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A Multiple-Domain Framework Of Clinical, Economic, And Patient-Reported Outcomes For Evaluating Benefits Of Intervention In Atopic Dermatitis

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Running Head:

Multiple-Domain Framework of Clinical, Economic and Patient Outcomes for Evaluating AD Intervention

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Abstract

Atopic dermatitis (AD) increases health care utilization, affects patient quality of life, places a burden on caregivers, decreases patient/parent productivity, and adds to health care costs. Few studies have examined the effect of specific treatment modalities across a variety of AD-related outcomes. This prospective, multi-center, open-label longitudinal study of adult and pediatric patients with moderate-to-severe disease was conducted to evaluate the effect of a specific therapeutic intervention on AD-related outcomes over six months. Surveys collected physician clinical assessments and patient- and caregiver-reported data across the following domains: clinical outcome, health care utilization/costs, quality of life, physical appearance, productivity/absenteeism, and medication compliance. This study is intended to help guide future research efforts on the net costs and benefits of different interventions across a diverse set of domains and in larger populations.

Background

Atopic dermatitis (AD) is a common disease, especially among children.^{1,2} Several studies have demonstrated that the economic burden of illness is substantial and similar to other chronic medical conditions such as emphysema, epilepsy, and psoriasis.^{3,4,5,6,7,8}

Evaluations of the burden of illness associated with AD should include both: (1) direct treatment and management costs; and (2) indirect costs in terms of productivity loss and quality-of-life impact for both patients and caregivers.^{9,10,11,12,13,14,15,16,17,18,19,20} A recent study assessed AD in terms of total burden of illness and its effect on quality of life, and demonstrated substantial costs for special household items and days lost from work.²¹

Most studies published to date on the total burden of illness of AD have been observational in nature.^{3,6} In both retrospective and prospective studies, economic and burden-of-illness data were based on medical care prescribed by patients' providers.

In this study, our objective was to determine the feasibility of a multidimensional study framework to evaluate the impact on the social and financial burden of illness of a specific intervention. We chose to include patient-reported outcomes (physician visits, quality of life, out-of-pocket costs, productivity, compliance), in addition to clinical assessments (Table 1). We examined the effects of a topical non-steroidal immunomodulator, monotherapy ointment: tacrolimus (Protopic ointment, Astellas Pharma, Deerfield, IL), on patients with moderate-to-severe AD^{22,23,24,25,26} as the primary therapeutic intervention. We explored various outcomes (including patient- and caregiver-reported outcomes) associated with tacrolimus ointment alongside other over-the-counter and non-prescription medications beyond traditional efficacy endpoints.

Methods

Study Design and Treatment

The Treatment, Resources, and Impact of Atopic Dermatitis (TRIAD) study was designed as a six-month, open-label, non-comparative, multi-center study for the treatment of moderate-to-severe AD with tacrolimus ointment. Adult and pediatric patients were prescribed 0.1% and 0.03% topical tacrolimus ointments, respectively.

The study compared clinical, economic, and quality-of-life variables prior to treatment with tacrolimus ointment to outcomes after six months of treatment. Tacrolimus ointment was used in accordance with the physician's instructions. Treatment could be adjusted or discontinued at the physician's discretion. Patients could discontinue participation in the study prior to completing six months of treatment, but were asked to complete an end-of-study assessment.

While enrolled in the study, patients were not permitted to use topical steroids or other topical immunomodulators. Patients were permitted to continue prior medications (prescription and/or non-prescription) and treatments to care for their AD. Selected treatments used by patients with investigator approval included emollients, antihistamines, medicated baths, and herbal remedies. There was no use of cyclosporine or UV therapy, and only one patient used oral corticosteroids (prednisone for asthma exacerbation for one week). Study protocols were approved by each center's institutional review boards.

Patient Selection

Adult and pediatric (ages 5 to 16 years) patients were eligible to participate. Patients must have been diagnosed with moderate-to-severe AD using Rajka and Langeland criteria involving at least 10% of body surface area.²⁷

Patients were excluded from the study if they had clinically infected AD prior to treatment with tacrolimus ointment, had a systemic disease contraindicated for the use of tacrolimus ointment, or had other chronic conditions (e.g., cystic fibrosis) which would require intensive management during the study period. Patients could not have been treated with tacrolimus ointment in the four weeks prior to study enrollment or other systemic immunomodulator agents in the four months prior to study enrollment. In addition, treatment with systemic immunomodulator agents was not allowed while the patient was on study.

