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Complete Skin Clearance and PASI response rates in clinical practice- Predictors, Health Related Quality of Life improvements and implications for treatment goals

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Conflict of interest Statement
MSE is responsible for dermatology in the project management for the national guidelines for psoriasis at the Swedish Board of Health and Welfare. J.M. Norlin has been involved in the health economic analyses of the national guidelines for psoriasis at the Swedish Board of Health and Welfare. K Nilsson, U. Persson have no conflict of interest to declare.

What's already known about this topic?

- Randomized Clinical Trials of biologics as well as treatment guidelines include treatment goals based on a percent improvement compared with baseline Psoriasis Area and Severity Index such as PASI75 or PASI90.
- Few studies have assessed which factors are associated with a high skin clearance rates, or Health Related Quality of Life improvements associated with different levels of skin clearance in clinical practice.

What does this study add?

- A high absolute PASI before switch to biologics and low BMI are associated with higher PASI percentage response.
- Few patients with baseline PASI >30 achieved Complete Skin Clearance.
- All responder groups achieved significant Health Related Quality of Life improvements.
- Patients achieving Complete Skin Clearance (PASI100) had lower absolute PASI before switch and lower improvements in absolute PASI and Health Related Quality of Life than patients with almost cleared skin.

Abstract

Background: PASI90 is suggested to be the new standard endpoint RCTs of biologics for psoriasis, whereas treatment guidelines often still refer to PASI75.

Objectives: To analyse in a real-world setting**:** Firstly, what factors are associated with higher levels of treatment response to biologics. Secondly, the Health Related Quality of Life gains associated with different response levels in clinical practice.

Methods: Biologically-naïve patients with PASI, DLQI and EQ-5D outcomes before (maximum 6 months) and after (3-12 months) switch to biologics during registration in the Swedish Register for systemic treatment of psoriasis, PsoReg, were included (n=515). Patient characteristics associated with higher treatment response were analysed by regression analyses. Improvements in absolute PASI, DLQI and EQ-5D were assessed in different PASI percent response levels.

Results: High PASI percentage response was associated with higher PASI before switch and lower BMI. DLQI and EQ-5D improved within all responder groups ($p<0.001$). The magnitude of improvements in DLQI ($p=0.02$) differed between responder groups. The mean (SD) DLQI improvement for PASI75-<90, PASI90-<100 responders and patients achieving Complete Skin Clearance (PASI100) were 9.9 (7.4), 11.5 (7.0) and 8.0 (6.1), respectively.

Conclusion: PASI percentage change is largely dependent on absolute PASI before switch. Patients in clinical practice lack "baseline" PASI values as they may switch directly from one treatment to another or stay successfully treated for a longer time period. Treatment goals such as PASI90 are thus not suitable for treatment guidelines or for follow-up in clinical practice.

Introduction

The post TNF-biologics make Complete Skin Clearance (CSC; frequently described as PASI100) or almost skin clearance an achievable treatment goal for the majority of people with psoriasis. Traditionally, the primary endpoint in psoriasis RCTs has been the number of patients achieving a 75 percent reduction in the PASI compared to baseline, PASI75 [1-5]. With the IL-inhibitors, endpoints of PASI90 or PASI100 are included in RCTs [6-9] and PASI90 is suggested to be the new standard endpoint in RCTs of biologics for psoriasis [10-12].

The main objective of RCTs is to determine efficacy and safety of pharmaceuticals. However, the experimental setting in RCTs differ from the use of pharmaceuticals in clinical practice. In RCTs patients have a so-called "wash-out period" before initiation of treatment in order to estimate the full treatment effect of the new pharmaceutical and PASI>10 is often used as an inclusion criterion. In clinical practice it would be unethical to ask patients to stop their current treatment regime before initiating treatment with biologics. Moreover, whereas patients in RCTs are followed-up according to a pre-defined protocol, patients in clinical practice have follow-up visits with varying time intervals and physicians can individualise treatments in terms of dosing and treatment combinations.

