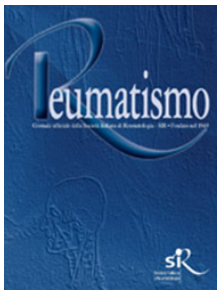

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PASSing to the patient side: early achieving of an acceptable symptom state in patients with rheumatoid arthritis treated with Janus kinase inhibitors

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Summary

Objective. Patients Acceptable Symptom State (PASS) is a single dichotomized question assessing health satisfaction. We aimed to investigate PASS achievement within 4 weeks of treatment with Janus kinase (JAK) inhibitors (Jakinibs) and its association with treatment response after 4 and 12 weeks in rheumatoid arthritis (RA) patients.

Methods. We recruited consecutive RA patients starting baricitinib or tofacitinib. At baseline, 4 and 12 weeks, we calculated disease activity [Disease Activity Score on 28 joints (DAS28), Clinical Disease Activity Index, Simplified Disease Activity Index], disease status [remission and low-disease activity (LDA)], percentage of patients achieving PASS, and the time to attain PASS. We assessed the impact of clinically relevant variables on PASS achievement by logistic regression analysis.

Results. We enrolled 113 patients [98 (86.7%) females; median age 59.6 (interquartile range 16.9), median disease duration 144 (132) months]. 90 (79.6%) patients achieved PASS after 10 (8) days. A similar percentage of PASS achievers and non-achievers was in remission/LDA at weeks 4 and 12, but the reduction of disease activity was significantly greater in PASS achievers. All patients achieving Boolean remission at weeks 4 and 12 had achieved PASS within 4 weeks. The impact of Patients Global Assessment (PGA) on DAS28 was significantly greater in PASS non-achievers compared to PASS achievers; inversely, the impact of C-reactive protein was more relevant in PASS achievers. At multivariate analysis, pain and PGA were significantly associated with PASS.

Conclusions. In our cohort, Jakinibs allowed an early achievement of PASS in a great percentage of RA patients. PASS is strictly dependent on PGA and pain and could suggest, early in the management of RA patients, therapeutic success.

Introduction

Although the treat-to-target strategy for the management of rheumatoid arthritis (RA) and the availability of many disease-modifying antirheumatic drugs (DMARDs) have greatly improved patient outcomes, RA is still often a cause of disability and poor quality of life (1). Pain, fatigue, and independence are the three most important domains that patients consider essential to self-define themselves in remission (2). The clinometric composite indices to assess disease activity include both objective measures, swollen and tender joint (TJ) count as well as levels of C-reactive protein (CRP) or erythrocyte sedimentation rate, and the Patients Global Assessment (PGA); the latter has a great impact on disease activity scores and may impede the achievement of treatment target (3). While in the early RA phases inflammatory markers such as the swollen joint (SJ) count and CRP can notably shape patient perception, PGA is primarily influenced by pain and disability in patients with established arthritis (4).

The first overarching principle guiding the European League Against Rheumatism (EULAR) recommendation for the management of RA highlights the need to involve patients in their treatment (5). Patient-centered care should take the patient's perspective into account, and patient-reported outcomes (PRO) should always be collected during the visit in parallel with clinically reported outcomes. To better reflect PGA variability and disease activity a recent update of the definition of Boolean remission slightly adjusts the PGA threshold to ≤2 (6).

Patients Acceptable Symptom State (PASS) is a single-question outcome tool quick and easy to use in routine clinical practice, consisting of a question with a dichotomized answer (7). In RA patients, the achievement of an acceptable symptom state is associated with disease activity and pain control (8-12).

Janus kinase (JAK) inhibitors (Jakinibs) have been demonstrated to improve PROs in randomized clinical trials as well as in real-life settings (13-20). However, no previous studies evaluated the satisfaction of patients treated with Jakinibs. In light of their rapid effect on pain, we sought to determine the impact of baricitinib and tofacitinib on health status satisfaction, investigate factors affecting PASS achievement, and evaluate whether the PASS could predict the short-term treatment response.

