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Satisfaction with medication is high for biologics in psoriasis. *Results from the BioCAPTURE network.*

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Running title:

Satisfaction with medication for biologics in psoriasis.

What's already known about this topic?

- Maximum satisfaction with medication is thought to be positively related to adherence, health-related quality of life and patients' preferences.
- As shown in cross-sectional research, patients' dissatisfaction with treatment plays an important role in the field of psoriasis. Biologics-treated patients showed highest satisfaction among psoriasis patients.
- In an open-label extension-trial with etanercept, significant improvement on domains 'global satisfaction', 'effectiveness' and 'convenience' were achieved after 3 months of treatment.

What does this study add?

- A prospective, longitudinal study on satisfaction with etanercept, adalimumab and ustekinumab for psoriasis patients in daily practice.
- Significantly improved satisfaction rates (TSQM) were achieved in this group after three and six months. As reported by the patient, the domains 'effectiveness' and 'convenience' showed most room for improvement.
- After 6 months, biologics-inexperienced patients scored significantly better on domain 'global satisfaction' as compared to biologics-experienced patients.

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Conflicts of interest:

J.M.P.A. van den Reek carries out clinical trials for AbbVie and Janssen. J.M.P.A. van den Reek has received speaking fees from AbbVie and reimbursement for attending a symposium from Janssen, AbbVie and Pfizer.

P.P.M. van Lümig carried out clinical trials for AbbVie and Janssen. P.P.M. van Lümig has received speaking and consulting fees from Wyeth and Schering-Plough and has received reimbursement for attending a symposium from Janssen, Schering-Plough and Pfizer.

J. Zweegers carries out trials for Abbvie and Janssen. J. Zweegers has received reimbursement for attending a symposium from AbbVie.

P.C.M. van de Kerkhof serves as a consultant and or speaker for Galderma, Janssen Cilag, Schering-Plough, Celgene, Centocor, Allmirall, Hermal, UCB, Wyeth, Pfizer, Sofinnova, AbbVie, Actelion, Galderma, Novartis, Janssen-Cilag, LEO Pharma, Galapagos, Ely Lilly, Sandoz, PCM van de Kerkhof serves as chairman of data management safety reviewboard for Mitsubishi. All fees were paid directly to the institution or to the International Psoriasis Council. P.C.M. van de Kerkhof receives research grants from Glaxo Smith Klein (GSK), Centocor, Wyeth, Pfizer, Celgene, Schering-Plough, Merck Serono, AbbVie, Philips Lighting, Ely Lilly. All grants were paid directly to the institution.

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that manufacture drugs used for the treatment of psoriasis including Abbott, Janssen, MSD, and Pfizer.

M.D. Njoo serves as a consultant for Janssen.

W.P. Arnold served as a consultant for Abbvie and Janssen and travelled with Pfizer, Abbvie and Janssen to medical congresses for 50% of the fees.

The other authors declare no conflicts of interest.

Abstract

Background: Although effectiveness of biologics for psoriasis has been measured extensively with objective outcome measures, studies based on subjective, patient-reported outcome measures remain scarce in this field.

Objectives: (1) To investigate satisfaction with medication as measured by the Treatment Satisfaction Questionnaire for Medication (TSQM) for biologics in daily practice psoriasis care in the first 6 months of treatment. (2) To identify possible differences in satisfaction with medication between biologics-experienced versus biologics-inexperienced patients.

Methods: TSQM baseline measurements were compared with measurements after 6 months by Wilcoxon signed-rank test for paired comparisons. Two distinct analyses were presented: (1) intention-to-treat approach with last observation carried forward (ITT with LOCF) and (2) as treated approach. The difference between biologics-experienced versus -inexperienced patients for TSQM was analysed using ITT with LOCF. At month 6, outcomes for biologics-experienced and -inexperienced patients were compared by Mann-Whitney U test.

Results: 106 patients were eligible for analysis. Patients were treated with etanercept (n=34), adalimumab (n=49), or ustekinumab (n=23). 54% of patients were biologics-inexperienced. On all domains of TSQM (effectiveness, side-effects, convenience and global satisfaction), a statistical significant improvement was seen comparing month 3 or 6 with baseline (all *p-values* ≤ 0.02). After 6 months, biologics- inexperienced patients scored better on the domain 'global satisfaction' than biologics-experienced patients (*p* <0.01).

