CLINICAL REPORT

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Validation of the Itch Severity Item as a Measurement Tool for Pruritus in Patients with Psoriasis: Results from a Phase 3 Tofacitinib Program

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Tofacitinib is an oral Janus kinase inhibitor. This _post-hoc_ analysis aimed to investigate the psychometric properties of the Itch Severity Item (ISI), a numeric rating scale from 0 (no itching) to 10 (worst possible itching) for pruritus in psoriasis, and review the effect of tofacitinib on pruritus in patients with psoriasis participating in Phase 3 studies ($N = 3,641$). The ISI showed high test–retest reliability (intra-class correlation coefficient: 0.84). The clinically important difference was defined as a 1.48-point change, using Patient Global Assessment as an anchor. Mean changes from baseline in ISI scores with tofacitinib were significantly greater than placebo by Day 2 and exceeded the clinically important difference by Week 4 and Week 2 for tofacitinib 5 and 10 mg twice daily, respectively. The sound psychometric properties of the ISI as an assessment tool for pruritus in psoriasis were confirmed. Tofacitinib provided clinically meaningful improvements in psoriatic pruritus versus placebo.

Key words: pruritus; psoriasis; tofacitinib; Itch Severity Item; clinically important difference; Patient Global Assessment.

Pruritus is a common symptom of psoriasis, affecting 64–97% of patients with psoriasis (1–5) and resulting in reduced health-related quality of life (HRQoL) (6). Pruritus has been rated as the most bothersome symptom for patients (7), and is more likely to result in reduced productivity or absence from work than other symptoms such as pain (8).

Despite the high prevalence and impact of pruritus, anti-pruritic therapies are generally ineffective (9, 10), and there is a paucity of clinically relevant data in relation to plaque psoriasis and the efficacy of treatments to relieve itch.

Tofacitinib is an oral Janus kinase inhibitor. The efficacy and safety of tofacitinib 5 and 10 mg twice daily (BID) in patients with moderate to severe chronic plaque psoriasis has been demonstrated in Phase 2 (11) and Phase 3 (12–15) trials of up to 56 weeks' duration, and in a long-term extension study with efficacy endpoints reported through

24 months and safety reported over 33 months of exposure (13). Co-primary efficacy endpoints of the Phase 2 and Phase 3 studies included the proportions of patients achieving a Physician's Global Assessment (PGA) of 'clear' or 'almost clear', and the proportions of patients achieving a reduction ≥75% in the Psoriasis Area and Severity Index (PASI75). The efficacy and safety of tofacitinib has also been studied in several immune-mediated inflammatory diseases, including rheumatoid arthritis (16–21), psoriatic arthritis (22–24), ankylosing spondylitis (25), Crohn's disease (26–28), and ulcerative colitis (29, 30). Moreover, the impact of tofacitinib on pruritus has previously been reported in Phase 2 studies of tofacitinib as a topical treatment for atopic dermatitis (31) and psoriasis (32), and Phase 2 and 3 studies of tofacitinib as an oral treatment for psoriasis (33–36).

Because patients with psoriasis experience reduced HRQoL (6), some generic instruments that assess life quality, irrespective of the illness or condition of the patient, may be useful in evaluating their wellbeing and functioning. Examples of generic questionnaires that capture various aspects of health status include the 5-level EuroQoL 5-dimension scale (EQ-5D-5L) (37) and the Medical Outcomes Study 36-item Short Form (SF-36) (38). On the other hand, disease-specific instruments have the advantage of being specifically tailored to measure the special or distinctive characteristics found in particular conditions or diseases. Examples of disease-specific instruments include the Dermatology Life Quality Index (DLQI) (39) and PASI (40), which are used to assess dermatology-related HRQoL and clinical outcomes in psoriasis. However, neither provide a direct measure of pruritus.