Materials and Methods

Study design and patients' enrollment

In this observational, monocentric, prospective study, we enrolled consecutive adult patients with RA diagnosed according to 2010 EULAR/American College of Rheumatology (ACR) criteria (21) who started either baricitinib or tofacitinib from January 2019 to January 2022. At the baseline visit and after 4 and 12 weeks of treatment with baricitinib or tofacitinib, we recorded demographic and clinical data including disease duration, previous treatment with conventional synthetic DMARDs, biological DMARDs, targeted synthetic DMARDs and ongoing treatment with csDMARDs and glucocorticoids (GCs). We recorded the number of TJs and SJs, CRP, positivity to anti-citrullinated protein antibodies (ACPA), and rheumatoid factor. We also collected the PGA and pain scores on a 0-100 mm visual analog scale (VAS). Concomitant fibromyalgia (FM) was diagnosed according to the 2016 revised criteria of the ACR (22). The clinical evaluation was performed by the same two rheumatologists at each visit. At baseline and after 4 weeks of treatment, we calculated the composite indices of disease activity [CRP-based Disease Activity Score on 28 joints (DAS28), Simplified Disease Activity Index (SDAI) and Clinical Disease Activity Index (CDAI)] and the percentage of patients who achieved the treatment target: index-based remission or low disease activity, Boolean remission, Boolean 2.0 and "near-remission" (6, 23). PASS was investigated at baseline and after 4 weeks of treatment by asking the Italian version of the following question: "considering all the different ways your disease is affecting you, if you would stay in this state for the next months, do you consider that your current state is satisfactory?" (7, 8). To assess "time to PASS," at the baseline visit we asked patients to note after how many days of treatment they began to perceive their health as acceptable. We analyzed

factors associated with an acceptable symptom state and baseline predictors of PASS achievement. Patients who missed the first follow-up visit after 4 weeks were excluded from the study.

All patients signed a written consent to participate; the study was declared to the local Ethical Committee and conducted in compliance with personal data protection regulations.

Statistical analysis

Data were expressed as median and interquartile range (IQR); Mann-Whitney and Chi-square tests were used to compare the distribution of continuous or categorical variables. Multivariate logistic regression analysis, accounting for the main clinically relevant variables (age, sex, disease duration, ACPA, concomitant FM, previous treatment lines, concomitant methotrexate (MTX), ongoing GC dose at baseline, VAS pain and PGA, DAS28, CDAI, and SDAI scores), was used to assess the impact of baseline characteristics on PASS achievement. Multivariate logistic regression analysis was also used to assess possible correlations between clinically relevant variables at week 4 (GC dose, VAS pain and PGA, DAS28, CDAI, and SDAI scores adjusted for age and gender) and the PASS achievement. All statistical tests were performed at a two-sided significance level of 0.05 with SPSS statistical software (SPSS, Chicago, IL, USA).

Results

We enrolled 113 patients with RA (98 females and 15 males) with a median age of 59.6 (IQR 16.9) years and a median disease duration of 144 (IQR 132) months. Table 1 summarizes the demographic and clinical features of patients at baseline; 76 patients have been treated with baricitinib and 37 with tofacitinib, with no significant differences between the two groups in the demographic and clinical characteristics. None of the patients considered their symptom state acceptable at baseline.

Patients Acceptable Symptom State achievement and disease activity after 4 and 12 weeks of treatment

Overall, 90 (79.6%) patients achieved PASS at week 4, with a similar percentage in the baricitinib (60/76, 78.9%) and the tofacitinib-treated groups (30/37, 81.1%), p=ns. The median time for PASS achievement was 10 (8) days; 38 out of 90 patients (42.2%) attained PASS within the first 7 days of treatment and 14 (15.5%) already within only 3 days.

After 4 weeks of treatment, we detected a significant reduction of DAS28, CDAI, and SDAI in the overall population ($p<0.001$ for all). When dividing the cohort according to PASS achievement at week 4, we found a significantly greater reduction of CDAI and SDAI – but not DAS28 – in PASS achievers; after 12 weeks, instead, all disease activity indices (DAS28, CDAI, and SDAI) decreased significantly more in PASS achievers (Figure 1). Overall, at week 12 DAS28, CDAI and SDAI scores decreased by 28 (31)%, 50 (38)%, and 48 (38)%. When considering patients who attained PASS and those who did not, the extent of the reduction of disease activity indices was significantly greater in PASS achievers [median DAS28 34 (31)%, CDAI 54 (37)%, SDAI 55 (36.3)%] compared to those who did not attain PASS [17.5 (27.6)%, 37 (31)% and 37.5 (31.5)% for DAS28, CDAI and SDAI] ($p=0.007$, $p=0.005$ and $p=0.02$, respectively). Figure 2 summarizes the effect of PGA, TJ count, SJ count, CRP, and Physician Global Assessment (PhGA) on DAS28 and SDAI scores in the overall population, PASS achievers, and PASS non-achievers. At week 4, only for DAS28 calculation, PGA contribution was significantly higher and CRP significantly lower in patients who did not achieve PASS compared to PASS achievers.