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Conclusion/Discussion: This study provides a prospective, longitudinal analysis of TSQM for biologics in daily practice psoriasis care. High satisfaction rates were achieved in this group. The domains 'effectiveness' and 'convenience' showed most room for improvement as reported by the patient.

Introduction

In recent years, effective targeted biological treatments have become available for the treatment of patients with moderate to severe psoriasis. The effectiveness of these agents has been measured extensively with objective outcome measures like PASI scores.¹⁻³ In the evaluation of treatments, patient reported outcomes (PROs) are important as well.⁴⁻⁶ An underreported PRO in the field of psoriasis treatment is 'satisfaction with medication'. The treatment satisfaction questionnaire for medication (TSQM)⁷ has been developed to capture satisfaction with medication for different indications. This generic questionnaire provides insight in different domains of treatment satisfaction.⁷

In treating psoriasis patients, maximum satisfaction with medication should be aimed for since it is thought to be positively related to adherence, health-related quality of life and patients' preferences.⁸⁻¹¹ It also provides insight in what should be improved on the drug itself according to its users.⁸⁻¹⁰ Vender et al. provided an analysis based on the TSQM for etanercept in an open-label trial. They found significant improvement on the domains 'global satisfaction', 'effectiveness' and 'convenience' after 3 months of treatment.¹² Driessen et al. cross-sectionally investigated treatment satisfaction using TSQM in a biologics-treated daily practice cohort.¹³ Recently, Duffin et al. analysed TSQM in a cross-sectional study comparing different anti-psoriatic treatments.¹⁴ The present study provides a prospective, longitudinal analysis of patients starting or switching biologics in daily practice.

The primary objective of this prospective study was to investigate satisfaction with medication as measured by TSQM (version II) for biological therapies in daily practice psoriasis care in the first 6 months of treatment. The secondary objective was to identify

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possible differences in satisfaction with medication between biologics-experienced versus biologics-inexperienced patients.

Methods

The Bio-CAPTURE database

Data were extracted from a prospective registry containing daily practice data from all patients with psoriasis treated with biologics (Bio-CAPTURE, Continuous Assessment of Psoriasis Treatment Use REgistry with biologics). The registry contains data on effectiveness, PROs, and pharmacovigilance. It is based at the department of Dermatology of the Radboud University Medical Center (Nijmegen) and founded in 2005. Eight regional nonacademic centers participated in the registry since 2011. All consecutive patients treated with biologics were enrolled in this registry. Patients were treated according to the opinion of the treating dermatologist with etanercept, adalimumab, infliximab, or ustekinumab. Preferably, patients were treated according to the regimens recommended by the European Medicines Agency (EMA) label and the European and Dutch national guidelines for biologic treatment.¹⁵⁻¹⁷ If necessary, dosage adjustments, interval changes, and/or combination therapy with topical or other anti-psoriatic systemic therapies were applied. The registry was approved by the medical ethics committee. Informed consent from patients was not mandatory according to the Dutch law in this non-interventional study, but is presently retrieved from every newly included patient.

TSQM

From January 2010 until July 2013, all patients starting a biologic for the first time, or switching to another biologic were asked to fill out TSQM (version II). This questionnaire is included in the Bio-CAPTURE study. In this time frame, etanercept, adalimumab and ustekinumab were equally available in daily practice. Patients received questionnaires at baseline and after 3 and 6 months, or until the moment of discontinuation (when patients stopped <6 months of therapy). The Treatment Satisfaction Questionnaire for Medication (TSQM) (version II) is a generic and multi-linguistically validated questionnaire developed for different patients and medications and therefore applicable to our patient-group. The TSQM

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covers four important domains of satisfaction with medication: efficacy, convenience, general satisfaction and side-effects. The scores for the domains range from 0 (extremely dissatisfied) to 100 (extremely satisfied).⁷ The questionnaire refers to the time frame 2-3 weeks prior to the moment of completing the questionnaire. Therefore, the baseline measures provide information about the last treatment used shortly before the initiation of the biologic in this study.

Data collection and extraction

At every visit, all data on effectiveness and safety (adverse events, medication changes) were collected on a standardized case report form (CRF) by a trained physician or nurse. The data manager entered the data in the Bio-CAPTURE database and checked the source documents for incomplete or incorrect data on the CRF. Every three months, patients received questionnaires (TSQM) by mail. After retrieving completed TSQM questionnaires, scores were entered in the Bio-CAPTURE database as well. Data from this database were extracted and imported into IBM SPSS Statistics 20 for further analysis.