The Itch Severity Item (ISI) is an 11-point numeric rating scale (NRS) that was used to assess the severity of pruritus in the Phase 3 clinical trials of tofacitinib for the treatment of patients with moderate to severe chronic plaque psoriasis (34–36). Other Itch NRSs have been validated for use in patients with chronic pruritus (41) and patients with moderate to severe plaque psoriasis (42). An earlier version of the ISI has previously been validated as an assessment tool for pruritus in a Phase 2 study of oral tofacitinib in patients with psoriasis (43).

Here, we extend these previous analyses in Phase 2 studies and evaluate the psychometric properties of the

ISI as a simple measurement tool for pruritus in plaque psoriasis, and review the effects of tofacitinib on pruritus using a large, Phase 3 study population.

METHODS

Study design

This analysis included pooled data from 4 parallel-group Phase 3 randomized clinical trials (RCTs) of tofacitinib for the treatment of psoriasis: Oral-treatment Psoriasis Trial (OPT) Pivotal 1 (NCT01276639; $n = 901$; initial treatment period=16 weeks) (12); OPT Pivotal 2 (NCT01309737; $n = 960$; initial treatment period=16 weeks) (12); OPT Compare (NCT01241591; $n = 1,106$; initial treatment period=12 weeks) (14); and OPT Retreatment (NCT01186744; $n = 674$; initial treatment period [Period A]= 24 weeks) (15).

All of the studies were blinded and included tofacitinib 5 and 10 mg BID treatment groups. OPT Pivotal 1, OPT Pivotal 2, and OPT Compare included a placebo-control group, and OPT Compare also included etanercept 50 mg twice weekly (BIW) as an active comparator. The OPT Retreatment study did not have a placebo-control arm during the initial study period.

For this analysis, data for OPT Pivotal 1 and OPT Pivotal 2 were used from study visits conducted at Weeks 2, 4, 8, 12, and 16. Data for OPT Compare were from study visits at Weeks 2, 4, 8, and 12, and those for OPT Retreatment were from the initial treatment period at Weeks 4, 8, 16, and 24. Further details of the study designs and patient populations have been published previously (12, 14, 15).

The studies were conducted in accordance with the Declaration of Helsinki, the International Conference on Harmonisation Good Clinical Practice Guidelines, and the local country regulations. The study protocols were approved by the Institutional Review Board and the Independent Ethics Committee at each site. Patients provided written, informed consent prior to enrollment in the study.

Measurement of the Itch Severity Item

The ISI is a single-item, patient-reported horizontal NRS ranging from 0 ('no itching') to 10 ('worst possible itching'). The ISI assessed 'worst itching due to psoriasis over the past 24 hours' (**Fig. 1**).

Patients completed the ISI daily at the same time as they took their evening dose of medication for the first two weeks of treatment using a written patient diary (OPT Pivotal 1; OPT Pivotal 2; OPT Compare), and then at study visits (all studies).

Other clinical outcomes

Other assessments included PASI, PGA, DLQI, Patient Global Assessment (PtGA) of Psoriasis, SF-36, and patient satisfaction with study medication.

Statistical analysis

The test–retest reliability of the ISI was evaluated using intraclass correlation coefficients (ICC) based on all screening and

Select the number that best describes your **worst itching due to psoriasis** over the past 24 hours. (Check one number only)

| 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 |

No itching — Worst possible itching

Fig. 1. Itch Severity Item for assessing pruritus in patients with psoriasis.

baseline ISI scores (patients in OPT Pivotal 1, OPT Pivotal 2, and OPT Compare were required to complete the ISI daily starting one week before the baseline visit. Screening occurred within 2–4 weeks prior to the baseline visit in OPT Pivotal 1 and OPT Pivotal 2, and within 4 weeks prior to the baseline visit in OPT Compare and Retreatment). The calculation of the ICC, as with all psychometric analyses, included all treatment groups combined. The ICC was estimated based on the between-patient error variance and within-patient error variance. ICC values > 0.9 are considered excellent, whereas those between 0.7 and 0.9 are considered acceptable and those < 0.7 are inadequate (44).

