Dermatol Ther (Heidelb) (2017) 7:243–248
DOI 10.1007/s13555-017-0181-6

BRIEF REPORT

Dupilumab Improves General Health-Related Quality-of-Life in Patients with Moderate-to-Severe Atopic Dermatitis: Pooled Results from Two Randomized, Controlled Phase 3 Clinical Trials

Eric L. Simpson

Received: February 14, 2017 / Published online: May 13, 2017

ABSTRACT

Introduction: Patients with moderate-to-severe atopic dermatitis (AD) report a multidimensional disease burden that includes impaired health-related quality-of-life (HRQoL). Changes in overall health status and specific dimensions that contribute to HRQoL were evaluated in adults with moderate-to-severe AD who participated in phase 3 clinical trials of dupilumab, which is a fully human monoclonal antibody that inhibits signaling of cytokines IL-4 and IL-13.

Methods: Two dupilumab phase 3 clinical trials of identical design included the 5-dimension 3-level EuroQol (EQ-5D) as a measure of HRQoL. EQ-5D data from the two trials were pooled in an analysis that, using analysis of covariance, compared subcutaneous dupilumab 300 mg once weekly (qw) or every 2 weeks (q2w) versus placebo for EQ-5D utility score change from baseline overall and for clinical responders. The proportions of patients who reported different levels of problems on the individual dimension of the EQ-5D were also compared by treatment group.

Results: Patients ($n = 1379$) were 57.9% male with a mean (SD) age of 38.3 (14.3) years; baseline EQ-5D utility scores ranged from 0.611 to 0.629 across treatment groups. EQ-5D least squares mean change from baseline at week 16 was 0.031 with placebo, and was significantly greater with dupilumab qw (0.207) and q2w (0.210) (both $P < 0.0001$), which exceeded the minimal clinically important difference and resulted in scores that approached population norms. Changes from baseline among patients who achieved AD clinical response were greater than changes among the total population. Improvements were driven by the individual EQ-5D dimensions with the greatest burden at baseline (i.e., pain/discomfort, anxiety/depression and usual activities).

Conclusion: In adults with moderate-to-severe AD, dupilumab resulted in improvements in HRQoL that were statistically significant relative to placebo and were clinically meaningful.

Funding: Sanofi and Regeneron Pharmaceuticals, Inc.

Trial registration: ClinicalTrials.gov identifiers, NCT02277743 and NCT02277769, EudraCT Numbers 2014-001198-15 and 2014-002619-40.

Keywords: Atopic dermatitis; Dupilumab; EQ-5D; Health-related quality-of-life; Minimal clinically important difference; Treatment responders; Utility scores

Enhanced content To view enhanced content for this article go to http://www.medengine.com/Redeem/9C18F060292A40A9.

E. L. Simpson (✉)
Department of Dermatology, Oregon Health and Science University, Portland, OR, USA
e-mail: simpsone@ohsu.edu

INTRODUCTION

Atopic dermatitis (AD), a chronic immune-mediated disease characterized by intense pruritus, is associated with debilitating effects on patients' lives. Patients with moderate-to-severe AD report a multidimensional burden including itch, pain, sleep disturbance, anxiety and depression, and impaired health-related quality-of-life (HRQoL) [1].

Dupilumab is a fully human monoclonal antibody that targets the interleukin (IL)-4 receptor-alpha subunit and inhibits signaling of cytokines IL-4 and IL-13, both of which drive, at least in part, atopic diseases including AD [2]. The efficacy and safety of dupilumab was evaluated in two phase 3 clinical trials in adults with moderate-to-severe AD whose disease was inadequately controlled by topical treatment, SOLO 1 and SOLO 2 (ClinicalTrials.gov Number, NCT02277743 and NCT02277769, respectively) [3]. Published results from both trials consistently showed that, compared with placebo, subcutaneous dupilumab 300 mg once weekly (qw) or every 2 weeks (q2w) significantly improved objective signs and symptoms of AD including pruritus, symptoms of anxiety and depression, and HRQoL assessed using a dermatology-specific measure [3].

This analysis further expands on the effects of dupilumab on HRQoL by using the 5-dimension 3-level EuroQoL (EQ-5D) [4], which was included in SOLO 1 and SOLO 2, to evaluate changes in overall health status and specific dimensions that contribute to HRQoL.