Disease Assessment

BSA. Physicians used a methodology consistent with “rule of nines” to estimate Body Surface Area (BSA). The physician estimated the percentage of BSA affected in each of four body regions: head and neck (H), upper extremities (UL), trunk and groin (T), and lower extremities (LL); and multiplied each by a body proportion factor. In patients greater than 7 years, these were 10% (H), 20% (UL), 30% (T), and 40% (LL). In pediatric patients between 5 and 6 years, the factors were 20% (H), 20% (UL), 30% (T), and 30% (LL).

EASI. The Eczema Area and Severity Index (EASI) is a well-validated, comprehensive instrument for measuring the extent and severity of AD across objective parameters.²⁸ A composite EASI score is obtained by tabulating the severity of erythema, induration/papulation/edema, excoriations, and lichenification on a 4-point scale (none, mild, moderate, severe) in each of the four body regions, multiplying each first by the percentage of area involved on a 7-point scale (0%, 1%-9%, 10%-29%, 30%-49%, 50%-69%, 70%-89%, 90%-100%) and then multiplying by weight body proportion factors identical to BSA calculations, before taking the sum.

Clinical Evaluations

Prior to initiation of the study, consent forms were completed and signed by the patients and/or the parents/guardians and returned to the study coordinator. The following baseline clinical evaluations were completed prior to study enrollment:

- Demographic and medical/AD history
- Brief physical exam including height, weight, and vital signs
- Verification of inclusion/exclusion criteria
- Confirmation of diagnosis of AD per Hanifin/Rajka criteria²⁹
- Assessment of extent and severity of AD using the EASI
- Assessment of BSA involvement and body regions affected by AD
- Assessment of individual signs of AD
- Recording of medications taken within the last four weeks

Additional clinical BSA and EASI assessments were performed during study visits scheduled at Months 1, 3, and 6/End of Study.

Resource and Burden-of-Illness Evaluations

Additional questionnaires were administered to the patients/parents/caregivers at baseline and on a monthly basis to assess non-clinical outcomes. All non-clinical evaluations were self-reported. Most questions asked patients to recall AD-related experiences over the past one to four weeks before study evaluations. Patients/parents/caregivers were provided with diaries to assist in recalling events between evaluation periods. These questionnaires were used to capture information regarding health care utilization, out-of-pocket health care costs, quality of life, physical appearance, productivity/absenteeism, and medication compliance.

Patients were asked to report their out-of-pocket health care costs net of insurance co-payments and deductibles. Patients were instructed to include out-of-pocket costs associated with tacrolimus ointment therapy, irrespective of how they acquired the drug and cost-sharing arrangements with third-party payers. Total health care expenditures from the perspective of patients' insurers were not captured.

Previously validated instruments were used whenever possible. Patient quality of life was assessed using both general (Short Form 12 [SF-12])³⁰ and dermatology-specific (Dermatology Life Quality Index (DLQI) or Children's Dermatology Life Quality Index [CDLQI]) instruments.^{31,32,33,34,35} For pediatric patients, additional questions were added to address the burden of AD on parents and caregivers.^{8,11,19} Patient perception of appearance was measured using the Bergner Physical Appearance scale.³⁶ The Bergner scale was used for children as well, though it has not yet been validated in the pediatric population. Responses related to number of health care encounters and absenteeism were recorded as continuous variables and converted to categorical variables for analytic purposes. Responses to other questions (for example, difficulty complying with medication regimens) were recorded on a Likert scale.

Data Analysis

We performed comparisons of patient outcomes from Baseline to assessments at: (1) Month 1; and (2) Month 6 or the End of Study. Whenever appropriate, data on adult and pediatric patients were analyzed together. Quality-of-life data for adult and pediatric patients were analyzed separately. All analyses were performed using SPSS Base 11.0. Statistical tests were performed using Student's or paired samples t-tests for continuous variables, and chi-square or Fischer's exact tests for categorical variables. A two-sided p-value of <0.05 was considered to be statistically significant.