Pearson's correlation coefficients (CC) were used to determine the relationship between pruritus and other clinical assessments for psoriasis (45). In this analysis, the Pearson CC were calculated between the ISI and the PASI, PGA, DLQI, PtGA, SF-36 physical and mental component summary scores (PCS and MCS), and patient satisfaction to evaluate the relationship between the ISI and other clinical or patient-reported outcomes.

The clinically important difference (CID) for the ISI was defined using a repeated-measures longitudinal model to estimate the relationship between the ISI score and the PtGA (43). The PtGA provides the patient's assessment of overall cutaneous disease. It has the following categories: 'severe' (4), 'moderate' (3), 'mild' (2), 'almost clear' (1), and 'clear' (no psoriasis; 0). The CID was calculated based on the difference in the least squares (LS) means between any two adjacent categories of the PtGA (e.g. from 'almost clear' to 'clear'). The model used restricted maximum likelihood estimation to predict LS means and *t*-tests to test their differences (44, 46). The CID for the pooled analysis was determined using data from the initial treatment period of OPT Retreatment and all available data from the other 3 studies.

When PtGA was used as a continuous anchor to calculate the CID, a linear relationship was imposed between ISI and PtGA. To assess the linearity assumption, PtGA was also used as a categorical anchor in sensitivity analyses and, as a result, no functional relationship was imposed between the ISI and PtGA in this analysis.

For each study, mean changes in ISI score throughout time within treatment groups were estimated for treatment comparison using a repeated-measures longitudinal model (44).

RESULTS

Test–retest reliability of the Itch Severity Item

The test–retest reliability for the ISI in OPT Pivotal 1 had the highest ICC (0.87); this was followed by OPT Pivotal 2 (0.86), OPT Compare (0.82), and OPT Retreatment (0.69). The test–retest reliability for the ISI using pooled data from all 4 studies resulted in an ICC of 0.84, indicating an overall high level of test–retest reliability.

Correlation of Itch Severity Item with other clinical study endpoints

Across all 4 Phase 3 RCTs, the ISI score significantly correlated with PASI (CC range: 0.56–0.61), PGA (0.52–0.61), DLQI (0.67–0.73), PtGA (0.61–0.68), and patient satisfaction (0.57–0.63) (all $p < 0.0001$) at the end of the initial treatment periods (**Table I**). Stronger correlations were reported at the end of the initial treatment periods compared with baseline, where pretreatment responses are expected to be homogeneous or similar. This was expected, given the more restricted range of scores at

Table I. Correlation between ISI score and other clinical study endpoints: PASI, PGA, DLQI, PtGA, SF-36 PCS and MCS, and patient satisfaction

	Time point	PASI CC (n)	PGA CC (n)	DLQI CC (n)	PtGA CC (n)	SF-36 PCS CC (n)	SF-36 MCS CC (n)	Patient satisfaction CC (n)
OPT Pivotal 1	Baseline	0.058 (847)	0.067 (847)	0.408 (846)***	0.322 (844)***	−0.238 (840)***	−0.219 (840)***	N/A
	Week 16	0.612 (797)***	0.612 (797)***	0.702 (789)***	0.659 (790)***	−0.351 (784)***	−0.309 (784)***	0.626 (787)***
OPT Pivotal 2	Baseline	0.120 (925)**	0.084 (925)*	0.448 (924)***	0.380 (924)***	−0.265 (922)***	−0.248 (922)***	N/A
	Week 16	0.580 (849)***	0.598 (849)***	0.673 (844)***	0.682 (842)***	−0.315 (837)***	−0.298 (837)***	0.574 (839)***
OPT Compare	Baseline	0.116 (1,065)**	0.136 (1,065)***	0.501 (1,060)***	0.327 (1,062)***	−0.329 (1,055)***	−0.326 (1,055)***	N/A
	Week 12	0.593 (1,025)***	0.562 (1,025)***	0.668 (1,010)***	0.605 (1,013)***	−0.393 (1,026)***	−0.357 (1,026)***	0.582 (1,012)***
OPT Retreatment	Baseline	0.107 (666)*	0.115 (666)*	0.517 (663)***	0.358 (665)***	−0.299 (664)***	−0.293 (664)***	N/A
	Week 24	0.563 (552)***	0.518 (551)***	0.734 (549)***	0.682 (549)***	−0.273 (548)***	−0.387 (548)***	N/A