Patient characteristics also differ between RCTs and clinical practice. In clinical practice the patient population is typically heterogeneous, older, has more comorbidities, and may be less adherent to life-style- and treatment recommendations than patients included in RCTs. Few studies have investigated what factors predict treatment response of biologics in psoriasis in clinical practice [13,14]. Yet, characteristics predicting a high response could be useful for physicians trying to individualise and optimise treatment.

The clinical relevance of PASI has been questioned and PASI is therefore often complemented by Health Related Quality of Life (HRQoL) instruments, such as the Dermatology Life Quality Index, DLQI, in both clinical trials and in observational studies of psoriasis. EQ-5D is a generic measure of HRQoL, which is essential for estimating QALYs and cost-effectiveness analyses for reimbursement decision-making.

Treatment guidelines often refer to PASI75 as a treatment goal [15,16], yet few studies from clinical practice investigates the relationship between HRQoL and levels of PASI percentage change, such as PASI75 or PASI90.

The objective of this study was twofold; firstly, what patient characteristics are associated with higher levels of treatment response to biologics and secondly, to analyse the HRQoL improvements associated with different levels of treatment response in clinical practice.

Materials and Methods

Material

This study was based on the Swedish National Registry for Systemic Treatment of Psoriasis (PsoReg). The objective of the registry is to follow up safety and effectiveness of biologics[17]. PsoReg includes: clinical types/variants of psoriasis, systemic treatments, general health parameters and outcome measures such as PASI[18], DLQI[19] and EQ-5D[20]. EQ-5D-3L is a standardised instrument of patient-reported health status. It is widely used in health economic evaluations to calculate Quality-Adjusted-Life-Years (QALYs). Previously published utility weights from the UK were applied to health profiles in this study as no Swedish utility weights were available for the 3-level version[21]. Data was extracted in May 2017 with 6349 registered patients since registry start. Observations reflect clinical practice: they occur when patients visit their physician, and no visit is mandatory or protocol-driven.

Included patients and observations

Patients that had used efalizumab were excluded since the drug was withdrawn in 2009.

Bio-naïve patients who switched from non-biologic systemics to biologics treatment during registration were included. Only patients who had outcomes registered no more than 6 months prior to switch and another registered 3-12 months after switch were included. In accordance with treatment guidelines[15], only assessments made at least 3 months after switch were included to allow for treatment response. The latest registration before switch and the last observation after switch within the defined time periods were used in analyses. Note that patients may have discontinued the biologic treatment at follow-up after switch, or they may have had a treatment holiday before the assessment.

Study Design

Differences in patient characteristics between patients with different levels of treatment response, Low- or non-responders (PASI ≤0-<75), PASI75-<90, PASI90-<100 and patients with Complete Skin Clearance (CSC), were analysed. The relationship between the level of response in terms of percentage change in PASI as a continuous variable was investigated in a multiple regression analysis. Absolute PASI before switch, age, sex, BMI, debut age (>30), smoking, high-risk alcohol consumption, plaque psoriasis, PsA, nail psoriasis, guttate, pustular psoriasis, erythroderma and acrodermatitis continua suppurativa were included as variables in the regression analyses.

Absolute PASI, DLQI and EQ-5D before and after switch was presented in subgroups of patients with no response or worse (PASI≤0), low response (PASI1-<50 and PASI50-<75), and response in

terms of PASI75-<90, PASI90-<100 and CSC. Improvements in absolute PASI, DLQI and EQ-5D in subgroups with PASI response of PASI75-<90, PASI90-<100 and CSC.

Sensitivity Analyses

PASI is developed for plaque psoriasis. Patients with uncommon clinical types or symptoms (guttate, pustular psoriasis, erythrodermic psoriasis or acrodermatitis) were therefore excluded in an alternative analysis of factors influencing treatment response as well as HRQoL improvements. Likewise, another analysis was performed were patients which had discontinued their treatment or had used the drug less than 12 weeks at follow-up were excluded.