In week 4, at univariate analysis, we detected a significant correlation between PASS attainment and disease activity evaluated with CDAI ($p=0.0035$) and SDAI ($p=0.0014$) but not with DAS28 ($p=0.07$). However, we did not find any significant difference in the percentage of patients reaching the treatment target after 4 weeks (either low disease activity or remission evaluated by DAS28, CDAI, and SDAI) according to PASS. Those patients achieving PASS had significantly lower scores

in pain and PGA ($p<0.0001$ for both). We observed a significant reduction of PhGA after 4 weeks of treatment ($p<0.001$); the reduction of PhGA significantly correlated with the reduction of PGA. Additionally, we performed a linear regression model and confirmed the association of both PGA ($p<0.001$) and PhGA ($p=0.0065$) with PASS.

Baseline predictors of Patients Acceptable Symptom State achievement

When evaluating the possible predictors of PASS achievement, we found a positive correlation between concomitant MTX at baseline and the probability of having a PASS at week 4 ($p=0.009$, $\beta=1.72$): this association was confirmed at stepwise multivariate analysis after adjusting for age, sex and disease duration. When comparing the baseline disease activity in patients who were treated or not with concomitant MTX, we found significantly lower disease activity ($p=0.002$ for DAS28, CDAI, SDAI), PGA ($p=0.016$) and pain ($p=0.025$) scores in MTX-treated patients.

Baseline age, sex, disease duration, ACPA, concomitant FM, previous treatment lines, ongoing GC dose at baseline, VAS pain and PGA, DAS28, CDAI, and SDAI scores were not predictors of PASS achievement at multivariate analysis (Table 2).

Early Patients Acceptable Symptom State as predictor of target achievement at week 4 week 12

At week 4, 29.4%, 11.8%, and 11.8% of the 113 patients achieved remission according to DAS28, CDAI, and SDAI, and 23.5%, 38.8%, and 37.6% were in low disease activity, respectively, without any significant difference between PASS achievers and non-achievers. Boolean remission was achieved by 9.4% of patients, while according to the Boolean 2.0 definition, this percentage increased to 12.3% with a Cohen κ agreement between the two definitions of Boolean remission of 0.85. Another 9.43% of patients were in near-remission due to PGA.

Of the 113 patients enrolled, disease activity indices were available for 101 subjects at week 12; 10 patients missed the week-12 assessment due to the limited access to care imposed by the lockdown at the time of the COVID-19 pandemic, the other 2 patients withdrew Jakinibs for lymphopenia and lack of adherence. At week 12, 55.4% of patients achieved the target (either remission or low disease activity) according to DAS28 and 61% according to CDAI and SDAI. Of those patients who achieved the treatment target at week 12, up to 87.9% and 90.2% according to DAS28 and CDA/SDAI, respectively, had already achieved PASS at week 4. At univariate analysis, PASS was significantly associated with target achievement ($p=0.013$ for DAS28, $p<0.0001$ for CDAI and SDAI). After adjusting for age, sex, disease duration, ACPA, concomitant FM, and previous treatment lines, the multivariate analysis confirmed the association between PASS and disease activity ($p=0.038$, $\beta=1.8$ for DAS28; $p=0.001$, $\beta=5.9$ for CDAI and SDAI). At week 12, 13.4% of patients achieved the Boolean remission, 17.5 the Boolean 2.0 definition (Cohen $\kappa=0.84$), and 18.6% were in near remission due to PGA.

Finally, in our cohort, we observed a significant reduction in GC dosage (median prednisone equivalent daily dose) from a median dose of 5 (IQR 6.8) at baseline to a median of 2.5 (IQR 5) at week 12 only in PASS achievers (Figure 3).

