ACI (52.2% ± 1.0) and CsA (28.6% ± 2.7). Retention rate of MTX at month 24 and 30 was also significantly higher compared to CsA (p=0.001). There were no differences between TNF-α blockers and any conventional drugs at month 12.



Number at risk

TNF- alpha blockers	171	142	103	82	64
MTX	156	125	88	61	33
CsA	34	25	9	4	3
ACI	24	21	14	12	5

Figure 1 - Global retention rate of TNF-α blockers and conventional drugs in patients with psoriasis. At month 24 and 30 (but not 12) retention rate of TNF-α blockers was significantly higher compared to any conventional drugs (p=0.001). Retention rate of MTX was also significantly higher compared to CsA (p=0.001). Kaplan-Meier survival analysis. Vertical bars represent 95% confidence intervals.

Discontinuation due to intolerance or inefficacy

When considering discontinuation exclusively due to intolerance, RR of TNF-α blockers at month 24 was 93.6% (± 2.2 SE) and it was significantly superior than any conventional drugs (Figure 2A). The most common reasons of intolerance for TNF-α blockers were severe infections (mostly respiratory), for ACI was cheilitis, for MTX nausea and for CsA nausea, asthenia and hypertension (data not shown). At month 24, the lowest RR was observed for CsA (27.7% ± 10.9). RR of MTX and ACI at any time point were similar, being 73.5% ± 4.1 and 70.4% ± 10.3 at month 24, respectively (non statistically significant). There was no difference in discontinuation due to inefficacy between TNF-α blockers and any conventional drugs, as well as among conventional drugs at any time points (p=0.6). In particular, RR of TNF-α blockers was 86.7% (± 2.8 SE), MTX 83.6% (± 3.6), CsA 73.7% (± 9.3) and ACI 74.2% (9.9) at month 24,respectively (Figure 2B). In a separate analysis of patients receiving TNF-α blockers, no differences in the RR among ETA, IFX and ADA were detected. Concomitant administration of MTX had no impact on the RR, both when considering the whole group, or when analyzing separately IFX, ETA and ADA.

Multivariate analysis

Risk factors for early drug discontinuation were estimated using the Cox proportional hazards regression model (Table 2).The risk for early discontinuation was higher for any conventional drugs compared to TNF-α blockers. In particular, the hazard ratio (HR) for early discontinuation in patients receiving ACI was 8.44 (95% C.I 2.93- 24.25; p=0.001), CsA 7.20 (95% C.I. 3.77 - 13.74; p=0.001) and MTX 3.56 (95% C.I. 1.96- 6.47; p=0.003). Patients who had been treated with more than three drugs had an increased risk of drug discontinuation due to inefficacy (HR 1.37; 95% C.I. 1.10-1.79; p=0.032). Similarly, patients with higher BMI had a higher risk of drug interruption for intolerance (HR 1.91; 95% C.I. 1.68-2.1; p=0.008). Elderly patients had a reduced risk of drug discontinuation due to inefficacy (HR 0.97; 95% C.I. 0.95-0.99; p=0.036). Severity and duration of psoriasis, presence of PsA, diabetes or hypertension did not influence the RR. Further models analyzing smoking, presence of metabolic syndrome, dyslipidemia, steatosis, duration of PsA did not give statistically significant results.

Discussion

This study compared the long-term survival of conventional versus biological drugs in the therapy of moderate-to-severe psoriasis, and the major finding was that the RR of TNF-α blockers was higher than conventional drugs starting from 24 months of continuous therapy. Main cause of drug discontinuation was intolerance, followed by far by inefficacy. The RR of systemic drugs was negatively influenced by a higher BMI and the previous failure with three or more systemic drugs. In contrast, the

Table 2 - Multivariate analysis of predictors of early discontinuation of systemic drugs (Cox proportional hazards regression model).