METHODS

The EQ-5D describes health states through the generation of a utility score based on levels of impairment on 5 dimensions; utility scores represent health states anchored at perfect health (=1) and death (=0), although states lower than 0 are attainable. Since trial designs were identical [3], we report EQ-5D results from both trials in a pooled analysis using censoring after rescue and last-observation-carried-forward. Protocols for both trials were approved by the appropriate institutional review boards/ethics committees at each study site, and all patients provided written informed consent prior to study participation.

Treatments were compared overall and for clinical responders using analysis of covariance (ANCOVA) with baseline as covariate and treatment, region, and baseline Investigator's Global Assessment (IGA) strata as fixed factors; a study identifier was included as an additional factor for the pooled analysis. Changes from baseline in EQ-5D scores are presented as least squares means, i.e., results from the ANCOVA model that adjusted for the covariate. Clinical responders were defined as patients who achieved at week 16: IGA score of 0 or 1 (clear or almost clear) *and* a reduction from baseline $\geq$2 points (primary study endpoint), and improvements in the Eczema Area and Severity Index (EASI) [5] $\geq$50% and $\geq$75%; EASI $\geq$75% response was the key secondary endpoint.

The proportions of patients who reported the different levels of problems on the individual dimension of the EQ-5D were also compared by treatment group using Fisher's exact test.

RESULTS

Patients ($n = 1379$) were 57.9% male with a mean (SD) age of 38.3 (14.3) years. Baseline EQ-5D utility scores ranged from 0.611 to 0.629 across treatment groups (Table 1). These scores indicated impaired HRQoL, which was slightly worse than the HRQoL reported for moderate-to-severe psoriasis (0.642) [6], as well as the general population norms for the UK (0.856) and US (0.867) [7]. Patients treated with dupilumab at both dosing regimens reported significant improvements in HRQoL by week 16 as indicated by increases in EQ-5D utility scores (Table 1). These increases resulted in scores that approached population norms [4]; were in the same range as that of biologic agents for psoriasis with the strongest effects on EQ-5D [8]; and were clinically meaningful, as they exceeded the reported minimal clinically important difference of 0.082 [9].

Changes from baseline were also clinically meaningful when analyzed by response levels

Table 1 Change from baseline in EQ-5D utility scores at week 16, with censoring after rescue treatment and last-observation-carried-forward for imputation of missing data (full analysis set)

	Placebo qw, *n* = 460	Dupilumab 300 mg qw, *n* = 462	Dupilumab 300 mg q2w, *n* = 457
All patients			
Baseline, mean (SD)	0.611 (0.340)	0.607 (0.338)	0.629 (0.319)
LS mean change (SE)	0.031 (0.012)	0.207 (0.012)	0.210 (0.012)
P vs. placebo[a]	–	<0.0001	<0.0001
Responders[b]			
IGA, *n* (%)	43 (9.3)	169 (36.6)[c]	170 (37.2)[c]
Baseline, mean (SD)	0.746 (0.33)	0.664 (0.30)	0.668 (0.30)
LS mean change (SE)	0.192 (0.02)	0.261 (0.01)	0.238 (0.01)
P vs. placebo[a]	–	0.2951	0.8232
EASI ≥50%, *n* (%)	107 (23.3)	282 (61.0)[c]	306 (67.0)[c]
Baseline, mean (SD)	0.693 (0.334)	0.636 (0.314)	0.627 (0.325)
LS mean change (SE)	0.189 (0.016)	0.255 (0.010)	0.253 (0.010)
P vs. placebo[a]	–	0.0003	0.0004
EASI ≥75%, *n* (%)	61 (13.3)	232 (50.2)[c]	218 (47.7)[c]
Baseline, mean (SD)	0.712 (0.347)	0.629 (0.314)	0.631 (0.327)
LS mean change (SE)	0.251 (0.020)	0.262 (0.010)	0.257 (0.011)
P vs. placebo[a]	–	0.6089	0.7825

EASI Eczema Area and Severity Index, *EQ-5D* 5-dimension 3-level EuroQol, *IGA* Investigator's Global Assessment, *LS* least squares, *qw* once weekly, *q2w* every 2 weeks

[a] Treatments were compared using analysis of covariance with baseline as covariate and treatment, region, and baseline IGA strata as fixed factors; a study identifier was included as an additional factor for the pooled analysis

[b] Responders were defined as patients who achieved at week 16 an IGA score of 0 or 1 (clear or almost clear) *and* a reduction from baseline ≥2 points; and improvements ≥50% and ≥75% in the EASI