Statistical analysis

TSQM data on etanercept, adalimumab and ustekinumab were analysed. Descriptive statistics (means \pm SD or medians [range]) were used to summarize TSQM data. The four TSQM subdomains were analysed separately. To explore the additional effects of biologics on each domain, baseline measurements were compared with measurements after 3, and after 6 months by Wilcoxon signed-rank test for paired comparisons.

In order to detect possible bias due to missing values or selection, two ways of analysis were presented: (1) an intention-to-treat with last observation carried forward (ITT with LOCF) analysis which represents the most conservative approach, (2) an as treated analysis, which represents the most positive approach.¹⁸ In the ITT with LOCF analysis, missing values on month 3 were imputed by baseline values and missing values on month 6 were imputed by month 3 values. To investigate the influence of prior experiences with biological treatments on TSQM, patients were classified as biologics-experienced (prior treatment with biologics) or biologics-inexperienced (no prior treatment with biologics). Descriptive statistics were summarized and differences for main characteristics for biologics-experienced and biologics-

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inexperienced patients were tested. Categorical variables were compared using Pearson's Chi-squared tests or Fisher's exact. Continuous variables with a parametric distribution were analysed using an independent t-test and continuous variables with a non-parametric distribution using a Mann-Whitney U test (ITT with LOCF). At month 6, outcomes of biologics-experienced and -inexperienced patients were directly compared by Mann-Whitney U test to identify possible differences in satisfaction at this endpoint. Additionally, other factors that could theoretically influence satisfaction with medication were analysed using a Mann-Whitney U test for month 6 outcomes (ITT with LOCF). These variables were: age, disease duration and gender. Patients aged <40 years and \geq 40 years were compared. We chose this cut-off point in order to take important age-specific issues into account such as: study, first working years and family planning (<40 years) versus late working years with established careers and a higher prevalence of comorbidities (>40 years). Regarding disease duration, we compared patients with a relatively short disease duration (<10 years) versus patients with more established psoriasis (\geq 10 years).

A p-value of <0.05 was considered significant in all analyses. IBM SPSS Statistics 20 was used to perform the analyses.

Results

Patient and treatment characteristics

A total of 117 unique patients were included in this study. Eleven patients were excluded: 9 patients were less than 6 months in follow-up, and 2 patients were lost to follow up. This resulted in 106 patients eligible for analysis using either adalimumab (n=49, 46%), etanercept (n=34, 32%), or ustekinumab (n=23, 22%). Patient characteristics are presented in Table 1. Little more than half of the patients were biologics-inexperienced (n=57, 53.8%). Baseline median scores on TSQM were 50% [0-100%] for effectiveness, 91.7% [8.3-100.0%] for side-effects, 66.7% [0.0-100.0%] for convenience, and 58.3% [0.0-100.0%] for global satisfaction.

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Baseline measures represent satisfaction with medication in the period directly preceding the start of the studied biologic. The most frequently used agents in this period were methotrexate monotherapy (n=27, 27%) and etanercept monotherapy (n=15, 15%). Thirty patients (30%) were not on systemic antipsoriatic therapy in this time frame. Other therapies used in this period are outlined in Table 2.

Satisfaction with treatment after 3 and after 6 months

Using ITT with LOCF, median scores on month 3 were as follows: 66.7% for effectiveness, 100% for side-effects, 66.7% for convenience, and 75.0% for global satisfaction. At month 6, median scores were: 66.7% for effectiveness, 100.0% for side-effects, 77.8% for convenience, and 83.3% for global satisfaction. As can be read from these scores, the domains 'effectiveness' and 'convenience' showed most room for improvement at month 6.

On all domains, a statistical significant improvement was seen comparing subsequent measurements (month 3 and 6) with baseline (all $p \leq 0.02$, paired Wilcoxon-signed rank test) (Fig. 1).

Comparable results were seen with the *as treated* analysis: all domains showed statistically significant improvement comparing subsequent measurements (month 3 and 6) with baseline (all $p \leq 0.02$, paired Wilcoxon-signed rank test) (Fig. 2).