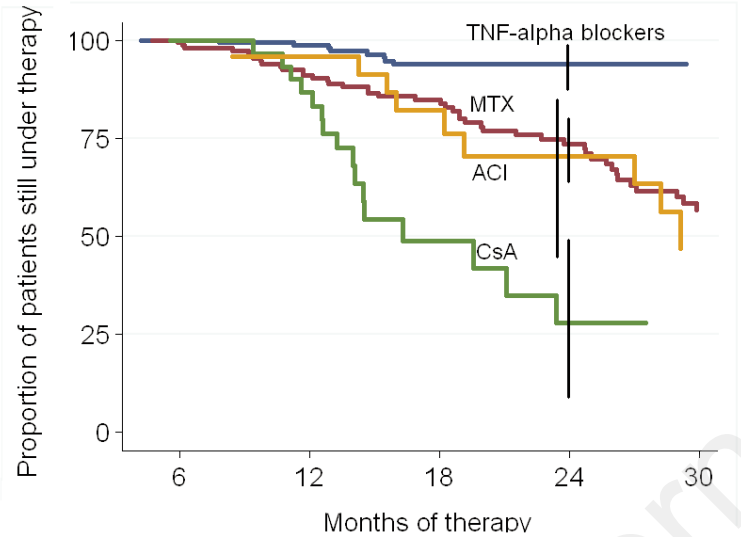
		Global		Intolerance		Inefficacy	
	N. of patients	Hazard. Ratio (95% C.I.)	p	Hazard Ratio (95% C.I.)	p	Hazard Ratio (95% C.I.)	p
Age[a]	NA	0.98 (0.96- 0.99)	0.023	0.98 (0.97-1.00)	0.257	0.97 (0.95-0.99)	0.036
Sex							
Female	129	1 *		1*		1*	
Male	263	1.07 (0.72-1.57)	0.729	1.26 (0.78-2.04)	0.339	0.75 (0.42-1.34)	0.346
BMI	NA	0.97 (0.93- 1.02)	0.344	1.91 (1.68-2.1)	0.008	1.03 (0.98-1.10)	0.190
Hypertension							
No	212	1*		1*		1*	
Yes	180	1.27 (0.83-1.94)	0.264	1.11 (0.64-1.94)	0.687	1.49 (0.77-2.86)	0.830
Diabetes							
No	334	1*		1*		1*	
Yes	58	0.86 (0.50- 1.47)	0.597	0.87 (0.43-1.76)	0.715	0.92 (0.43-1.96)	0.566
PASI at baseline[a]	NA	0.98 (0.96-1.01)	0.179	0.96 (0.93-1.00)	0.079	1.00 (0.97-1.03)	0.857
Duration of psoriasis[a]	NA	1.00 (0.99-1.02)	0.408	0.97 (0.93-1.02)	0.543	1.01 (0.99-1.03)	0.808
PsA							
No	206	1*		1*		1*	
Yes	186	0.91 (0.78-1.06)	0.227	0.84(0.70-1.04)	0.114	0.96 (0.77-1.19)	0.809
Type of drug							
TNF-a blockers	175	1*		1*		1*	
MTX	158	3.56 (1.96- 6.47)	0.003	6.67 (3.27-13.6)	0.002	1.90 (0.97-3.71)	0.058
ACI	24	8.44 (2.93- 24.25)	0.001	15.1 (6.5-35.4)	0.001	3.72 (1.43-9.69)	0.007
CsA	35	7.20 (3.77- 13.74)	0.001	5.65 (2.2-14.5)	0.001	12.23 (4.28-34.9)	0.000
Previous systemic therapies	352	1*		1*		1*	
0 to 2	40	1.10 (0.85-1.42)	0.464	0.97 (0.58-1.60)	0.912	1.37 (1.10-1.79)	0.032
3 or more							

[a] These values were inserted into the model as continuous variables

1* Reference.