A common phenomenon in longitudinal studies is patient dropout. Dropouts can occur due to lack of efficacy or adverse events. In other cases, patients may drop out of research studies if they experience marked improvement in their disease. The cause for dropout was obtained in every instance; however, end-of-study evaluations could not be performed on any dropouts. To adjust for patients from the study when end-of-study evaluations were not

performed, we employed the last observation carried forward (LOCF) methodology to analyze data only for individuals who completed an end-of-study clinical assessment.³⁷

Results

Number of Study Sites and Patient Enrollment

Five investigational sites from around the country enrolled a total of 48 patients. Data were collected from January 2002 through June 2003. Of the 48 patients enrolled, 40 completed a Month 1 evaluation, and 32 completed a Month 6/end-of-study evaluation. The eight patients who did not continue the study beyond the Baseline evaluation were not evaluable, so they were excluded from the data analysis. Of the 40 evaluable patients, seven patients dropped out of the study and did not complete a Month 6/end-of-study evaluation. These seven dropouts are conditionally included in the analyses as detailed below.

Of the 40 patients who enrolled and were evaluated at Month 1, 18 were adult and 22 were pediatric. The mean age was 23.76 years, 67.5% were female, 52.5% were Caucasian, and 72.5% had moderate AD (Table 2). The seven patients who dropped out before completing Month 6 evaluations had a mean age of 18.81, 71.4% were female, 42.9% were Caucasian, and 85.7% had moderate AD.

Of the seven patients who dropped out without completing a Month 6/end-of-study evaluation, only one patient dropped out due to an adverse event (discomfort at the application site). The remaining six patients dropped out because their disease had improved markedly and they did not feel a need to continue with study visits and to complete the instruments.

The disease extent and severity of the dropout group were different compared to the group that remained in the study after completing their Month 1 evaluations. Most noticeably, dropout patients had significantly less severe disease at Baseline (BSA 17.4% versus 27.1% respectively, $p=0.252$; EASI 6.6 for dropouts versus 11.5 for continuers, difference=4.83, CI -0.52 to 10.17, $p=0.075$).

Clinical Evaluations

At Baseline, patients (n=40) had a mean BSA affected of 25.4% and a mean EASI score of 10.6 (Table 3). At Month 1, the BSA affected was reduced to 17.0% and EASI was 6.6 (difference=4.01, CI 2.76 to 5.26, $p<0.001$). For patients who completed Month 6/end-of-study visits (n=32), BSA and EASI values were 27.1% at Baseline versus 20.6% at Month 6/End of Study (difference=7.06, CI 1.39 to 12.43, $p=0.016$), and 11.5 versus 8.8, respectively (difference=2.79, CI 0.72 to 4.86, $p=0.010$). Compared to the total patient enrollment, patients who completed the study had statistically insignificant greater BSAs affected and EASI scores on the Month 6/end-of-study evaluation ($p=0.522$; $p=0.931$).

We further examined differences in mean BSA and EASI for adult and pediatric patients. Adult patients (n=18) displayed statistically insignificant decreases of mean BSA and mean EASI score between Baseline, Month 1, and Month 6. However, pediatric patients (n=22) displayed a statistically significant decrease in mean EASI score from Baseline at 11.1 to 7.1 at Month 1 (difference=3.95, CI 0.98 to 6.92, $p=0.010$) and an insignificant decrease to 8.4 at Month 6 ($p=0.156$).

Disease severity also decreased over time. At Baseline, 72.5% had moderate disease and 27.5% patients had severe disease. At Month 1, patients reported statistically significant decreases in moderate and severe disease (41.0% mild disease, 43.6% moderate disease, 16.4% severe disease; $p=0.007$). By the end of the study, only 6.5% of patients had severe disease ($p=0.015$). All individual clinical signs were significantly better at Months 1 ($p=0.050$) and 6 ($p=0.050$) compared to Baseline except oozing ($p=0.451$; $p=0.501$).

In adult and pediatric patient subgroups, disease severity also decreased over time. Of adult patients at Baseline, 72.2% had moderate disease and 27.8% had severe disease. By Month 1, many cases of moderate and severe disease gave way to mild disease (50% mild disease, 42.9% moderate disease, 7.1% severe disease; $p=0.003$). At Month 6/End of Study, 10% had mild disease, 80% had moderate disease, and 10% had severe disease ($p=0.220$). For pediatric patients at Baseline, 72.8% had moderate disease and 27.2% had severe disease. At Month 1, pediatric patient disease severity had statistically improved (40.9% mild disease, 52.4% moderate disease, 4.8% severe

disease; $p=0.002$). By Month 6/End of Study, disease severity had also decreased significantly (40% mild disease, 55% moderate disease, 5% severe disease; $p=0.006$).