Statistical Analyses

Differences in characteristics and outcome measures between groups of patients were analysed through statistical tests as appropriate. The Kruskal-Wallis test was used to test whether there was a statistically significant difference in any of the PASI percentage responder groups. Wilcoxon signed-rank test was used to test for differences in absolute PASI, DLQI and EQ-5D outcomes before and after switch to biologics within the PASI percentage responder groups.

Data analysis was performed using STATA; StataCorp. 2015. Stata Statistical Software: Release 14. College Station, TX: StataCorp LP. and R; R Core Team. 2015. Version 3.4.2. Vienna, Austria: R Foundation for Statistical Computing, statistical packages.

Results

In total, 6349 patients were enrolled in PsoReg at the time of data extraction (Fig. 1). Two patients withdrew from registration, 104 had no contacts (including PASI, DLQI and EQ-5D) registered, 518 had no registered treatments and 130 were excluded as they received efalizumab before enrolment in PsoReg or during registration.

A total of 515 included patients were biologically-naïve and switched to biologics during registration and had same-date observations of PASI, DLQI and EQ-5D. Adalimumab was used as the first biologic in 44 percent of included patients, etanercept in 38 percent, ustekinumab in 14 percent, infliximab in two percent and sekukinumab in two percent of patients.

About one in four achieved a PASI90-100 (n=132) and one in four achieved between PASI75-<90 (n=131); about 50 percent did not achieve PASI75 (n=252).

The distribution of age, sex and BMI differed somewhat between PASI percentage responder groups (Table 1). The time between the assessment before switch and switch also differed. The mean (SD) number of days were 21 (36), 13 (30) and 28 (41) for PASI75-<90, PASI90-<100 responders and patients achieving CSC, respectively (p=0.015). The time between the switch and

the follow-up assessment after switch did not differ between responder groups (p=0.626). The mean (SD) number of months were 7.8 (2.8), 7.6 (2.7) and 8.1 (2.7) for PASI75-<90, PASI90-<100 responders and patients with CSC, respectively.

The regression result suggests that having a high PASI before switch and a lower BMI were associated with higher percentage response in PASI (Supplementary file). The regression had a slightly better goodness of fit when including the quadratic term of absolute PASI before switch.

The relationship between the continuous variable percentage change in PASI and absolute PASI before switch is illustrated in a scatterplot (Fig. 2). The fitted line is based on a simple regression using absolute PASI before switch and its quadratic term as explanatory variables. This illustrates that a higher percentage change of PASI is achieved as the absolute PASI before switch increases, up to a level of absolute PASI before switch above 30. (Note that sample size in the group PASI before switch above 30 was small, n=16).

The absolute PASI before switch differed between the different levels of PASI percent response (p<0.001). At higher intervals of response, the absolute PASI before switch was higher, except for the CSC group (Fig. 3).

Improvements in absolute PASI and DLQI (Fig. 3) before and after switch to biologics were statistically significant within all responder groups, as well as among non-responders (p<0.001). Improvements in EQ-5D before and after switch to biologics were statistically significant within all responder groups (p<0.001), but not among non-responders who had PASI0 or worse (p=0.862).

The magnitude of improvements in absolute PASI and DLQI (p=0.02) differed between responder groups. The mean (SD) PASI improvement for PASI75-<90, PASI90-<100 responders and patients who achieved CSC were 11.1 (5.4), 14.5 (7.8) and 9.6 (5.6), respectively (p<0.001). The mean (SD) DLQI improvement for PASI75-<90, PASI90-<100 responders and patients who achieved CSC were 9.9 (7.4), 11.5 (7.0) and 8.0 (6.1), respectively (p=0.02). The EQ-5D improvements were not statistically significant (p=0.403).

Patients who achieved CSC had on average lower absolute PASI before switch (p=0.004) and lower DLQI improvements than the PASI90-<100 (p=0.05) responder group. Differences in EQ-5D improvements between the patients who achieved CSC and PASI90-<100 responder group were not statistically significant (p=0.313).