Discussion

The results of this study show that most RA patients treated with Jakinibs, either baricitinib or tofacitinib, reported a satisfactory health status already after 4 weeks of treatment. In the context of a patient-centered approach to RA, we used for the first time the PASS question to assess patients' satisfaction with treatment with Jakinibs, receiving a positive answer from about 80% of patients. To the best of our knowledge, this is the first study evaluating the efficacy of RA treatment through the PASS question.

As already reported in the literature, PASS achievement was associated with PGA and pain scores. In addition to clinical outcomes, there is a growing need for decision-making that focuses on the individual patient's perceived health status. PROs include several tools used to capture patients'

experiences of symptoms, health status, and quality of life. Completing questionnaires can take time, so most PROs are rarely used in clinical practice. PGA is the exception, being included in the calculation of disease activity. PGA is a subjective measure poorly associated with objective measures, such as TJs and acute phase proteins, and radiographic outcome (4, 23). The subjective nature of the patient's global health and its close relationship with pain, fatigue, and disability make PGA the main limiting factor in achieving remission (23, 24). In our cohort, PGA hindered the early achievement of Boolean remission in 15% of cases at week 4 and 18% at week 12. In patients with long-standing RA such as those included in this study, structural damage may account for a high PGA score even in the absence of inflammation. Brites *et al*. showed that, in patients in PGA-near-remission at two consecutive visits, ultrasound assessment did not detect any subclinical inflammation, confirming the discrepancy between PGA and objective signs of synovitis (25). However, even in RA patients with established disease, Jakinibs allowed an improvement in PGA that was significantly greater in the active drug arms compared with placebo, already after 2 weeks of treatment (26, 27). Patients enrolled in our study had a long-standing disease lasting about 10 years and failed several treatment lines; however, age, disease duration, and previous failures did not influence the satisfaction with baricitinib and tofacitinib. In our cohort, we opted for a dichotomous (yes/no) representation of PASS, as opposed to the 0-100 scale utilized in some papers (28). We thought that having a quick and immediately understandable question could improve patient-physician communication adding valuable information to the PGA. Moreover, it gave us the opportunity to better estimate the "time-to-PASS" and influenced positively the efficiency and utility of our evaluation process.

Less than one-third of patients had already achieved remission at week 4, even if about 80% achieved an acceptable symptom state. This apparent discrepancy may be related to the different PGA phrasing and challenges in patients' interpretation (difficulties in understanding the meaning, scaling, and purpose of PGA) (3). On the contrary, PASS is a single, dichotomized question, easy to understand and reflecting patients' satisfaction with their current symptom state. Moreover, data from the literature as well as our experience (data not shown) highlighted that the cut-off points of disease activity indices – either DAS28 or CDAI – for being in PASS are in the range of moderate disease activity (11, 29, 30). As previously reported in the literature, we found a significant correlation between PASS attainment and disease activity evaluated with CDAI and SDAI but not DAS28 (11, 12, 30, 31). Similarly, Heiberg *et al.* showed a better agreement between PASS and CDAI/SDAI, supporting the notion that these two indices better reflect the patients' perception of a satisfactory condition (29). Indeed, when considering DAS28, we found that PGA can discriminate between PASS achievers and non-achievers.

Patients considering themselves in acceptable status already after 4 weeks of treatment with Jakinibs had lower disease activity; nonetheless, the percentage of patients achieving remission or low disease activity as early as week 4 did not differ according to PASS. However, an early affirmative response to the PASS question was significantly associated with the achievement of the treatment target after 12 weeks of treatment. As suggested by the EULAR recommendations for RA management, the 3-month timepoint is crucial to determining the treatment efficacy (5). Notably, those patients who considered their health status satisfactory also more significantly reduced the GC daily dose after three months of treatment, compared to PASS non-achievers. The reduction of GCs is one of the main goals of the treatment strategy, and the possibility of using PASS as an easy and quick tool to assess patients' satisfaction could support clinicians to taper and discontinue the dose of GC. A previous study from our group demonstrated how the use of tofacitinib allowed to stop the daily prednisone dose within 12 weeks of treatment, thanks to the ability of Jakinib to control pain (32).