Health Care Utilization

At Baseline, 20% of patients had two or more physician visits in the last four weeks. Following the introduction of tacrolimus ointment, patients incurred fewer physician visits over the duration of the study. No patients required additional physician visits beyond the scheduled study visit at Month 1 ($p=0.005$) or at Month 6/End of Study ($p=0.005$).

Patients used fewer prescription medications over the course of the study. At Baseline, 32.5% of patients reported being treated with two or more prescriptions (mostly antihistamines and antibiotics). By Month 6/End of Study, reports of usage of two or more prescriptions dropped significantly to 3.0% ($p=0.001$).

The study also recorded non-prescription medications usage (namely over-the-counter analgesics like diphenhydramine). Usage declined over time, but decreases were not statistically significant ($p=0.531$). No patients reported AD-related inpatient hospitalizations in the month prior to their baseline assessment, and no patient hospitalizations occurred while on study.

Health Care Costs

Total patient out-of-pocket costs for health care followed a downward trend, though the differences between evaluations were not statistically significant. Monthly patient out-of-pocket costs averaged US\$42.92 at Baseline and decreased to US\$26.77 at Month 1 ($p=0.062$).

Quality of Life

Changes in patient quality of life over time were mixed depending on the instrument and time interval analyzed. Quality of life (as measured by the CDLQI) improved significantly based on comparisons of mean scores of children at Baseline and Month 1 (11.1 versus 7.1; difference=3.96, CI 1.64 to 6.27, $p=0.002$), and Baseline and Month 6/End of Study (10.9 versus 5.2; difference=5.71, CI 3.28 to 8.15, $p=0.000$). Adult patient DLQI scores showed downward trends, but were not statistically significant ($p=0.138$; $p=0.202$). SF-12 scores showed mixed trends for physical and mental components; none was statistically significant.

Statistically significant improvements in quality of life of the parent or caregiver were observed. Of the patients who completed Month 6/End of Study evaluations, 80.9% of parents/caregivers had their sleep affected at Baseline. In contrast, significantly fewer reported sleep problems by End of Study (42.9%; $p=0.011$). Similarly, parents and caregivers reported a significant positive effect on their leisure activities (55.0% affected at Baseline versus 19.0% at End of Study, $p=0.017$). Other domains such as impact of AD on daily activities ($p=0.680$), family relationships ($p=0.502$), and emotional distress ($p=0.365$) showed positive but insignificant trends (Figure 1).

There were no statistically relevant changes in patient self-reported or caregiver-reported physical appearance (Month 1, $p=0.288$; Month 6/End of Study, $p=0.205$).

Productivity and Absenteeism

At Baseline, 27.5% of patients reported missing at least 1 hour of work in the past week due to AD. At Month 1, there was a statistically insignificant decrease in reports of missed work (15.0%; $p=0.149$). However, patients who completed an end-of-study evaluation displayed a significant decrease in missed work with 30.3% missing some work at Baseline compared to 0.0% by Month 6/End of Study ($p=0.001$) (Figure 2). Similarly, significantly fewer patients reported problems working or spending time outside of home at End of Study (21.2%) compared to 54.5% of patients at Baseline ($p=0.005$). Reported negative effects on performance at work due to AD showed a statistically insignificant downward trend of 13.6% at Baseline versus 4.5% at Month 6/End of Study ($p=0.607$).

A statistically insignificant downward trend in missed school due to AD was also observed in pediatric patients with 22.7% missing some school at Baseline and no missed school by the second month and continuing through Month 6/End of Study ($p=0.107$).

Medication Compliance

Patient perceptions about their medication regimens significantly improved over time. At Baseline, 50.0% of patients reported “feeling good” about their AD medications (defined as answering “moderately,” “quite a bit,” or “all the time”). By Month 1, a significantly higher percentage of patients reported “feeling good” about their medications (88.9%; $p=0.023$). Patient compliance with AD medications showed a statistically insignificant increase from 84.0% of patients at Baseline to 100.0% of patients at Month 6/End of Study ($p=0.400$).