[c] $P < 0.001$ vs. placebo for proportion of responders

(Table 1), showing that IGA and EASI responders have a clinically meaningful change in utility scores, suggesting that improvements in utility scores are likely associated with clinical response. This relationship between clinical improvement and change in utility scores is further supported by the observation that changes in utility scores among dupilumab responders were consistently higher than the overall mean changes in utility scores with dupilumab. It should also be noted that, since clinical responders are defined by the response criteria regardless of treatment allocation, it is not surprising that placebo IGA and EASI responders had meaningful changes in EQ-5D. Improvements in HRQoL in these patients would also be expected to be driven by the clinical improvements in AD. This was evidenced by similar changes in EQ-5D utility scores for the placebo and dupilumab IGA and EASI 75% responders, even though the proportions of responders were significantly higher with dupilumab (Table 2).

At baseline, patients reported large burdens on the individual EQ-5D dimensions of pain/discomfort, anxiety/depression and

Table 2 Patients who reported at least some problems on individual EQ-5D dimensions at baseline and 16 weeks

EQ-5D dimension	Number (%) of patients					
	Placebo qw		Dupilumab 300 mg qw		Dupilumab 300 mg q2w	
	Baseline, $n = 459$	Week 16, $n = 423$	Baseline, $n = 462$	Week 16, $n = 431$	Baseline, $n = 457$	Week 16, $n = 440$
Mobility						
No problems	380 (82.8)	364 (86.1)	364 (79.0)	406 (94.2)[a]	367 (80.3)	407 (92.5)[b]
Some problems	75 (16.3)	58 (13.7)	92 (20.0)	25 (5.8)[a]	87 (19.0)	33 (7.5)[b]
Confined to bed	4 (0.9)	1 (0.2)	5 (1.1)	0	3 (0.7)	0
Self-care						
No problems	389 (84.7)	374 (88.4)	399 (86.6)	415 (96.3)[a]	386 (84.5)	417 (94.8)[c]
Some problems	70 (15.3)	49 (11.6)	60 (13.0)	16 (3.7)[a]	69 (15.1)	22 (5.0)[c]
Unable to do	0	0	2 (0.4)	0	2 (0.4)	1 (0.2)
Usual activities						
No problems	245 (53.4)	294 (69.5)	247 (53.6)	370 (85.8)[a]	268 (58.6)	374 (85.0)[a]
Some problems	191 (41.6)	119 (28.1)	192 (41.6)	58 (13.5)[a]	171 (37.4)	64 (14.5)[a]
Unable to do	23 (5.0)	10 (2.4)	22 (4.8)	3 (0.7)	18 (3.9)	2 (0.5)[b]
Pain/discomfort						
No problems	97 (21.1)	166 (39.2)	84 (18.2)	268 (62.2)[a]	87 (19.0)	273 (62.0)[a]
Some problems	254 (55.3)	225 (53.2)	274 (59.4)	156 (36.2)[a]	283 (61.9)	163 (37.0)[a]
Extreme pain/discomfort	108 (23.5)	32 (7.6)	103 (22.3)	7 (1.6)[a]	87 (19.0)	4 (0.9)[a]
Anxiety/depression						
No problems	231 (50.3)	273 (64.5)	227 (49.2)	316 (73.3)[b]	236 (51.6)	329 (74.8)[b]
Some problems	194 (42.3)	131 (31.0)	201 (43.6)	110 (25.5)	193 (42.2)	107 (24.3)[b]
Extremely anxious or depressed	34 (7.4)	19 (4.5)	33 (7.2)	5 (1.2)[a]	28 (6.1)	4 (0.9)[b]

EQ-5D 5-dimension 3-level EuroQol, *qw* once weekly, *q2w* every 2 weeks
[a] $P \leq 0.0001$, [b] $P < 0.05$, and [c] $P < 0.001$ vs. placebo at 16 weeks using Fisher's exact test

usual activities as indicated by substantial proportions of patients with "problems" (Table 2). Improvements in the EQ-5D at week 16 were primarily driven by increased proportions of patients reporting "no problems" in these three dimensions with dupilumab qw (62.2–85.8%) and q2w (62.0–85.0%) relative to placebo (39.2–69.5%; all $P < 0.05$) (Table 2).

