Supplementary Online Content

Ponds FA, Fockens P, Lei A. Effect of peroral endoscopic myotomy vs pneumatic dilation on symptom severity and treatment outcomes among treatment-naive patients with achalasia: a randomized clinical trial. *JAMA*. doi:10.1001/jama.2019.8859

Supplement 2. Statistical analysis plan

This supplementary material has been provided by the authors to give readers additional information about their work.

Statistical analysis plan

Pneumodilation Or Endoscopic Myotomy in achalasia (POEMA) Trial

1.1 Introduction

In this multicenter randomized controlled trial, the efficacy of a new treatment for achalasia, peroral endoscopic myotomy (POEM) is compared to the current standard treatment: pneumodilation. In the study protocol extended information is provided on the trial design, randomization procedure including stratification factors, sample size, stopping regulation and management of adverse and serious adverse events. The trial is designed to recruit 130 patients in total and the primary endpoint will be measured two years after treatment. Follow-up of the patients will be extended up to five years. This document will provide information on the statistical analysis of the data after two-year follow-up. Data will be collected at baseline and after treatment, at 3 months, 1 and 2 years follow-up.

1.2 Primary outcome

The primary outcome of this study is treatment success at 2 years, defined as an Eckardt score ≤3 in the absence of severe complications (SAE) or need for endoscopic or surgical retreatment. The success rates in the two treatment groups will be analyzed by comparing proportions by Chi-square.

1.3 Secondary outcome

Different parameters will be analyzed as secondary outcome measures:

- Eckardt score
- Lower esophageal sphincter pressure and integrative relaxation pressure (IRP), as measured with high-resolution manometry
- Esophageal stasis and diameter measured with a timed barium esophagogram
- Presence of reflux symptoms, reflux esophagitis and esophageal acid exposure
- Health related quality of life and achalasia-specific quality of life
- Complication rate
- Number of endoscopic or surgical retreatment

The parameters are measured at baseline, 3 months, 1 and 2 years follow-up. Continuous data will be presented as mean with standard deviation (SD) or median with interquartile range (IQR) or range, according to distribution. Categorical data will be presented in

percentages with SD. Continuous data will be compared using unpaired Student's t-test or Mann-Whitney U-test and categorical data will be analyzed by Chi-square or Fisher's exact test. To account for repeated measures linear mixed model is used. The effect of treatment type on continuous outcome parameters, like Eckardt score and IRP is analyzed with fixed effect for time and treatment.

1.4 Missing data

Any missing data are reported. Patients that are lost to follow-up before treatment failure or the primary endpoint at 2-year follow-up, will be excluded from the analysis because the primary outcome is unknown. Previous collected data of these patients on earlier follow-up moments will not be discarded and used for outcome analysis at these time points. We assume that the estimated lost to follow-up of patients without a primary outcome of 5% is realistic and will not influence data analysis with the current sample size. However, an additional sensitivity analysis, addressing missing data for the primary outcome by multiple imputation will be performed.

Missing data of the secondary outcome parameters will be excluded from the analysis. Fifty percent of the secondary outcome parameters is categorical data which makes multiple imputation difficult and the option last case carried forward was assessed as outdated. If a patient had withdrawn consent no further data will be collected. However, data collected thus far will be used for analyses.

1.5 Analysis methods

Two types of analyses will be performed: 1) intention-to-treat in which patients at time of treatment failure will be excluded from further analysis; 2) per protocol excluding patients that not followed the treatment protocol. The intention-to-treat analysis will be used as the main analysis. Patients will be analyzed according to their randomization group. Primary and secondary outcomes at 3 months and 1 year follow-up and the efficacy of retreatment with PD after treatment failure will be assessed as post-hoc analysis.