Sensitivity Analyses

Two sensitivity analyses were performed: one where patients with uncommon clinical types or symptoms were excluded (n=51), and one where patients which had discontinued their treatment at follow-up or had used the drug less than 12 weeks were excluded (n=37). In the latter analyses nail

psoriasis had a statistically significant negative association with PASI response (p=0.007). Apart from that difference, results were robust in both alternative analyses (data not shown).

Discussion

Patient characteristics associated with a high PASI percentage response were a high absolute PASI before switch and lower BMI. The results suggest that a higher percentage change of PASI is achieved with higher absolute PASI values before switch, up to a certain level. For patients with baseline PASI above 30, few achieved high levels of skin clearance.

The HRQoL improvements per responder group were in proportion to the improvements in absolute PASI; the higher the absolute PASI improvement, the higher the HRQoL gains. Unsurprisingly, absolute PASI improvements were corresponding to the PASI before switch; the higher PASI before switch the higher the room for improvement in absolute PASI. Patients who achieved CSC had lower absolute PASI before switch compared to PASI90-<100 patients, and consequently they had lower absolute PASI improvements and lower HRQoL improvements.

A number of studies have investigated factors associated with treatment response in a clinical trial setting [13,22], but we found no studies from Swedish clinical practice. A register-based study from the Netherlands, which included 454 treatment episodes from 326 patients, found that the most important predictor for achieving a PASI90 response at week 24 was baseline PASI ≥ 10. The result is consistent with our finding that a higher absolute PASI before switch was associated with a higher PASI percentage response. Treatment response of absolute PASI<5 was also investigated and found in 59 percent of patients. Predictors for PASI ≤ 5 at week 24 were a lower baseline BMI and baseline PASI <10. The study did not report to what extent patients had absolute PASI<5 before biologic treatment was initiated. A lower BMI is in accordance with our finding.

In a large multicentre study, Warren and colleagues investigated predictors of PASI 90 at 6 and 12 months following treatment initiation [23]. Non-white ethnicity, female sex, smoking, unemployment, psoriasis of the palms and soles and the presence of small chronic plaques were associated with reduced odds of achieving PASI 90. Similar to our study, higher baseline PASI and lower weight was associated with increased odds of achieving PASI 90.

A literature review by Edson-Heredia and colleagues identified demographic, lifestyle, and clinical factors associated with response to biologics in psoriasis [14]. The study included 15 studies that considered non-genetic factors affecting treatment response in biologics in patients with psoriasis. The authors concluded that age, gender, ethnicity, alcohol consumption, smoking, geographic location, age at diagnosis, duration and severity of psoriasis, and baseline C-reactive protein levels did not consistently affect response to biologic psoriasis therapy. Consistent with our results, they

found that increased BMI was adversely associated with treatment response. Contrary to our results, the authors concluded that most studies found no association between disease severity and treatment response (mostly measured by PASI75).

To our knowledge, all previous research investigating the relationship between HRQoL and skin clearance per PASI percent responder group is from a clinical trial setting. Several RCTs report higher DLQI improvements in PASI90-<100 patients compared to PASI75-<90 patients [24-29]. We found no studies reporting DLQI nor EQ-5D response at different levels of PASI percentage response from a clinical practice setting.

Minimal clinically important difference (MCID) for the DLQI has been defined as 3–6 points[30,31]. All responder groups in our study had DLQI improvements that can be defined as clinically meaningful. However, the magnitude of improvements differed between groups.

An advantage of this register-based study is that a large patient population from clinical practice was included. A limitation is that the registry still mainly includes patients using the first-generation biologics (TNF-alpha and anti-IL-12/23), and the results may therefore not be generalizable for patients using IL-inhibitors/receptor antagonists. The proportion of patients with higher clearance rates is likely to be higher in the future when more patients have access to the second generation biologics.

A limitation of this study, which is inherent in the register-based design, is that there are no scheduled visits and consequently follow-up times and treatment durations differ between patients. To address this, only PASI, DLQI and EQ-5D outcomes a maximum of 6 months before and 3-12 months after switch to biologics were included. Furthermore, some patients may have discontinued their treatment at follow-up, which differs from a protocol-driven design. A sensitivity analysis showed that results were robust when excluding patients that had discontinued the treatment at follow-up.