Satisfaction with treatment for biologics-experienced versus –inexperienced patients

Table 3 shows patient and treatment characteristics of biologics-experienced and –inexperienced patients. Age, gender, and BMI were equally distributed among groups. Biologics-experienced patients used adalimumab more frequently and –inexperienced patients used etanercept more frequently. More biologics-inexperienced patients were treated in a non-academic center. Disease duration was longer among biologics-experienced patients. Both biologics-experienced and biologics-inexperienced patients were analysed for their TSQM response in time (ITT with LOCF). Both groups showed statistically significant improvements on domains 'efficacy', 'convenience' and 'global satisfaction' (all $p < 0.05$, paired Wilcoxon-signed rank test) after 3 and after 6 months as compared to baseline.

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Biologics-inexperienced patients achieved a significant improvement ($p < 0.01$) on the domain 'side-effects' after 3 and after 6 months as compared to baseline. In contrast, biologics-experienced patients achieved no major difference on this domain ($p = 0.8$ and $p = 0.3$ after 3 and 6 months, respectively).

To directly compare month 6 outcomes for biologics-experienced versus -inexperienced patients, a Mann-Whitney U-test was carried out (ITT with LOCF). This analysis revealed no differences between these groups on domains 'effectiveness', 'side-effects', and 'convenience' ($p = 0.14$, $p = 0.28$, $p = 0.63$, resp.). However, on the domain 'global satisfaction', significantly better outcomes were measured for biologics-inexperienced patients ($p < 0.01$) (Fig. 3).

Satisfaction with treatment split for age, disease duration, and gender

Patients aged < 40 years ($n = 25$) and ≥ 40 years ($n = 81$) were compared regarding their response on month 6 of TSQM. No statistical significant differences in these endpoint measures were found between groups (Mann-Whitney U test: Effectiveness ($p = 0.886$), Side-effects ($p = 0.595$), Convenience ($p = 0.051$), Global Satisfaction ($p = 0.997$)).

Patients with a relatively short disease duration (< 10 years, $n = 17$) versus patients with more established psoriasis (≥ 10 years, $n = 86$) were compared for their response on month 6 of TSQM. This comparison revealed a statistical significant difference on domain 'convenience' in favor of patients with a longer disease duration (≥ 10 years). No difference between groups for the three other TSQM domains was seen at month 6 (Mann-Whitney U test: Effectiveness ($p = 0.871$), Side-effects ($p = 0.472$), Convenience ($p = 0.039$), Global Satisfaction ($p = 0.540$)).

No difference between male ($n = 62$) and female ($n = 44$) patients on all TSQM domains was seen at month 6 (Mann-Whitney U test: Effectiveness ($p = 0.121$), Side-effects ($p = 0.467$), Convenience ($p = 0.539$), Global Satisfaction ($p = 0.464$)).

Discussion

For the total group of patients treated with adalimumab, etanercept or ustekinumab, a statistically significant improvement was seen on all domains of TSQM comparing baseline with month 3 and 6 measures. Both biologics-experienced and -inexperienced patients showed significant improvements on most domains of the TSQM. Patients inexperienced with biologics scored significantly better on domain 'global satisfaction' as compared to experienced patients after 6 months of treatment.

Driessen et al. cross-sectionally investigated treatment satisfaction in a biologics-treated daily practice cohort and found the highest scores on the domain 'side-effects' (91%), followed by 'convenience', 'global satisfaction' and 'effectiveness' (80%, 78% and 71%, resp.).¹³ Vender and colleagues measured the treatment satisfaction using the TSQM in an open-label study with etanercept in psoriasis during 1 year. Significant improvement in time was seen on all domains except on the domain 'side effects'.¹² The present study provides an analysis of satisfaction with medication for three different biologics (adalimumab, etanercept and ustekinumab) instead of an analysis on etanercept alone. In addition, the present study has a prospective and longitudinal study design.