*$p < 0.05$; **$p < 0.001$; ***$p < 0.0001$.
CC: correlation coefficient; DLQI: Dermatology Life Quality Index; ISI: Itch Severity Item; MCS: mental component summary; N/A: not applicable; OPT: Oral-treatment Psoriasis Trial; PASI: Psoriasis Area and Severity Index; PCS: physical component summary; PGA: Physician Global Assessment; PtGA: Patient Global Assessment; SF-36: Short Form-36.

baseline. The DLQI score was the most highly correlated with ISI. At the end of the initial treatment periods, the strength of the correlations between the ISI scores and SF-36 scores was consistently lower than that of other measures (Table I).

Clinically important difference for the Itch Severity Item

The estimated CID for the ISI, calculated using PtGA as a continuous anchor and the mean difference on ISI corresponding to a one-category difference on the PtGA, was 1.48 (95% confidence interval: 1.45, 1.51) (**Table II**). The estimated CIDs based on the individual studies were similar, justifying the pooling of data.

The sensitivity analysis, using pooled PtGA data from all 4 studies as a categorical predictor, showed an extremely close functional relationship to the results obtained using pooled PtGA data as a continuous predictor (**Fig. 2**), supporting the linearity assumption for the relationship between ISI and PtGA.

Clinically meaningful improvements in Itch Severity Item score with tofacitinib treatment

The efficacy of tofacitinib in reducing pruritus based on ISI score in patients with psoriasis has previously been reported (34–36). Placebo-adjusted mean decreases from baseline ISI scores surpassed the CID determined in this analysis (1.48), at ≤2 weeks with both tofacitinib doses in OPT Pivotal 1 (−1.48 at Day 13 and −1.55 at Day 6 for tofacitinib 5 and 10 mg BID, respectively), and with tofacitinib 10 mg BID in OPT Pivotal 2 (−1.56 at Day 11) and OPT Compare (−1.57 at Day 9), indicating clinically relevant improvements in pruritus with tofacitinib. The

Table II. Clinically important difference (CID) for the Itch Severity Item

Study	CID (95% CI)
Pooled	1.48 (1.45, 1.51)
OPT Pivotal 1	1.39 (1.35, 1.44)
OPT Pivotal 2	1.41 (1.37, 1.45)
OPT Compare	1.39 (1.32, 1.45)
OPT Retreatment	1.87 (1.80, 1.94)

CI: confidence interval; OPT: Oral-treatment Psoriasis Trial.

CID was surpassed at Week 4 with tofacitinib 5 mg BID in OPT Pivotal 2 and OPT Compare, as well as with etanercept 50 mg BIW in OPT Compare (placebo-adjusted LS mean changes from baseline in ISI: −1.94, −1.79, and −1.75, respectively). At the end of the initial treatment period, tofacitinib 5 and 10 mg BID achieved placebo-adjusted mean changes from baseline of −2.66 and −3.79, respectively, in OPT Pivotal 1; −2.89 and −3.50 in OPT Pivotal 2; and −2.66 and −3.42 in OPT Compare (all $p < 0.0001$ vs placebo). Changes from baseline in ISI did not surpass the CID in patients treated with placebo in any study.

OPT Retreatment did not include a placebo group during the initial treatment period; nevertheless, both tofacitinib doses showed improvement in ISI > 1.48 points by the first assessment at Week 4 (LS mean changes from baseline in ISI: −3.59 and −4.58 for tofacitinib 5 and 10 mg BID, respectively).