Pain is one of the priorities for RA patients, and pain control is one of the main domains affecting PASS attainment. The switch from negative to positive answers to the PASS question in a high percentage of our patients is probably associated with the rapid effect of Jakinibs on pain; indeed, in our analysis, pain was independently associated with PASS achievement.

Interestingly, we also found a significant association between PASS and PhGA. The concordance between patient and clinician assessment of disease during the treatment with Jakinibs has been highlighted only in one previous study on 122 RA patients treated with tofacitinib (33).
Confirming the fast effect of Jakinibs, the median time to PASS has been 10 days, and more than 40% of patients achieved PASS after just one week of treatment. Many hypotheses are being explored to explain the unique effect of Jakinibs on pain, suggesting an additional effect of these drugs on nociception (34). Of note, in our cohort, concomitant FM did not influence the patients' satisfaction.
In our cohort, all patients completed the 12-week follow-up. In such a short period we did not observe any drug withdrawal for safety reasons – in particular, no major cardiovascular events or malignancies were reported – among the patients included in the study. The enrolment period ended at the time of the publication of the ORAL Surveillance study and before the European Medical Agency warning on Jakinibs was issued (34). A recent report on Italian patients confirmed a reassuring safety profile of tofacitinib and baricitinib in the real-world setting (35-37).
A possible limitation of our study is the early evaluation of the treatment target; 4 weeks is a short time to establish the treatment efficacy through the achievement of remission or low disease activity, but failure to obtain PASS early in the course of the treatment does not preclude a subsequent response. We hypothesize that allowing patients to quickly reach an acceptable symptom state might increase adherence and treatment continuation, improving the therapeutic alliance.

Conclusions

Caring for RA patients should mean not only achieving the clinical target but also improving the patients' quality of life. Besides the evaluation of disease activity, a single question inquiring about satisfaction with health status could help rheumatologists understand patient needs and the adequacy of treatment. In our experience, PASS is strictly associated with PGA, and both are influenced by pain; also, compared to PGA, the PASS question is more comprehensible for the patient, and it may suggest early therapeutic success, especially for such drugs with a rapid effect on pain, allowing a faster tapering of GCs.

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Table 1. Patients' demographic and clinical characteristics at baseline.

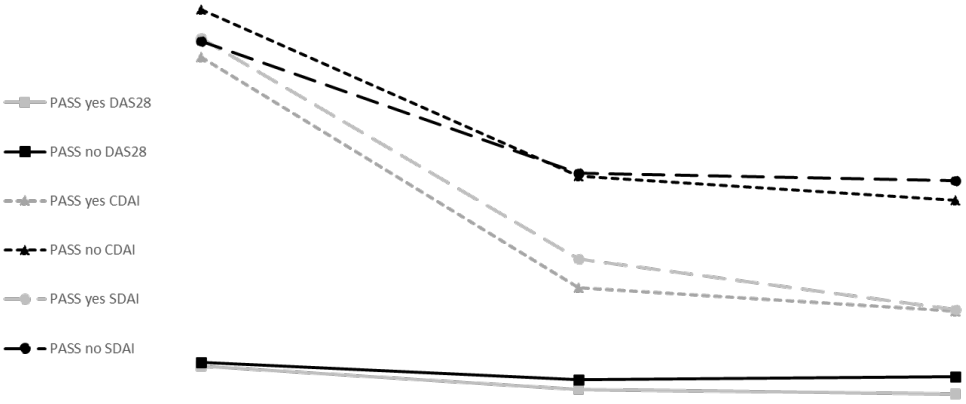
	Whole cohort	Baricitinib	Tofacitinib	p
Patients, n	113	76	37	
Age, years*	59.6 (16.9)	58.5 (14.6)	64 (16.5)	ns
Female: Male	98:15	66:10	32:5	ns
Disease duration, months*	144 (132)	144 (144)	150 (102)	ns
bDMARDs naïve, n (%)	25 (22.1)	14 (18.4)	11 (29.7)	ns
1 previous bDMARD, n (%)	20 (17.7)	13 (17.1)	7 (18.9)	ns
≥ 2 previous bDMARDs, n (%)	68 (60.2)	49 (64.4)	19 (51.3)	ns
Previous tsDMARDs, n (%)	3 (2.6)	0	3 (8.1)	NA
Concomitant MTX, n (%)	44 (38.9)	32 (42.1)	12 (32.4)	ns
Prednisone equivalent, mg/day*	5 (6.37)	5 (6.12)	5 (6.25)	ns

IQR, interquartile range; n, number; bDMARDs, biological disease modifying anti-rheumatic drugs; MTX, methotrexate; tsDMARDs, targeted disease modifying anti-rheumatic drugs; ns, not significant; NA, not available; *data expressed as median (IQR).

