Rescuing Standard Analyses of Immunosuppressive Rescue Therapy in Randomized Controlled Trials: Alternative Approaches in a Sclerosis in a Clinical Trial

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ACE

Abstract #72239

BACKGROUND

- Treatment with CTLA4Ig, abatacept (ABA), in early diffuse cutaneous systemic sclerosis (dcSSc; the Phase 2 ASSET trial) showed evidence of improvements in modified Rodnan skin score (mRSS) and secondary outcome measures at month 12 (2018 ACR abstract # **900**).
- This randomized placebo-controlled trial used the **gold** standard for providing the highest-quality evidence of treatment efficacy; however, requiring participants with early dcSSc to take long-term placebo raises feasibility and ethical concerns.
- Many studies, including ASSET, allow rescue therapy when a participant's condition worsens.
- Statistically, adjusting for rescue therapy to derive appropriate conclusions about treatment efficacy is complicated because it is a post-randomization variable.
- We applied several analytic approaches to address rescue therapy in the primary endpoint in ASSET – change from baseline to month 12 in mRSS.

METHODS

- ASSET was an investigator-initiated, multicenter double-blind, randomized placebo-controlled trial.
- Eligible subjects were randomized in a 1:1 ratio to 12 mo 125 mg SC ABA or matching placebo, stratified by duration of dcSSc (≤18 vs >18 to ≤36 months).
- After 6 mo of treatment, investigators were given a choice to <u>add</u> rescue therapy for worsening skin disease (>5 units worsening of mRSS) or worsening ILD (absolute decline in FVC% predicted by ≥ 10% or absolute decline in DLCO% predicted by ≥ 15)
- If subject worsened at 3 mo, investigators could <u>begin</u> escape therapy, but were to <u>stop</u> study medication.

METHODS

- The primary analysis for treatment comparisons was based on the ITT principle for inclusion of participants, but we eliminated data after the onset of rescue therapy. (Table 2, method #1)
- Linear mixed models were used to assess treatment differences in change in mRSS scores.
- Alternative approaches included applying the approach of performing a strict ITT analysis and including all observations (i.e., including post-rescue therapy values) (Table 2, method #2), and excluding observations after the start of rescue therapy with additional terms for rescue therapy and treatment X rescue therapy interaction. (Table 2, method #3)

RESULTS

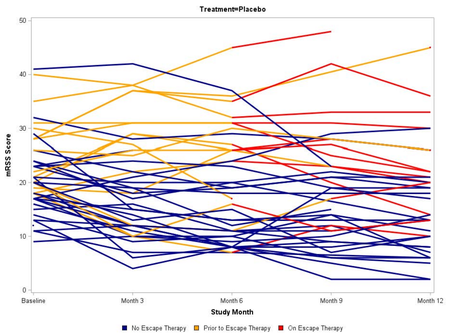
- 88 subjects (44 ABA, 44 PBO) were randomized.
- 34 (77%) of ABA subjects completed 12 months on study; 35 (80% of PBO subjects completed 12 months on study.

Table 1: Number (%) of subjects receiving rescue therapy by treatment group

	Abatacept N=44	Placebo N=44
Overall*	7 (16%)	16 (36%)
Started ≤ 3 mo	1 (2%)	0
Started >3 and ≤ 6 mo	2 (5%)	3 (7%)
Started >6 and ≤ 12 mo	4 (9%)	13 (30%)

*p=0.03 comparing overall % subjects receiving rescue treatment.
Note: Escape therapy included methotrexate, mycophenolate mofetil, cyclophosphamide, hydroxychloroquine, azathioprine or intravenous immunoglobulin (IVIG). Other biologic therapies were not acceptable as escape therapy.

RESULTS



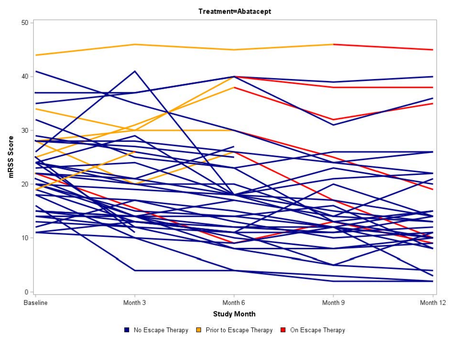


Table 2: Treatment comparisons in change from baseline to month 12 in mRSS using different methods to address rescue therapy

Method	Abatacept N=44	Placebo N=44	Treatment Diff (ABA-PBO)	
	LS mean (SE)	LS mean (SE)	LS mean (SE)	P-value
#1. Values censored after start of rescue therapy – no rescue therapy covariates	-6.24 (1.143)	-4.49 (1.144)	-1.75 (1.611)	0.2794
#2. No values censored after start of rescue therapy – no rescue therapy covariate	-6.64 (1.098)	-4.22 (1.039)	-2.42 (1.502)	0.1088
#3. Values censored after start of rescue therapy – rescue therapy covariates	-5.58 (1.317)	-3.48 (1.003)	-2.11 (1.634)	0.1983

mRSS scores have a range from 0 to 51, with higher score indicating greater severity of SSc.
#1 and #2. Estimates and p-values from a linear mixed model with treatment group, month (3, 6, 9 and 12), treatment group x month interaction, duration of dcSSC (≤18 vs >18 to ≤36 months), and baseline mRSS as fixed effects and participant as a random effect. #3. Model also includes rescue therapy indicator and treatment group x rescue therapy interaction.
LS mean = least squares mean; SE=standard error

- The smallest mean treatment difference occurred by eliminating values after start of rescue therapy (method #1)
- The largest mean treatment difference occurred when all values were included, as might be expected with twice as many placebo participants starting rescue therapy (method #2)
- Censoring values and incorporating rescue therapy as a covariate resulted in an intermediate treatment estimate (method #3)
- No statistically significant treatment differences were observed from any model.

CONCLUSIONS

- The National Academy of Sciences panel on handling missing data in clinical trials emphasizes limiting missing data in the design of clinical trials [1]. One of their 8 ideas included "allow the use of rescue medications that are designated as components of a treatment regimen in the study protocol."
- Recent FDA and EMA guidances [2, 3] emphasize selecting the correct estimand -- the right quantity to be estimated -- at the design stage to address the right question regarding treatment differences when non-adherence and missingness occur study conduct.
- There are multiple approaches in the literature addressing the difficulties with analyses and interpretation after recue therapy.
- In our study, there was differential use of rescue therapy by treatment, but several simple approaches to handling rescue therapy results in comparable conclusions, providing confidence in our primary analytic approach.
- More sophisticated analytic methods, such as jointly modeling the primary endpoint and the probability of rescue therapy may be useful.

REFERENCES

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2. E9(R1) Statistical Principles for Clinical Trials: Addendum: Estimands and Sensitivity Analysis in Clinical Trials. 16 June 2017.
3. European Medicines Agency. EMA/ CPMP/ EWP/ 1776 / 99 Rev. 1. Guideline on Missing Data in Confirmatory Clinical Trials, 2010.

DISCLOSURES

- **D. Khanna Grant/research support from:** NIH/NIAMS and NIH/NIAID, Bayer, BMS, Pfizer & **Consultant for:** Actelion, Bayer, BMS, Boehringer Ingelheim, Genentech/Roche, Sanofi-Aventis, GSK, Corbus, Cytori, EMD Serono
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