Discussion

Studies have revealed the extensive impact of AD, showing it to be a chronic disease with wide-ranging effects.

Ellis et al. estimated third-party payer costs of AD to range from US\$0.9 to US\$3.8 billion, comparable to costs of emphysema, psoriasis, or epilepsy.³ Barbeau et al. estimated total costs of AD in Canada to be CDN\$1.4 billion annually.³⁸ Through retrospective evaluations, Fivenson et al. examined the total burden of illness of AD, including quality of life and financial information.²¹ Indirect costs, such as days lost from work, were shown to be a large part of the burden.

We affirm the importance of presenting comprehensive assessments across a variety of AD-related outcomes. In this exploratory study, we demonstrate the feasibility of prospectively collecting qualitative and quantitative data for a diverse set of domains – a host of reported outcomes, including economic and quality of life for both patients and caregivers, as well as a clinical assessment. Furthermore, we apply this framework to study the impact of a specific intervention on AD, instead of analyzing the burden of the disease at a single point.

Our methodology was successful in showing statistically significant decreases in a range of categories associated with positive clinical and quality-of-life outcomes. Treatment of moderate-to-severe AD patients with tacrolimus ointment resulted in clinical improvements across various measures, such as BSA, EASI, Rajka and Langeland severity scores, as well as individual clinical signs, further validating the improvements. All of the measures recorded statistically significant immediate improvements at Month 1. Nearly all of the clinical improvements were sustained through Month 6. Some of the most dramatic benefits of treatment with tacrolimus ointment were seen in patient and parent/caregiver quality-of-life endpoints. Improvements were seen both through the use of validated quality-of-life instruments (DLQI, CDLQI) and selected measures. Parents and caregivers reported fewer problems with sleep, and more time for leisure activities. Patients treated with tacrolimus ointment not only missed less time from work and school, but the quality of their work improved.

We acknowledge the limitations associated with most exploratory studies. First, these studies lack a control group who could reveal possible placebo effects contributing to disease changes. However, mean improvements in various

scores in all areas were observed in Month 1 after tacrolimus therapy and were maintained for the six-month duration, long after expected effects of placebo or other medications used prior to the study. Though we did not have a control group, the therapy was likely to have a real and measurable effect on patient clinical symptoms and quality of life.

Though appropriate for an exploratory study, the small sample size was due to patients choosing not to continue participation beyond a baseline evaluation or patients dropping out in the middle of the study. Of the patients who dropped out from this study prematurely, in only one instance was this due to lack of efficacy or side effects. Almost all of the patients who dropped out of the study prematurely reported improvements in their condition and had reluctance to continue with protocol requirements.

Patients who had less severe disease and subsequently dropped out of the study before completion, skewed some of the results. For example, it appears as if patients' clinical improvements diminished over time (Table 3). On closer inspection, we realized that the patients who remained in the study until completion generally had more severe disease at baseline. By utilizing an LOCF methodology, we were able to make more thorough comparisons of the data. We acknowledge the limitations of the LOCF methodology. While it allows the use of patients who left the study for positive reasons, it would not capture potential flare-ups or problems they would have experienced after leaving.

It is common for health care stakeholders to want to quantify the value associated with new medical technologies. As this and other studies have shown, appropriate answers to these questions need to span a variety of outcomes and endpoints. We established a methodology that can illustrate the positive effects of a specific therapeutic intervention, not only on clinical endpoints, but also patient/caregiver quality of life and other patient-reported outcomes. The improvements in our study were achieved using tacrolimus ointment, but our study was intended to establish a framework to guide future research efforts in topical immunomodulators and other therapies on atopic dermatitis. To understand better the net costs and benefits of topical immunomodulator therapy, more exhaustive research across these domains is recommended, along with analyses of larger populations and multiple interventions.