Table 2. Univariate and multivariate logistic analysis for the determination of baseline demographic and clinical predictors of Patients Acceptable Symptom State achievement.

	Univariate analysis		Multivariate	
	β	p	β	p
Gender	-1.044	0.201	-4.618	0.244
Age	0.003	0.882	0.041	0.379
Fibromyalgia	**-1.150**	**0.027**	-1.860	0.229
Disease duration	0.001	0.635	0.015	0.143
Rheumatoid Factor +	-1.664	0.806	-0.643	0.973
ACPA +	0.310	0.598	0.476	0.764
Concomitant MTX	**1.720**	**0.009**	**2.656**	**0.015**
Previous csDMARDs	-0.184	0.401	-0.968	0.155
Previous bDMARDs	-0.026	0.857	-0.200	0.524
$DAS28_{CRP}$	0.059	0.779	1.656	0.360
CDAI	-0.018	0.359	0.534	0.189
SDAI	-0.007	0.694	0.374	0.303
Pain VAS	-0.009	0.421	0.49	0.361
PGA	-0.019	0.121	-0.090	0.130

ACPA, anti-citrullinated proteins antibodies; MTX, methotrexate; csDMARDs, conventional disease modifying anti-rheumatic drugs; bDMARDs, biological disease modifying anti-rheumatic drugs; $DAS28_{CRP}$, C-reactive protein-based Disease Activity Score on 28 joints; CDAI, Clinical Disease Activity; PGA, Patient Global Assessment.



	BASELINE			4 WEEKS			12 WEEKS		
	PASS achievers	PASS non achievers	p	PASS achievers	PASS non achievers	p	PASS achievers	PASS non achievers	p
$DAS28_{CRP}$	4.56 (1.8)	4.8 (1.1)	ns	3.1 (1.6)	3.7 (19)	ns	2.8 (1.5)	3.9 (1.4)	0.0128
CDAI	24 (14.3)	27 (17)	ns	9.5 (9.5)	16.5 (20.7)	0.0035	8 (10)	15 (12)	0.006
SDAI	25.2 (16.7)	25 (17.2)	ns	11.3 (10.9)	16.7 (19.7)	0.0154	8.1 (10)	16.2 (12.1)	0.007

Figure 1. Disease activity indices at baseline, 4 and 12 weeks of treatment with Janus kinase inhibitors according to the achievement of Patients Acceptable Symptom State (PASS) at week 4. Patients are divided into two groups according to week 4 PASS achievement (PASS yes *versus* PASS no). All data are expressed as median (interquartile range). $DAS28_{CRP}$, C-reactive protein-based Disease Activity Score on 28 joints; CDAI, Clinical Disease Activity Index; SDAI, Simplified Disease Activity Index.