It is conceivable that satisfaction rates in patients who have received prior biologics could be influenced by their former experiences. For instance, previous experiences on effectiveness, side-effects or practical issues with other drugs. In patients with rheumatoid arthritis (RA) however, the baseline level of treatment satisfaction with different medications was not different between anti-TNF-alpha experienced versus anti-TNF-alpha naive patients.¹⁹ Our findings correspond with these results in RA research; we found no differences between baseline scores on TSQM for biologics-experienced versus -inexperienced patients (data not shown). Moreover, we found that both groups significantly improved on all domains of TSQM in the first 6 months. The only exception was that biologics-experienced patients achieved no significant improvement on the domain 'side-effects'. This finding was due to a ceiling effect: this subgroup of patients started with a (maximum) median score of 100% at baseline, and this did not change after 3 and 6 months. When comparing the absolute scores directly between biologics-experienced and -inexperienced patients after 6 months,

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significantly higher scores were seen in biologics-inexperienced patients on the domain 'global satisfaction' ($p < 0.01$). A possible explanation could be that experienced patients have become more used to the positive effects of biologics in time. Patients with a longer disease duration (≥ 10 years) scored significantly better on the domain 'convenience' as compared with patients with a shorter disease duration. This could be explained by their long treatment history and –experiences which makes them more easily accustomed to new treatments.

In general, patients' dissatisfaction with their treatment plays an important role in the field of psoriasis. Although biological-treated patients show the highest satisfaction, there is still room for improvement as shown in cross-sectional research.^{13,14,20-22} The National Psoriasis Foundation found that 43% of patients with severe psoriasis (self-reported BSA $> 10\%$) was dissatisfied with their treatment.²⁰ A survey of van Cranenburgh et al. revealed that psoriasis patients rated 'treatment effectiveness' as the most *important* issue related to treatment satisfaction.²² It is therefore important to realize that we found this to be the factor with the most 'room for improvement'. Our results correspond with outcomes of Driessen et al. and Vender et al. who found most room for improvement for 'effectiveness' as well.^{12,13} This indicates that we should focus on ways to improve satisfaction with effectiveness when prescribing treatment with biologics in daily practice. These results suggest that development of treatments with higher efficacy is still needed in order to provide a solution for this unmet medical need. In addition, satisfaction with effectiveness of a drug could also rely on other factors, such as expectations of effectiveness.

A limitation of our study was that head-to-head comparisons between agents were not opportune due to group size. Furthermore, responder bias is an issue in questionnaire research and we had to deal with missing data. For this reason, we showed different analyses with and without imputation of missing data.¹⁸ A specific difficulty of the TSQM is that no threshold is established for meaningful changes.^{7,12} Shikiar and Rentz argue that patients' expectations influence satisfaction with a drug.⁸ This issue is important in patients with and without prior treatment with a biologic, because experience could be of great influence on patients' expectations.⁸ Patients' expectations are not incorporated in the TSQM questionnaire. Therefore, we compared biologics-experienced and -inexperienced

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patients in this study to deal with influence of prior experiences in our analyses. Biologics-experienced and -inexperienced patients showed a significantly different distribution of treatment setting (academic versus non-academic). Since TSQM is specifically targeted at the medication itself, and not to factors such as patient-doctor communication, we do not think that different treatment settings would be of influence on TSQM outcomes.

This study provides prospective, daily practice data on satisfaction with medication for biologics prescribed in psoriasis analysed with a validated questionnaire (TSQM). Moreover, separate analyses for biologics-experienced versus -inexperienced patients are presented. We found that patients treated with adalimumab, etanercept or ustekinumab were significantly more satisfied with their treatment after 3 and 6 months, as compared to the time before initiation of the studied drug. High satisfaction rates were achieved in this cohort after three and six months. For the domain 'side-effects', maximum (median) scores were reached. Most 'room for improvement' was seen on domains 'effectiveness' and 'convenience' (ITT with LOCF). A comparison of patients inexperienced versus experienced with biologics showed no differences in satisfaction with medication after 6 months, except for 'global satisfaction', which was significantly better for inexperienced patients. Although biologics are very potent drugs and an important addition for patients with difficult-to-treat psoriasis, further improvement of effectiveness and convenience of use is an important issue in the opinion of psoriasis patients.