Table 1. Study Domains and Instruments

Domain	Measurements	Instruments Used (if applicable)
Clinical/Disease Assessment	Area affected and severity of disease	EASI
	Body surface area affected	Percent BSA
	Clinical response and clearing of AD	Physician's global assessment
	Severity of AD	Rajka and Langeland's AD severity scoring scale
	Extent of six clinical signs (edema, erythema, excoriation, lichenification, oozing, and scaling)	Individual clinical signs of AD
Health Care Utilization	Physician visits, prescriptions used for AD or non-AD, and ER or clinic visits	
Health Care Costs	Payment and out-of-pocket costs per physician visit	
	Use and expenses for treatments related to AD (e.g., prescriptions, antihistamines, soaps, lotions)	
Quality of Life	General health related quality of life, primarily: mental and physical quality of life	SF-12
	Impact of skin diseases on quality of life for adult patients in the following areas: Symptoms, feelings; Daily activities; Leisure; Work/School; Personal relationships; Treatment	DLQI for ages 16 and over
	Impact of skin diseases on quality of life for pediatric patients in the following areas: Symptoms, feelings; Leisure; School/Holidays; Personal relationships; Sleep; Treatment	CDLQI for ages 5-16
	Impact of child's AD on parent/caregiver daily activities	
	Patient physical appearance	Bergner physical appearance scale
Productivity/Absenteeism	Work or school missed each study period	
	Other impacts on work, school, or career of patient or caregiver	
Compliance	Compliance with medication routine	
	Difficulty with current drug treatment; feelings towards medications	

Table 2. Patient Demographics at Baseline

	Total (N=40)		Dropouts (N=7)		Continuers (N=33)	
		N		N		N
Gender, %						
Male	32.5	13	28.6	2	33.3	11
Female	67.5	27	71.4	5	66.7	22
Race, %						
Caucasian	52.5	21	42.9	3	54.5	18
African American	30.0	12	14.3	1	33.3	11
Asian	2.5	1	14.3	1	0.0	0
Hispanic	10.0	4	28.6	2	6.1	2
Other	5.0	2	0.0	0	6.1	2
Age						
Adult, %	45.0	18	85.7	6	36.4	12
Adult, Mean (SD)	41.7 (14.0)		53.3 (20.9)		35.9 (8.8)	
Pediatric, %	55.0	22	14.3	1	63.6	21
Pediatric, Mean (SD)	9.2 (3.5)		13.97 (N/A)		9.0 (3.4)	
AD Severity, %						
Moderate	72.5	29	85.7	6	69.7	23
Severe	27.5	11	14.3	1	30.3	10

SD = Standard Deviation

Table 3. Change in BSA and EASI Scores from Baseline to End of Study

	Baseline		Month 1		Baseline vs M1	Month 6 / EOS		Baseline vs M6
	Mean	N	Mean	N	P value	Mean	N	P value
BSA	25.4	40	17.0	40	< 0.001	20.6	32	0.016
Adult	24.8	18	16.1	18	NS	24.9	11	NS
Pediatric	25.9	22	17.7	22	NS	18.3	21	NS
EASI	10.6	40	6.6	40	< 0.001	8.8	32	0.010
Adult	10.1	18	6.0	18	NS	9.6	11	NS
Pediatric	11.1	22	7.1	22	0.010	8.4	21	NS

p<0.05 for comparisons between BSA and EASI scores between Baseline and Month 1, and Baseline and Month 6/End of Study.

