

ABSTRACT

Background: Diarrhea is a common symptom in individuals with HIV infection and impacts quality of life. Whether effective anti-diarrheal therapy influences quality of life is unknown. SP-303 (Provir) and SB-300 (SB-NSF) are two formulations of an extract of a naturally occurring botanical, the latex of *Croton lechleri* (family *Euphorbiaceae*). The tree is found throughout the rainforest of South America and is known for its medicinal properties including relief of diarrhea.

Objective: To determine if quality of life changes when patients with HIV and chronic diarrhea are treated with an anti-diarrheal therapy.

Methods: Subjects with chronic diarrhea (>300g/d) were enrolled in clinical trials investigating two new anti-diarrheals (SP-303 and SB-300). They were asked to complete a twelve point questionnaire at baseline and follow-up (two or four weeks). Questions regarding the impact of diarrhea on activities of daily living (quality of life) included ability to perform errands, time spent at home, effect on sexual activity, and ability to sleep. Using a five point Likert scale, subjects' responses to statements were scored with none of the time (1), a little of the time (2), some of the time (3), most of the time (4), or all of the time (5). A sum score for all twelve activities was calculated from the baseline and follow-up questionnaires. Subjects were grouped as a responder (R) or non-responder (NR) to therapy based on decrease in stool weight and/or subjective improvement in diarrhea severity. Statistical analysis was performed using SAS. Changes in answers to individual questions and the sum of all scores were compared in responders vs. non-responders by Mann-Whitney Rank sum. Mean values (± Standard Deviation) are presented.

Results: Forty-two subjects (86% of eligible cohort) completed two questionnaires. The mean age was 42.7 years (range 28-58), mean CD4 count 260.0 cells/mm³ (175.7), mean years with known HIV infection 9.7 (3.6), mean years with AIDS diagnosis 4.1 (2.1), and median viral load 2569 copies (range 50-750000). At baseline, the scored responses ranged from a mean of 1.9 (0.9) for burden to others to 3.3 (1.3) for decreased sexual activity. The improvement in the sum QOL scores in responders vs. non-responders was statistically significant, 5.95 (9.96) vs. -1.39 (7.43), (p 0.02).

	Baseline Sum score	Mean Δ in sum score	Mean Δ in sexual activity score	Mean Δ in time resting score
R	32.5 (8.2)	5.95 (9.96)	0.74 (1.15)	0.37 (1.61)
NR	33.6 (7.9)	-1.39 (7.43)	-0.29 (1.01)	-0.22 (1.09)
p	NS	0.024	0.01	0.03

Conclusion:

- Diarrhea adversely impacts quality of life.
- Within two to four weeks, subjects who responded to the new anti-diarrheal had a statistically significant improvement in the sum score of the activities of daily living.
- Response to anti-diarrheal therapy was associated with statistically significant improvements in the categories of time spent resting, ability to leave home and sexual activity.

BACKGROUND

Diarrhea is a common symptom in individuals with HIV infection and impacts quality of life. SP-303 (Provir®) and SB-300 (SB-NSF®) are two formulations of an extract of a naturally occurring botanical, the latex of *Croton lechleri* (family *Euphorbiaceae*). The tree is found throughout the rainforest of South America and is known for its medicinal properties including relief of diarrhea. SP-303 (the principal active ingredient of SB-300) is an acid labile, proanthocyanidin oligomer, that was effective in previous studies of individuals with HIV infection and diarrhea (1).

A diarrhea-related quality of life (QOL) questionnaire measures a patient's perception of their diarrhea on activities of daily living. Chronic diarrhea may lead to decreases in physical functioning, perceived energy level and social interaction thereby diminishing the overall quality of life of patients infected with HIV (2, 3). Presence of weight loss and gastrointestinal symptoms has been associated with a decline in the ability to perform activities of daily living (4, 5). Quality of life measures of functional ability, global health, social contacts, and energy/fatigue have been shown to decline over one year among patients with HIV and chronic diarrhea (6). However, whether effective anti-diarrheal therapy influences quality of life is unknown.

STUDY AIMS

- To determine if quality of life changes when patients with HIV and chronic diarrhea are treated with an anti-diarrheal therapy.
- To evaluate the association between response to anti-diarrheal therapy and short-term changes in measures of quality of life.

METHODS

Study Population: Subjects with HIV and chronic diarrhea enrolled in two clinical trials investigating two new anti-diarrheals (SP-303 and SB-300). Thirty-one subjects with AIDS were enrolled in the SP-303 Phase III clinical trial from July 1998 to August 1998. Twenty subjects with HIV infection were enrolled in the SB-300 open-label study from July 1999 to August 1999.

Measurements: All subjects were asked to complete a twelve point questionnaire (Figure 1) at baseline and follow-up (two or four weeks). Questions regarding the impact of diarrhea on activities of daily living (quality of life) included ability to perform errands, time spent at home, effect on sexual activity, and ability to sleep. Using a five point Likert scale, subjects' responses to statements were scored with none of the time (1), a little of the time (2), some of the time (3), most of the time (4), or all of the time (5). A sum score for all twelve activities was calculated from the baseline and follow-up questionnaires.

Response: Subjects were grouped as a responder (R) or non-responder (NR) to therapy based on decrease in stool weight and/or subjective improvement in diarrhea severity. In the Phase III trial, response was defined as a 50% reduction in 24-hour stool weight on Day 7 vs. Baseline and subjective improvement. In the open-label study, response was defined as an improvement in the severity of diarrhea.