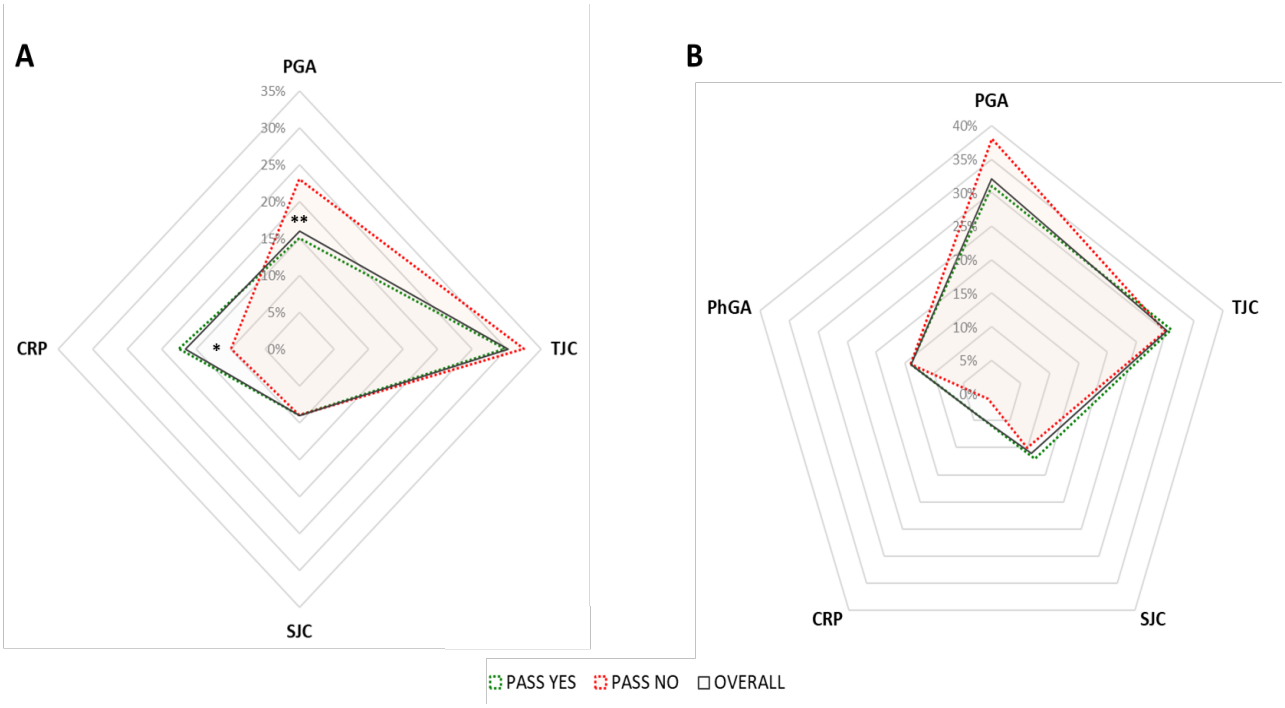


Figure 2. Contribution of each single item for the calculation of Disease Activity Score on 28 joints (A) and Simplified Disease Activity Index (B) in the overall population, Patients Acceptable Symptom State (PASS) achievers and PASS non-achievers at week 4. PGA, patient global assessment; TJC, tender joints count; SJC, swollen joint count; CRP, C-reactive protein; PhGA, physician global assessment. *p=0.02; **p=0.0008

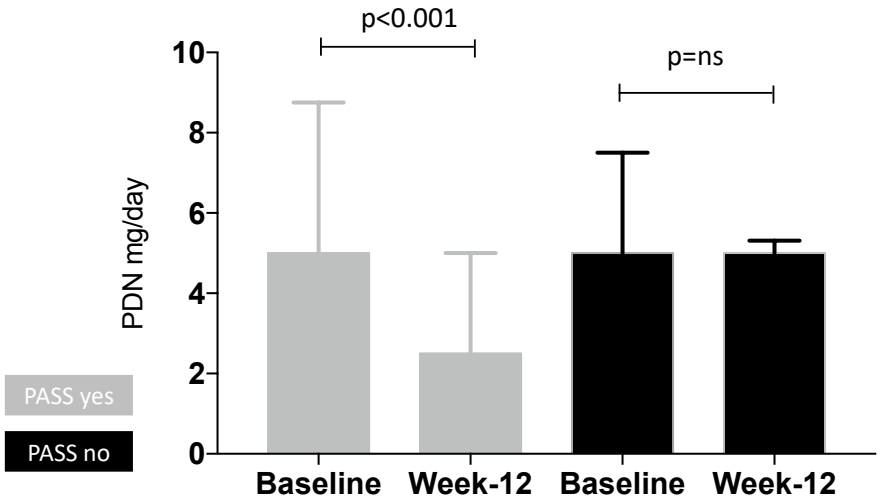


Figure 3. Glucocorticoid reduction after 12 weeks of treatment in Patients Acceptable Symptom State (PASS) achievers and PASS non-achievers. Patients are divided into two groups according to week 4 PASS achievement (PASS yes *versus* PASS no). All data are expressed as median (interquartile range). PDN, prednisone.