Another limitation is that PASI is developed to measure plaque psoriasis and it does not capture some of the clinical types or symptoms that occur in clinical practice, such as pustular psoriasis or acrodermatitis. The sensitivity analyses showed that results were robust when excluding patients with uncommon clinical types or symptoms.

A limitation of the CSC/PASI100 concept is that it implies that health care professionals have done a check of 100% of the patient's skin, including genitals and feet. This is not consistently done in clinical praxis, and it is even a challenge in clinical trials. The high clearance rates of the second generation of biologics demands a more stringent evaluation of the complete body surface. Despite this limitation, PASI is the most acknowledged assessment tool of the clinical aspect of psoriasis,

and the introduction of new more efficacious drugs has to impact the way the PASI is obtained in both RCT:s and in clinical practice.

It has been suggested that PASI90 should be the new standard endpoint when measuring efficacy of pharmaceuticals for psoriasis [10-12,31]. An outcome based on PASI percentage change works well in a trial setting, where patients have a "wash-out" period before the trial and a baseline value of the severity of disease. In clinical practice, on the other hand, patients lack "baseline" PASI values as they may switch directly from one treatment to another and it would be unethical to ask patients to stop their current treatment in order to investigate the severity of the underlying disease. Moreover, patients in clinical practice constitute a heterogenous group and visits are not scheduled on a regular basis.

In our study from clinical practice the mean PASI before treatment was about 12. In RCTs of biologics the mean baseline PASI is usually above 20. As PASI percentage change is largely dependent on the absolute PASI value before initiating treatment we cannot expect as high percent clearance rates in clinical practice and therefore treatment goals such as PASI90 are not suitable in clinical practice. Yet, many treatment guidelines suggest treatment goals of PASI75 or PASI50<75 combined with a DLQI target of <5[15,32].

The second generation biologics makes it possible to achieve Complete Skin Clearance or almost cleared skin. The derma community should therefore turn to new endpoints in clinical practice, which focus on skin clearence rather than a relative reduction of psoriasis lesions. Thresholds based on absolute PASI levels may be more relevant. This is in accordance with some recent treatment guidelines, which have suggested an absolute PASI <3 as a relevant treatment goal in clinical practice [33,34].

We further suggest that future RCTs should report absolute PASI at follow up, in order to improve the transferability between trial data and real-world data. This would support reimbursement decision-making which require information on whether treatments work, not only in the pre-marketing experimental RCT setting, but also post-marketing, under real-world conditions.

Future research should further investigate the causal relationship between BMI and response to treatment. A better understanding of this relationship could support physicians to improve the possibilities for patients' treatment success and overall health.

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Figure 1. Flow scheme of number of excluded patients and number of patients with PASI, DLQI and EQ-5D assessment before and after switch to a biologic treatment