Statistical Analysis: Statistical analysis was performed using SAS. Changes in answers to individual questions and the sum of all scores were compared in responders vs. non-responders by Mann-Whitney Rank sum. Mean values (± Standard Deviation) are presented.

Figure 1 Quality of Life Questionnaire

Please circle one number for each statement below.

During the past 4 weeks, because of my diarrhea:

	None of the time	A little of the time	Some of the time	Most of the time	All of the time
1. I spend most of the day resting	1	2	3	4	5
2. I feel that I am a burden to others	1	2	3	4	5
3. I can only do my usual work around the house for short periods of time	1	2	3	4	5
4. I cannot do errands like shopping that I usually do	1	2	3	4	5
5. I stay in bed more than usual	1	2	3	4	5
6. I only go to places with restrooms nearby	1	2	3	4	5
7. I stay away from home only for brief periods of time	1	2	3	4	5
8. I stay at home most of the time	1	2	3	4	5
9. I go out less to visit people	1	2	3	4	5
10. My sexual activity is decreased	1	2	3	4	5
11. I stay alone most of the time	1	2	3	4	5
12. I am unable to sleep through the night	1	2	3	4	5

RESULTS

Twenty-three (74%) of the Phase III trial participants completed two questionnaires and 19 (95%) of the open-label study participants completed two questionnaires. The demographic parameters of the group are shown in Table 1. The improvement in the sum QOL scores in responders vs. non-responders was statistically significant, 5.95 (9.96) vs. -1.39 (7.43), (p 0.024).

Table 1 Baseline Demographic Parameters

Patients		N=42
Age (years)	Mean (SD) Median Range	42.7 (7.1) 41.9 28-58
Sex	Male	40 (95%)
Race	Caucasian Hispanic Black	35 (83%) 4 (10%) 3 (7%)
CD4 Cell Count (cells/μl)	Mean (SD) Median Range	260.0 (175.7) 234.0 (3-650)
Viral Load (copies/ml)	Mean (SD) Median Range	70769 (146997) 2569 (50-750000)
Baseline Stool Frequency (stools/24h)	Mean (SD) Median Range	5.8 (2.4) 6 (1.5-12)
Baseline Stool Weight (grams/24 h)	Mean (SD) Median Range	807.2 (518.8) 628.8 (283.4-2577)
Years with HIV	Mean (SD)	9.7 (3.6)
Years with AIDS Diagnosis	Mean (SD)	4.1 (2.1)
AIDS defining diagnosis		41 (98%)
Opportunistic Infection		11 (27%)
CD4 cell count <200		28 (68%)
Wasting		2 (5%)

Table 2 Anti-retroviral Therapy

Anti-retroviral therapy	Number	Percent
None	3	7%
HAART	39	93%
Protease Inhibitor	38	90%
Viracept®	29	70%
Crixivan®	5	8%
Navir®	8	20%
Invirase®	8	20%
Amprenavir®	4	10%

Table 3 Impact of Diarrhea at Baseline

Question	Mean (SD)
1 (resting)	2.7 (0.9)
2 (burden to others)	1.9 (0.9)
3 (house work)	2.8 (1.1)
4 (errands)	2.2 (0.9)
5 (stay in bed)	2.2 (1.0)
6 (restrooms)	3.5 (1.3)
7 (away from home)	2.9 (1.1)
8 (stay at home)	2.8 (1.0)
9 (go out)	2.8 (1.0)
10 (sexual activity)	3.4 (1.3)
11 (stay alone)	3.0 (1.1)
12 (sleep)	3.0 (1.0)
Sum Score	33.1 (8.0)

Table 4 Change in Stool Weight & Frequency: Responders vs. Non-responders

	Responders Mean Change (SD)	Non-Responders Mean Change (SD)
Baseline Stool Weight (g/24h)	822 (515)	795 (533)
Follow-up Stool Weight	381 (237)	735 (509)
Baseline Stool Frequency	5.8 (2.6)	5.9 (2.3)
Follow-up Stool Frequency	3.0 (1.8)	5.1 (2.7)

Table 5 Change in QOL Scores with Diarrhea Treatment: Responders vs. Non-responders

Question	Responders Mean Change (SD)	Non-Responders Mean Change (SD)	p value
1 (resting)	0.53 (1.12)	-0.22 (0.74)	.03
2 (burden to others)	0.16 (0.76)	-0.26 (1.14)	.17
3 (house work)	0.58 (1.50)	-0.17 (1.40)	.13
4 (errands)	0.53 (1.22)	-0.09 (1.00)	.14
5 (stay in bed)	0.42 (1.22)	-0.30 (1.11)	.06
6 (restrooms)	0.37 (1.26)	-0.22 (1.00)	NS
7 (away from home)	0.37 (1.61)	-0.22 (1.09)	.04
8 (stay at home)	0.89 (1.05)	0.00 (1.21)	.02
9 (go out)	0.42 (1.02)	-0.13 (0.97)	.10
10 (sexual activity)	0.74 (1.15)	-0.29 (1.01)	.01
11 (stay alone)	0.58 (1.54)	0.17 (0.94)	NS
12 (sleep)	0.37 (1.16)	0.30 (0.70)	NS
Sum Score	5.95 (9.96)	-1.39 (7.43)	.02

CONCLUSIONS

- Diarrhea adversely impacts quality of life.
- Within two to four weeks, subjects who responded to the new anti-diarrheal had a statistically significant improvement in the sum score of the activities of daily living.
- Response to anti-diarrheal therapy was associated with statistically significant improvements in the categories of time spent resting, ability to leave home and sexual activity.

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