Table 1: Patient characteristics (n=106)

mean±SD, median [range], n (%)

General characteristics

-Gender (male)	62 (58.5)
-Age	48.2 ± 12.3
-Duration of disease*	20.4 [2.4-53.6]

Experience with prior biologics

-Experienced (non-naive)	49 (46.2%)
-Inexperienced (naive)	57 (53.8%)

Status at moment of analysis

-Active user of biologic for >4 months	99 (93.4%)
-Discontinued biologic <4 months	7 (6.6%)

Hospital

-Academic	71 (67.0%)
-Non-academic	35 (33.0%)

**at moment of entering this study, data from 3 patients missing*

Table 2: Systemic antipsoriatic treatment in last 4 weeks prior to initiation of the study-biologic (n=101[‡])

N(%)^{‡‡}

-No systemic antipsoriatic	30	(29.7)
-Methotrexate	27	(26.7)
-Etanercept	15	(14.9)
-Ciclosporin	9	(8.9)
-Adalimumab	8	(7.9)
-Fumaric acid esters	4	(4.0)
-UVB	2	(2.0)
-Acitretin	2	(2.0)
-Adalimumab + methotrexate	1	(1.0)
-Dithranol	1	(1.0)
-Infliximab	1	(1.0)
-Ustekinumab	1	(1.0)

[‡]5 cases unknown, ^{‡‡}Percentages based on available data

Table 3 Patient and treatment characteristics of patients experienced or non-experienced with prior biologics (n=106) (mean±SD, n(%), median[range])

	Non-experienced N=57	Experienced N=49	p-value*
Patient			
Gender (male)	33 (58%)	29 (59%)	0.893 ^β
Age	47.9±12.6	48.6±12.1	0.776 ^α
Duration of disease	19.1±11.7**	25.2±12.8***	0.012 ^α
BMI	27.2 [18.6-53.2] ^ω	29.2±5.4 ^{ωω}	0.199 ^π
Diabetes	3 (5%) ^τ	7 (14%)	0.185 ^χ
Treatment			
Adalimumab	24 (42%)	25 (51%)	
Etanercept	24 (42%)	10 (20%)	
Ustekinumab	9 (16%)	14 (29%)	0.043 ^β
Clinic			
Academic	32 (56%)	39 (80%)	
Non-academic	25 (44%)	10 (20%)	0.010 ^β

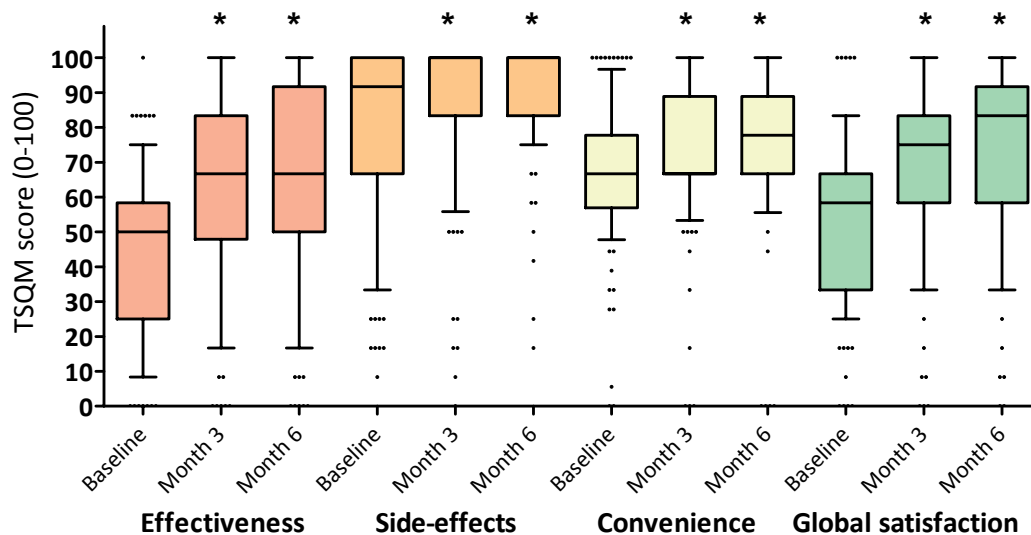
*based on the difference between naive and non-naive patients;^α independent t-test; ^β Pearsons Chi-square test, ^π Mann-Whitney U test, ^χFisher's exact test Data of 1^{**}, 2^{***}, 12^ω, 13^{ωω} and 2^τ patients missing.