NA, not applicable

A



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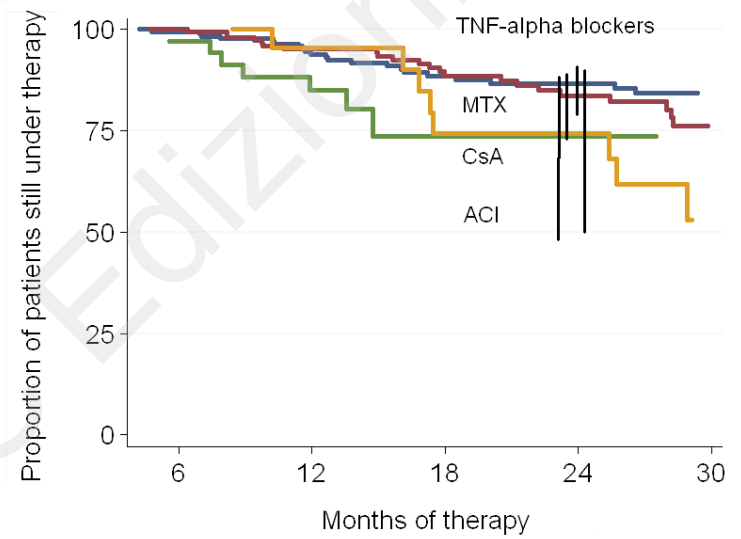

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MTX	156	125	88	61	33
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Figure 2 - Retention rate of TNF-α blockers (blue line) and conventional drugs with drug discontinuation due to intolerance (A) or inefficacy (B).At month 24 and 30 retention rate of TNF-α blockers was significantly higher compared to any conventional drugs (A, p=0.001). Differences between MTX or ACI versus CsA were statistically significant (A, p=0.001). There was no difference in RR due to inefficacy between TNF-α blockers and conventional drugs, as well as among them at any time points (B). Kaplan-Meier survival analysis. Vertical bars represent 95% confidence intervals.

severity and duration of psoriasis, the presence of PsA, diabetes or hypertension did not influence the RR. It is likely that the RR of TNF-α blockers is significantly higher compared to conventional drugs because they are better tolerated. Indeed, the proportion of patients who discontinued TNF-α blockers for intolerance was much lower compared to any conventional drugs. This is not surprising, since conventional drugs more easily induce organ toxicity which reduces patient adherence. In particular, CsA induces nephrotoxicity and hypertension (11), MTX liver damage (12) and ACI skin and mucosal toxicity (13). In addition, conventional systemic drugs are frequently discontinued before any side effects is emerging, for the fear of side effects. This is particularly the case for CsA. No differences were observed among the three TNF-α blockers (ETA, IFX and ADA). This result is in contrast to what has been observed by Gniadecki et al. in the Danish nationwide database DERMBIO (14). Indeed, this study reported that infliximab had the best RR compared to ADA and ETA with 70% patients being still on drug after 4 years of treatment. However, this difference seems very high according to other studies in patients with psoriasis, PsA or rheumatoid arthritis (15, 16). In particular, Brunasso et al. analyzed safety and tolerability of biologic therapies for psoriasis in a cohort of 103 patients who received 136 cycles of biologics, followed for an average of 39 months (15). They found that withdrawal was highest among IFX-treated patients, mainly due to severe adverse events such as infusion reactions (26%) and lack of adherence to therapy (21%).IFX had an incidence rate ratio of suspension of therapy due to serious adverse events 5.9 times higher than ETA and 9.8 times higher than efalizumab. In a large rheumatologic study, Glintborg et al. reported that RR of IFX was 41% after 2 years and documented that drug withdrawal was mainly due to a higher rate of adverse events (17).

Psoriasis is frequently associated to metabolic disorders including obesity (18). Obesity is a significant risk factor for the development of psoriasis and PsA (19, 20). A higher BMI may be directly correlated to the severity of psoriasis and it negatively affects the short-term clinical response to all systemic treatments, including conventional and biologics (21). In particular, Naldi et al. found that compared to normal weight the adjusted odds ratio for achieving PASI 75 in obese patients was 0.73 (95% Confidence Interval [CI] = 0.58-0.93) at 8 weeks and 0.62 (95% CI = 0.49-0.79) at 16 weeks. Biologics with a fixed dose regime, such as ETA, ADA, ustekinumab and alefacept have a compromised efficacy in heavier individuals (22). We found an independent association between high BMI values and interruption due to intolerance. The most common reasons of intolerance for TNF-α blockers were severe infections (mostly respiratory), for ACI was cheilitis, for MTX nausea and for CsA nausea, asthenia and hypertension. Similarly to our finding, Di Lernia et al. recently reported that the BMI affect the long-term survival rate of anti-TNF-α in patients with psoriasis (23). Thus, obesity could be considered a predictor of early drug discontinuation. Therefore, it is very important that lifestyle modifications, including a low calorie diet, supplement the pharmacological treatment in obese patients with psoriasis. Indeed, the medical board of the National Psoriasis Foundation recommends reducing excess body weight for obese patients with psoriasis, because this intervention could positively influence both the cardiovascular risk and the response to treatments (24). Rapid clearing of psoriasis have been reported in some obese patients following gastric bypass surgery (25). Accordingly, we found that a moderate weight loss (i.e. 5 to 10% of body weight) increases the responsiveness of obese patients with psoriasis to suboptimal doses of cyclosporine (26).