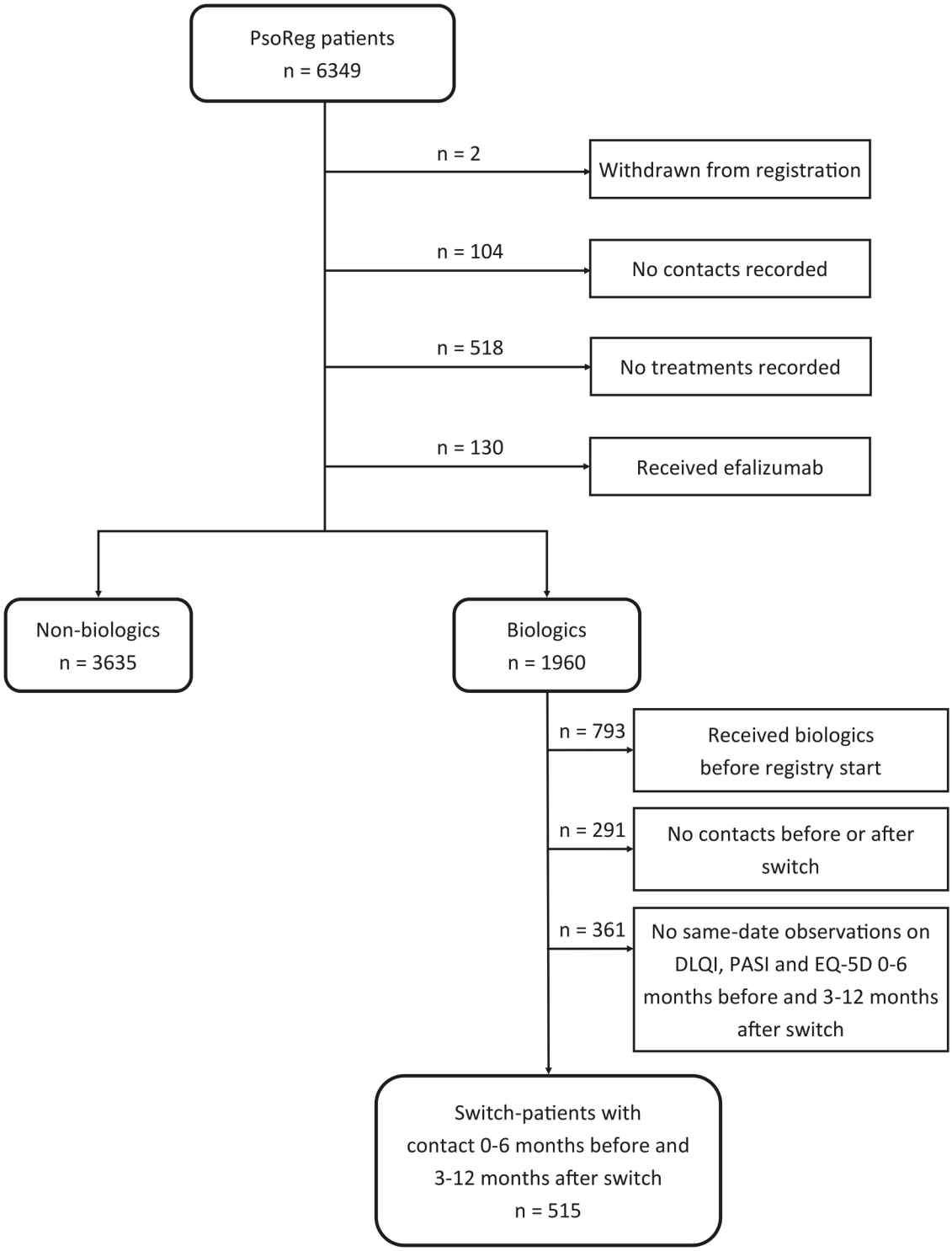

Figure 2. The relationship between percentage change in PASI and absolute PASI before switch