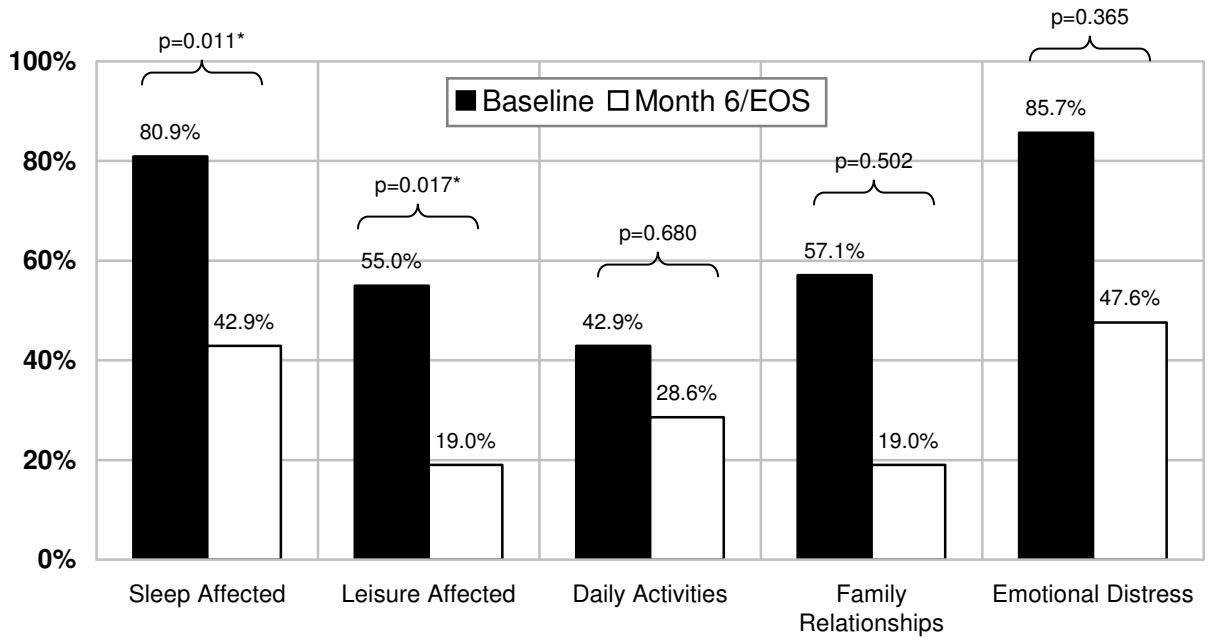
NS = Not Significant

Table 4. Change in Disease Severity from Baseline to End of Study

	Baseline		Month 1		Baseline vs M1	Month 6 / EOS		Baseline vs M6
	N	%	N	%	P value	Mean	N	P value
Adult								
Mild	0	0.0	7	50.0	0.003	1	10	NS
Moderate	13	72.2	6	42.9				
Severe	5	27.8	1	7.1				
Pediatric								
Mild	0	0.0	9	42.9	0.002	8	40	0.006
Moderate	16	72.7	11	52.4				
Severe	6	27.3	1	4.8				

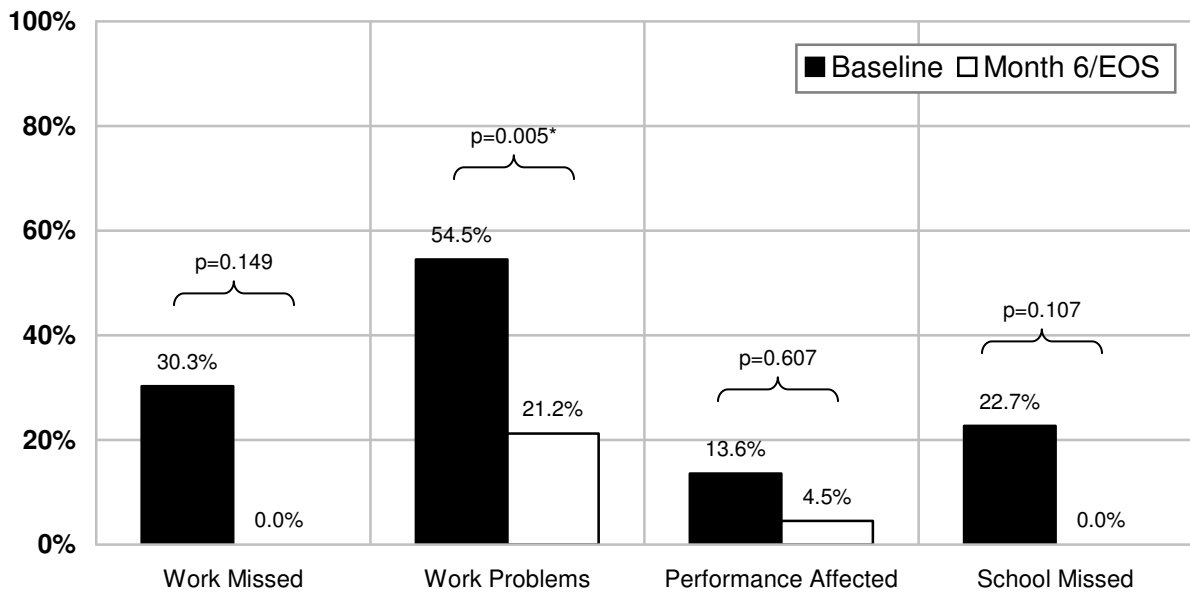
NS = Not Significant

Figure 1. Caregiver Quality of Life



* p<0.05, chi-square

Figure 2. Caregiver and Child Productivity



* p<0.05, chi-square

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