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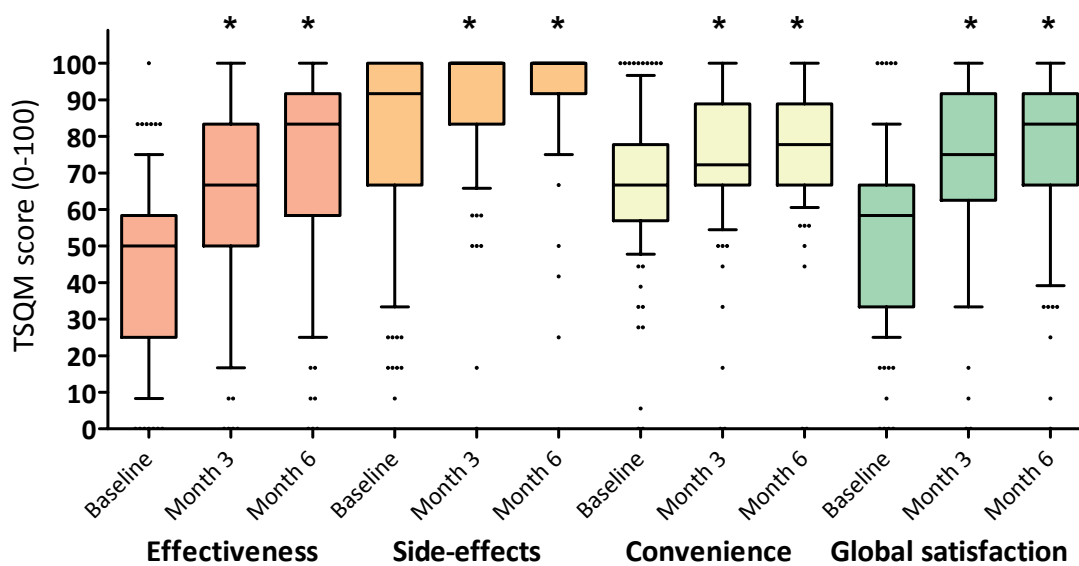
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Figure 1: TSQM measures for patients with psoriasis treated with biologics. - ITT with LOCF analysis

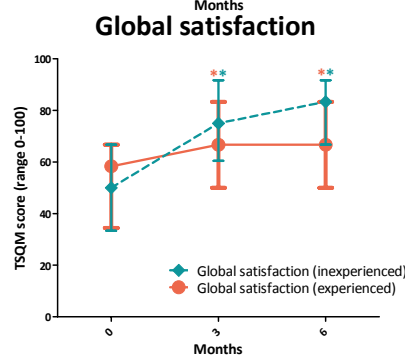
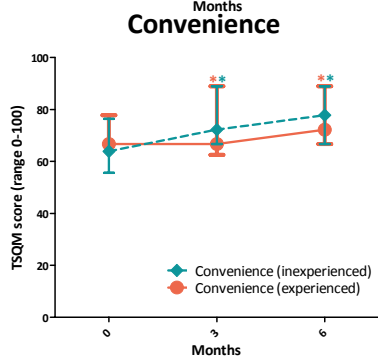
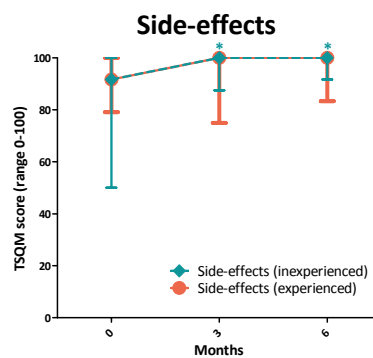
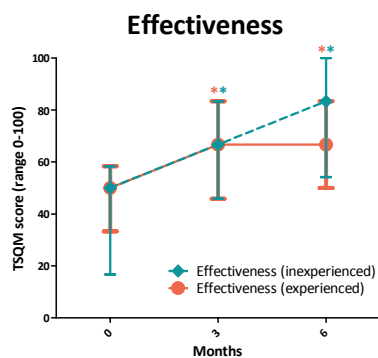


Whiskers represent 10-90 percentiles *Statistically significant improvement on Wilcoxon-signed rank-test as compared to baseline measurements

Figure 2: TSQM measures for psoriasis patients treated with biologics. - As-treated analysis



Whiskers represent 10-90 percentiles *Statistically significant improvement on Wilcoxon-signed rank-test as compared to baseline measurements



Each figure shows medians with interquartile ranges (whiskers). Asterisks (*) represent a significant improvement ($p < 0.05$) as compared to baseline for the specific TSQM domain. Color of asterisks corresponds with color of lines (see legend).