Limitations of our study include its retrospective, daily practice design. Our division is a tertiary referral center where more severe cases psoriasis are over-represented. Moreover, treatment assignment in our study was not randomized. However, randomized controlled trials (RTC) cannot evaluate daily efficacy of treatment. The study design focusing on daily practice has the advantage, in comparison to RTC, of showing the effects of drugs under typical everyday conditions, even if the result may be influenced by many factors including physicians' prescription habits. In RTC the inclusion and exclusion criteria select a subgroup of patients (27). Thus, RR is considered a relevant tool to evaluate the effectiveness and safety of a therapy (14). Lastly, the relatively small number of patients included in the study treated with ACI, CsA and the TNF-α blockers. In particular, the small sample size of patients treated with biological agents could have hidden possible differences in RR among them.

Long-term and safe disease control is a fundamental drug attribute for a chronic disease like psoriasis. It will therefore be worthwhile to further explore whether the higher RR of biologics could partially balance the higher costs compared to conventional drugs.

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References

1. Menter A, KormanNJ, ElmetsCA, Feldman SR, Gelfand JM, Gordon KB, et al. Guidelines of care for the management of psoriasis and psoriatic arthritis: section 6. Guidelines of care for the treatment of psoriasis and psoriatic arthritis: case-based presentations and evidence-based conclusions. J Am Acad Dermatol 2011;65:137-74.
2. Chan SA, Hussain F, Lawson LG, Ormerod AD. Factors affecting adherence to treatment of psoriasis: comparing biologic therapy to other modalities. J Dermatolog Treat 2011 Sep 7 [Epub ahead of print].
3. Noiles K, Vender R. Biologicsurvival. J Drugs Dermatol 2009;8:329-33.