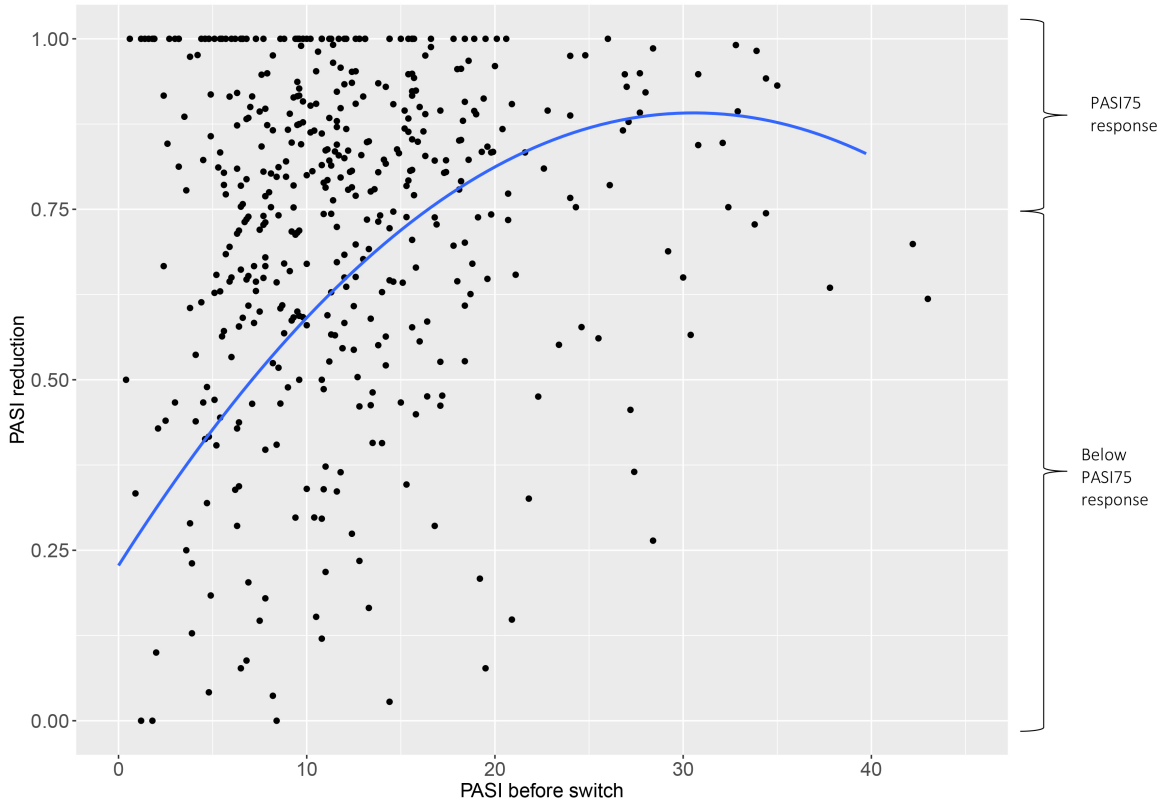

Figure 3. Absolute PASI (a), DLQI (b) and EQ-5D (c) before and after switch at different levels of PASI percent response (Mean, Sample Standard Deviation)