DISCUSSION

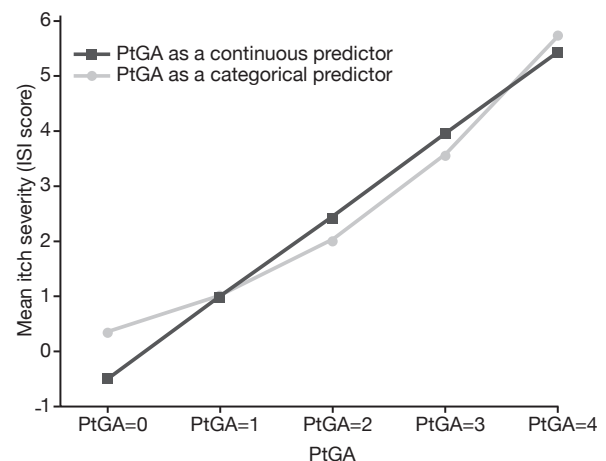The data reported here confirm the sound psychometric properties of the ISI. The test–retest reliability of the

Fig. 2. Sensitivity analysis[a] **in patients with psoriasis assessing the functional relationship between Itch Severity Item (ISI) and Patient Global Assessment (PtGA) as categorical or continuous variable.** [a]Using pooled ISI and PtGA data from OPT Pivotal 1, OPT Pivotal 2, OPT Compare, and OPT Retreatment.

daily ISI measurements ranged from 0.87 (OPT Pivotal 1) to 0.69 (OPT Retreatment) across the 4 Phase 3 studies. Although the ICC of 0.69 in OPT Retreatment was estimated to be less than 0.70, the difference is minimal when natural sampling error is considered. More important is the reason for the relatively lower ICC in OPT Retreatment: relative to the other 3 studies, this study had smaller estimated between-subject variability (the ICC is the ratio of between-subject variability to total variability), as patients gave more similar responses in their ISI scores owing presumably to the more homogeneous eligibility criteria in the study. Overall, the test–retest reliability of the daily ISI measurements was acceptable with a pooled ICC value of 0.84. This was slightly higher than the ICCs reported for another Itch NRS (0.71–0.74) (42), indicating higher reproducibility.

The ISI significantly correlated with other clinical and patient-reported outcomes, such as PASI, PGA, DLQI, PtGA, and patient satisfaction. The DLQI, which is specific to skin conditions, demonstrated the highest correlation with the ISI, whereas the generic SF-36 PCS and MCS scores showed the lowest correlations. This is likely because the SF-36 is a general measure of health status that is not as sensitive to the severity of itch as psoriasis-specific measures such as PASI and DLQI. The ISI showed similar responsiveness to clinician-reported outcomes such as PASI and PGA (CC: 0.52–0.61) as the previously reported Itch NRS (0.52–0.79); however, it is less responsive than the Itch NRS to changes in PtGA (0.61–0.68 vs 0.80–0.87) (42).

The CID estimate of 1.48 reported in this analysis using data from 4 Phase 3 RCTs was consistent with the CID estimate of 1.64 reported in a previous Phase 2 RCT (43). Both of these CID estimates are slightly lower than the CID reported by Reich et al. in Polish (2.7 ± 1.7 points) and German patients (2.7 ± 1.8 points) with chronic pruritus (47), and the CID estimated by Kimball et al. for the Itch NRS in patients with psoriasis (≥4-point change) (42). However, it should be noted that the methodologies for defining CID in these studies were significantly different from the methodology used in this analysis. In the Reich et al. study, the value of 2.7 points for the CID was estimated as the mean change one week apart on an 11-point numeric rating scale from 0 (no itch) to 10 points (worst imaginable itch) among subjects with a one-category improvement on a 4-category anchor on itch (0, no itch; 1, mild itch; 2, moderate itch; 3, severe itch) (47). This anchor, therefore, was essentially measuring the same concept of measurement (itch severity) one week apart, while our anchor measured overall cutaneous disease up to 24 weeks, which could have accounted for the difference in CID values between their study and ours. Kimball et al. used clinical improvements (vs no such improvement) as the anchor, based on physician's assessment of the patient's overall severity of disease based on plaque elevation, scaling, and erythema

(0 = clear to 5 = very severe), to estimate the CID as a 4-point reduction on the 11-point numeric rating scale from 0 ('no itching') to 10 ('worst imaginable itch') over 12 weeks of treatment (42). The anchor and the methodology used, therefore, were different from ours.