4. LambCA, Fried RG, Feldman SR. Giving patients 'perceived control' over psoriasis: advice for optimizing the physician-patient relationship.J DermatologTreat 2004;15:182-4.
5. Elliott RA, Barber N, Horne R. Cost-effectiveness of adherence-enhancinginterventions: a quality assessment of the evidence. Ann Pharmacother 2005;39:508-15.
6. Pathirana D, Ormerod AD, Saiag P, Smith C, Spuls PI, Nast A, et al. European S3-guidelines on the systemic treatment of psoriasis vulgaris. J Eur Acad Dermatol Venereol 2010;24:117-8.
7. Zlatkovic-Svenda MI, Kerimovic-Morina D, Stojanovic RM. Psoriatic arthritis criteria evaluation: CASPAR and Modified CASPAR. Clin Exp Rheumatol 2011;29:899-900.
8. Mrowietz U, Kragballe K, Reich K, Spuls P, Griffiths CE, Nast A, et al. Definition of treatment goals for moderate to severe psoriasis: a European consensus. Arch Dermatol Res 2011;303:1-10.
9. Lee SS, Park SH, Kim HJ, Kim SY, Kim MY, Kim DY, et al. Non-invasive assessment of hepatic steatosis: prospective comparison of the accuracy of imaging examinations. J Hepatol 2010;52:579-85.
10. Maggi S, Noale M, Zambon A, Limongi F, Romanato G, Crepaldi G. Validity of the ATP III diagnostic criteria for the metabolic syndrome in an elderly Italian Caucasian population: the Italian Longitudinal Study on Aging. Atherosclerosis 2008;197:877-82.
11. Maza A, Montaudié H, Sbidian E, Gallini A, Aractingi S, Aubin F, et al. Oral cyclosporin in psoriasis: a systematic review on treatment modalities, risk of kidney toxicity and evidence for use in non-plaque psoriasis. J Eur Acad Dermatol Venereol 2011; 25Suppl 2: 19-27.
12. Montaudié H, Sbidian E, Paul C, Maza A, Gallini A, Aractingi S, et al. Methotrexate in psoriasis: a systematic review of treatment modalities, incidence, risk factors and monitoring of liver toxicity. J Eur Acad Dermatol Venereol 2011;25Suppl 2:12-8.
13. Sbidian E, Maza A, Montaudié H, Gallini A, Aractingi S, Aubin F, et al. Efficacy and safety of oral retinoids in different psoriasis subtypes: a systematic literature review. J Eur Acad Dermatol Venereol 2011;25Suppl 2:28-33.
14. Gniadecki R, Kragballe K, DamTN, Skov L. Comparison of drug survival rates for adalimumab, etanercept and infliximab in patients with psoriasis vulgaris. Br J Dermatol2011;164:1091-6.
15. Brunasso AM, Puntoni M, Massone C. Drug survival rates of biologic treatments in patients with psoriasis vulgaris. Br J Dermatol 2011 Aug 1. doi: 10.1111/j.1365-2133.2011.10557.x. [Epub ahead of print].
16. Duclos M, Gossec L, Ruyssen-Witrand A, Salliot C, Luc M, Guignard S, et al. Retention rates of tumor necrosis factor blockers in daily practice in 770 rheumatic patients. J Rheumatol 2006;33:2433-8.
17. Glintborg B, Østergaard M, Dreyer L, KroghNS, Tarp U, Hansen MS, et al. Treatment response, drug survival, and predictors in 764 patients with psoriatic arthritis treated with anti-tumor necrosis factor α therapy: results from the nationwide Danish DANBIO registry. Arthritis Rheum 2011;63:382-90.
18. Gisondi P, Tessari G, Conti A, Piaserico S, Schianchi S, Peserico A, et al. Prevalence of metabolic syndrome in patients with psoriasis: a hospital-based case-control study. Br J Dermatol 2007; 157:68-73.
19. Naldi L, Chatenoud L, Linder D, Belloni Fortina A, Peserico A, Virgili AR, et al.Cigarette smoking, body mass index, and stressful life events as risk factors for psoriasis: results from an Italian case-control study. J Invest Dermatol 2005;125:61-7.
20. Soltani-Arabshahi R, Wong B, Feng BJ, Goldgar DE, Duffin KC, Krueger GG. Obesity in early adulthood as a risk factor for psoriatic arthritis. Arch Dermatol 2010;146:721-6.
21. Naldi L, Addis A, Chimenti S, Giannetti A, Picardo M, Tomino C, et al. Impact of body mass index and obesity on clinical response to systemic treatment for psoriasis. Evidence from the Psocare project. Dermatology 2008;217:365-73.
22. Clark L, Lebwohl M. The effect of weight on the efficacy of biologic therapy in patients with psoriasis. J Am Acad Dermatol 2008;58:443-6.
23. Di Lernia V, Tasin L, Pellicano R, Zumiani G, Albertini G. Impact of body mass index on retention rates of anti-TNF-alfa drugs in daily practice for psoriasis. Journal of Dermatological Treatment 2011; Early Online, 1-6.
24. Bremmer S, Van Voorhees AS, Hsu S, Korman NJ, Lebwohl MG, Young M, et al. Obesity and psoriasis: from the Medical Board of the National Psoriasis Foundation. J Am Acad Dermatol 2010;63:1058-69.
25. Hossler EW, Maroon MS, Mowad. Gastric bypass surgery improves psoriasis. CM. J Am Acad Dermatol 2011;65:198-200.
26. Gisondi P, Del Giglio M, Di Francesco V, Zamboni M, Girolomoni G. Weight loss improves the response of obese patients with moderate-to-severe chronic plaque psoriasis to low-dose cyclosporine therapy: a randomized, controlled, investigator-blinded clinical trial. Am J Clin Nutr 2008;88:1242-7.
27. Grol R, Grimshaw J. From best evidence to best practice: effective implementation of change in patients' care. Lancet 2003;362:1225-30.