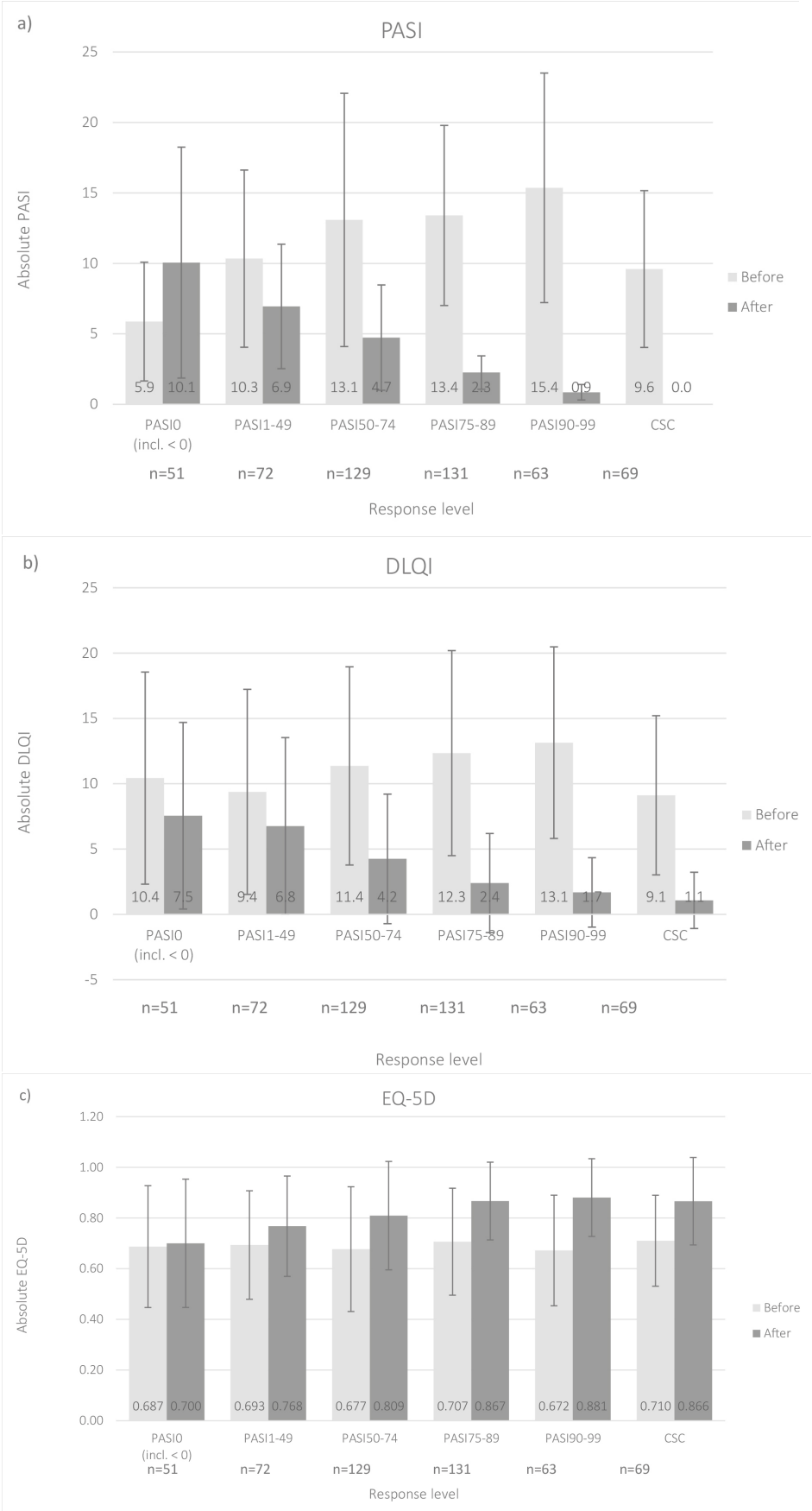

Table 1 Patient characteristics at visit before switch among low- or non-responders and responders in terms of PASI75, PASI90 and Complete Skin Clearance

	Low- or non-responders PASI<75 (n=252)	**Responders PASI≥75-PASI<90 (n=129)**	**Responders PASI≥90-PASI<100 (n=63)**	**Responders CSC (n=69)**	**P-value**
Men, n (%)	147 (59%)	96 (73%)	42 (67%)	40 (58%)	0.033
Age, Mean (SD)	48.5 (14)	46.5 (14.1)	43 (16.2)	45.5 (12.9)	0.021
BMI, median (IQR)	28.6 (25.2-32.1)	27.5 (23.9-31.2)	27.7 (23.7-31.2)	26.3 (22.5-31.5)	0.020
Debut age >30 years	60 (24%)	38 (29%)	11 (17%)	21 (30%)	0.186
High-risk alcohol consumption	6 (2%)	1 (1%)	1 (2%)	1 (1%)	0.703
Smoking	56 (22%)	23 (18%)	14 (22%)	10 (14%)	0.402
Clinical types or symptoms of psoriasis, n (%)					
Plaque psoriasis	218 (88%)	117 (89%)	54 (86%)	60 (87%)	0.900
Psoriasis arthritis	53 (21%)	24 (18%)	17 (27%)	18 (26%)	0.442
Nail psoriasis	76 (31%)	27 (21%)	14 (22%)	18 (26%)	0.172
Guttate	8 (3%)	5 (4%)	1 (2%)	2 (3%)	0.869
Pustular types*	11 (4%)	5 (4%)	2 (3%)	6 (9%)	0.382
Erythroderma	6 (2%)	2 (2%)	2 (3%)	2 (3%)	0.881
Acrodermatitis	1 (0%)	0 (0%)	0 (0%)	1 (1%)	0.433

*Pustular types include pal-pustular, non-palm pustular and general pustular psoriasis

Kruskal-Wallis test whether at least one sample differ from one other sample

CSC= Complete Skin Clearance