In our analysis, PtGA was chosen as the pre-specified anchor for three reasons: 1) the PtGA is a patient-reported outcome, the same as the ISI; 2) the PtGA is easy to understand and interpret with discrete responses; and 3) the PtGA was expected to show an appreciable correlation with ISI, which was confirmed in this analysis. While the PASI was expected to show an appreciable correlation with ISI, it is less easily interpreted than the PtGA and is not a patient-reported outcome. We favored a like-with-like comparison in linking the patient-reported ISI with the patient-reported PtGA. Our methodology to establish the CID of the ISI, which was based on the difference in means on ISI scores between any two adjacent categories of the PtGA (anchor) from a repeated-measures longitudinal model, incorporates all available data throughout the study (not just at two time points) to estimate the CID. In the primary analysis, the anchor PtGA was taken as a continuous predictor that reflects patient's assessment of overall cutaneous disease as an underlying continuum, along the entire continuum from 0 to 4 (not just at discrete levels). The repeated-measures longitudinal model employed also accounts for differences between studies and the correlated responses coming from the same individual over time, inspects the functional form of the relationship between the anchor (PtGA) and the outcome (ISI) (by taking PtGA as a categorical predictor, rather than as a continuous predictor, in a sensitivity analysis), and calibrates for measurement error by subtracting mean scores on the outcome between two adjacent categories on the anchor.

In addition to the psychometric validation evidence presented here, a number of factors support the continued use of the ISI as a measure of pruritus in clinical studies. The ISI was developed as an NRS, and it has been found that there are fewer missing data in the paper-based NRS compared with the visual analog scale (VAS) (41). The use of the NRS, as well as VAS, is recommended by the International Forum for the Study of Itch (48). Furthermore, the Itch NRS has been validated in patients with moderate to severe plaque psoriasis (42).

Based on assessment with the ISI, tofacitinib resulted in clinically meaningful improvements in pruritus in patients with psoriasis in Phase 3 studies (34–36). The placebo-adjusted change from baseline in ISI surpassed the CID after < 2 weeks of treatment with tofacitinib 10 mg BID and ≤ 4 weeks with tofacitinib 5 mg BID. Tofacitinib also produced a more rapid reduction in pruritus compared with etanercept. Furthermore, although, with the exception of etanercept, head-to-head studies are not available to make direct comparisons, tofacitinib appears to have particularly rapid action in relieving

pruritus symptoms compared with some biologic treatments and the phosphodiesterase 4 inhibitor apremilast (49, 50), and similar action to the Janus kinase inhibitor baricitinib (51).

A limitation of the study was that the focus was on the effect of oral tofacitinib on pruritus in patients with psoriasis; however, topical tofacitinib has also been shown to reduce pruritus in psoriasis (32). An additional limitation is that OPT Retreatment did not have a placebo group in the initial treatment period with which to compare the effects of the tofacitinib treatment in this analysis. However, a later phase of OPT Retreatment was placebo-controlled, and an increase in ISI was reported in patients who were re-randomized to placebo from tofacitinib (34). It has previously been reported that treatment with placebo can significantly reduce pruritus in patients with a variety of skin conditions (52). Nevertheless, despite the lack of a placebo-control arm in OPT Retreatment, the results were consistent with the other three studies, and the improvement from baseline in ISI surpassed the CID. The lack of an active comparator in OPT Pivotal 1, OPT Pivotal 2, and OPT Retreatment is also a limitation; however, it is evident from the results of these studies that tofacitinib results in clinically meaningful improvements in pruritus in patients with psoriasis.

In conclusion, we have confirmed the sound psychometric properties of the ISI, and demonstrated that the ISI is a useful tool to assess pruritus in psoriasis. The use of the ISI in Phase 3 RCTs revealed the clinically meaningful impact of tofacitinib in the treatment of pruritus in patients with psoriasis.

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