CONCLUSIONS

These results show that patients with moderate-to-severe AD have substantially impaired HRQoL, and that dupilumab treatment results in improvements in not just skin-specific but also general HRQoL that are statistically significant relative to placebo and are clinically meaningful. A limitation is that, in order to

quantify general health, the EQ-5D simplifies it into 5 dimensions. However, the advantage of assessing general health using the EQ-5D is that it allows comparison of disease burden and the impact of treatment on general health across diseases.

ACKNOWLEDGEMENTS

The study and article processing charges were funded by Sanofi and Regeneron Pharmaceuticals, Inc. The author would like to thank Abhijit Gadkari and Andreas Kuznik of Regeneron Pharmaceuticals, Inc. and Laurent Eckert and Gaëlle Bégo-Le Bagousse of Sanofi for their review and comments on this article. Medical writing support was provided by E. Jay Bienen, funded by Sanofi and Regeneron Pharmaceuticals, Inc. The author meets the International Committee of Medical Journal Editors (ICMJE) criteria for authorship for this manuscript, takes responsibility for the integrity of the work as a whole, and has given final approval for the version to be published. In addition, the author is responsible for all content and editorial decisions and received no honoraria related to the development of this publication. The author had full access to all the data in this study and takes complete responsibility for the integrity of the data and accuracy of the data analysis.

Disclosures. Dr Simpson's institution has received grants/research funding from Amgen, Inc., Anacor Pharmaceuticals Inc., Celgene Corporation, Chugai Pharma USA, LLC, Eli Lilly and Company, Galderma Research and Development, Genentech Inc., MedImmune LLC, Novartis Pharmaceuticals Corporation, Pfizer Inc., Regeneron Pharmaceuticals, Inc., Sanofi, Tioga Pharmaceuticals Inc., and is a consultant for Regeneron Pharmaceuticals, Inc., Sanofi, Anacor, Celgene Corporation, Galderma Research and Development, Genentech, MedImmune LLC, Pfizer Inc., Abbvie, Dermira, and Valeant.

Compliance with Ethics Guidelines. The protocols were approved by the appropriate institutional review boards/ethics committees at each study site. All patients provided written informed consent.

REFERENCES

1. Simpson EL, Bieber T, Eckert L, Wu R, Ardeleanu M, Graham N, et al. Patient burden of moderate-to-severe atopic dermatitis: insights from a phase 2b clinical trial of dupilumab in adults. J Am Acad Dermatol. 2016;74(3):491–8.

2. Gandhi NA, Bennett BL, Graham NM, Pirozzi G, Stahl N, Yancopoulos GD. Targeting key proximal drivers of type 2 inflammation in disease. Nat Rev Drug Discov. 2016;15(1):35–50.

3. Simpson EL, Bieber T, Guttman-Yassky E, Beck LA, Blauvelt A, Cork MJ, et al. Two phase 3 trials of dupilumab versus placebo in atopic dermatitis. N Engl J Med. 2016;375(24):2335–48.

4. Szende A, Janssen B, Cabases J, editors. Self-reported Population Health: An International Perspective Based on EQ-5D. Dordrecht: Springer; 2014.

5. Hanifin JM, Thurston M, Omoto M, Cherill R, Tofte SJ, Graeber M. The eczema area and severity index (EASI): assessment of reliability in atopic dermatitis. EASI Evaluator Group. Exp Dermatol. 2001;10(1):11–8.

6. National Institute for Health and Care Excellence. Secukinumab for treating moderate to severe plaque psoriasis. Technology appraisal guidance. 2015. https://www.nice.org.uk/guidance/ta350/resources/secukinumab-for-treating-moderate-to-severe-plaque-psoriasis-82602661589701. Accessed 13 Nov 2016.

7. Szende A, Janssen B. Population Norms for the EQ-5D. In: Cabases JM, Szende A, Janssen B, editors. Self-reported Population Health: an International Perspective Based on EQ-5D. Dordrecht: Springer; 2014. p. 19–30.

8. Institute for Clinical and Economic Review. Targeted Immunomodulators for the Treatment of Moderate-to-Severe Plaque Psoriasis: Effectiveness and Value. Evidence Report, November 4, 2016. https://icer-review.org/wp-content/uploads/2016/08/NE_CEPAC_Psoriasis_Evidence_Report_FINAL_110416.pdf. Accessed 22 Nov 2016.

9. Luo N, Johnson J, Coons SJ. Using instrument-defined health state transitions to estimate minimally important differences for four preference-based health-related quality of life instruments. Med Care. 2010;48(4):365–71.