Evaluation of the Rituximab trial for ME/CFS in the context of single-arm trial (SAT) methodology

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Project Objective

The presentation will address the following key points:

- Summarize the main findings from Dyachkova et al. (2024) regarding the use of SATs in clinical trials.
- Analyze the Rituximab clinical trial by Fluge et al. (2015) in the context of Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS), focusing on the use of SAT design.
- Evaluate how the Rituximab trial aligns with or challenges the considerations discussed in Dyachkova et al. (2024).

Review of Dyachkova et al (2024)

Do You Want to Stay Single? Considerations on Single- Arm Trials in Drug Development and the Postregulatory Space

Single-Arm Trials (SATs)

SATs are clinical trials in which all participants receive the same treatment or intervention, without a randomized control group. They are commonly used in specific situations where randomization or a control group may not be feasible or ethical, such as in the case of rare diseases or when a placebo treatment would be considered unethical. The Food and Drug Administration (FDA) and the European Medicines Agency (EMA) provide strict guidance for use and limitations.

Key Limitations of SATs

Table: Summary of key methodological limitations in single-arm trials (SATs).

Limitation	**Explanation**
No Control Group	Difficult to draw causal conclusions. Without a concurrent control group, it is hard to account for time-related or natural progression effects.
No Randomization	Increases risk of selection bias. Randomization helps create balanced groups and is essential for valid treatment comparisons.
No Blinding	Leads to subjective bias. Knowledge of treatment may influence assessment and reporting of both efficacy and safety outcomes.
External Confounding	Other variables (e.g., environment, co-interventions) may influence outcomes and can't be ruled out in the absence of controls.
Operational Biases	Participant behavior, dropout rates, and study assessments can be influenced by the open-label nature of the trial.

Clinical and Academic Perspective

- Prefer definitive answers from RCTs over SAT comparisons.
- Patients in an (external) control group might be systematically different from patients in SAT, especially if historical control is used. This might be due to change in clinical practice, change in assessment methods, unavailability of a biomarker of interest in the control group, other factors that impact the prognosis
- Top journals and Cochrane often avoid SATs.
- Difficult to interpret safety results in the absence of a control arm.
- Risk of reputational damage or perceived lack of scientific rigor.
- Claims of inappropriate reasons for conducting trial, especially if no real scientific objective or if it cannot be credibly achieved by trial.

When Are SATs Used?

- **Early Development:**
  - Signal seeking – detecting changes in the right direction.
  - Early safety evaluations (e.g., maximum tolerated dose).
  - Identification of biomarkers.
- **Natural History Studies:**
  - Understanding disease progression over time.
  - Mapping current treatment patterns and standard of care (SoC).
- **Late Phase Use:**
  - Common in oncology and rare diseases.
  - Used when spontaneous improvement is unlikely.
  - Applied when randomization may be unethical due to lack of SoC.
- **Postapproval and Medical Affairs:**
  - Evaluating treatment patterns, sequencing and adherence.
  - Identifying additional risks, benefits and new endpoints.
  - Many SATs are small and done soon after launch in countries not included or underrepresented in RCTs to provide input into local negotiations of market access, reimbursement and price.

Guidance Documents

Recent guidance from regulatory agencies such as FDA (2023) and EMA (2023) outlines how external controls and prespecified statistical methods can help reduce the biases inherent in SATs. These documents stress the importance of:

- External Control Arms: Using historical data or real-world evidence to contextualize SAT results.
- Prespecified Statistical Methodology: To address biases such as selection bias and confounding, and to improve the interpretability of SAT results.

Conclusion

SATs have a valuable role in drug development, particularly in early-stage research, rare diseases, oncology, and postmarketing surveillance. However, their limitations, particularly in causal inference and lack of blinding, mean that they are often seen as a low-risk, low-reward approach. While they can provide early signals or real-world evidence, RCTs remain the gold standard. Future use of SATs will likely benefit from improved methodologies, such as external control arms and advanced statistical techniques to mitigate their inherent biases. Statisticians play a crucial role in ensuring that the right trial design is chosen based on the specific research question to ensure high-quality, credible evidence.

The Rituximab Trial (Fluge et al., 2015)

Introduction

Myalgic Encephalopathy/Chronic Fatigue Syndrome (ME/CFS)
A disease of unknown etiology, characterized by severe fatigue, post-exertional malaise, cognitive disturbances, and other symptoms related to immune and autonomic function.
Rituximab for ME/CFS Treatment - Pilot Study
A pilot case series suggested clinical activity for B-cell depletion using rituximab. A Phase II randomized, double-blind, placebo-controlled study showed no significant difference at 3 months, but significant improvement in fatigue scores from 6–10 months, with $\frac{2}{3}$ patients responding positively.
Current Study
Following the initial study, an open-label Phase II study aims to further investigate long-term effects through maintenance dosing of rituximab over three years.

Study Design and Participants

Study Design:

- Single center, open-label, phase II, **one-armed with no randomization** trial
- 29 patients with ME/CFS (including 2 pilot patients)
- To evaluate the effect of rituximab induction and maintenance on response rates, durations, and adverse effects over 36 months follow-up.

Inclusion Criteria:

- Diagnosis of ME/CFS (Fukuda 1994 criteria)
- Age 18-66 years

Exclusion Criteria:

- Pregnancy, previous severe immune diseases, or known infections
- No prior systemic immunosuppressive treatment or relevant clinical risk factors

Endpoints

Primary Endpoint:

- Effect on self-reported ME/CFS symptoms during follow-up.
- Clinical response defined as Fatigue score ≥ 4.5 for at least 6 consecutive weeks, with at least one score > 5.0
  (scale 0–6; 3: no change from baseline; 4, 5, 6: slight, moderate, major improvement, respectively; 2, 1, 0: slight, moderate, major worsening, respectively)

Secondary Endpoints:

- Effects on the ME/CFS symptoms, at 3, 6, 10, 15, 20, 24, 30 and 36 months assessed by the SF-36 questionnaire
- Longest consecutive response period (continuous Fatigue score ≥ 4.5).
- Number of patients still in response at the end of the study (36 months).
- Toxicity and adverse effects during follow-up.

Purpose and Development Stage

Purpose: Authors designed their study as an exploratory, signal-seeking trial to follow up on pilot data and a small placebo-controlled study. In early drug development, single-arm designs can be acceptable for detecting a biological signal when patient numbers are limited. ME/CFS is rare with high unmet need, so an initial single-arm trial is justifiable. SAT was intended to inform the design of the subsequent randomized, controlled Phase III trial.

Limitation: Does not meet high evidence standards for causal claims. Without randomization or a control arm, causal attribution of benefit to rituximab (versus natural disease fluctuation, placebo effect, etc.) is not possible.

Why Didn't Use Randomization and a Control Group?

- The goal was not to confirm efficacy but to explore safety, feasibility, and potential response patterns.
- The researchers had previously conducted a small RCT in 2011 which showed some positive signals, but also delays in clinical response.
- Only 29 patients were enrolled, which is typically not large enough to power a proper RCT.
- Patients from a prior placebo-controlled trial were allowed to join this study, and it may have been considered unethical to re-randomize them, especially after prior non-response to placebo.
- ME/CFS has no established effective treatment, and patients often suffer significantly — this creates pressure to provide active intervention rather than placebo.

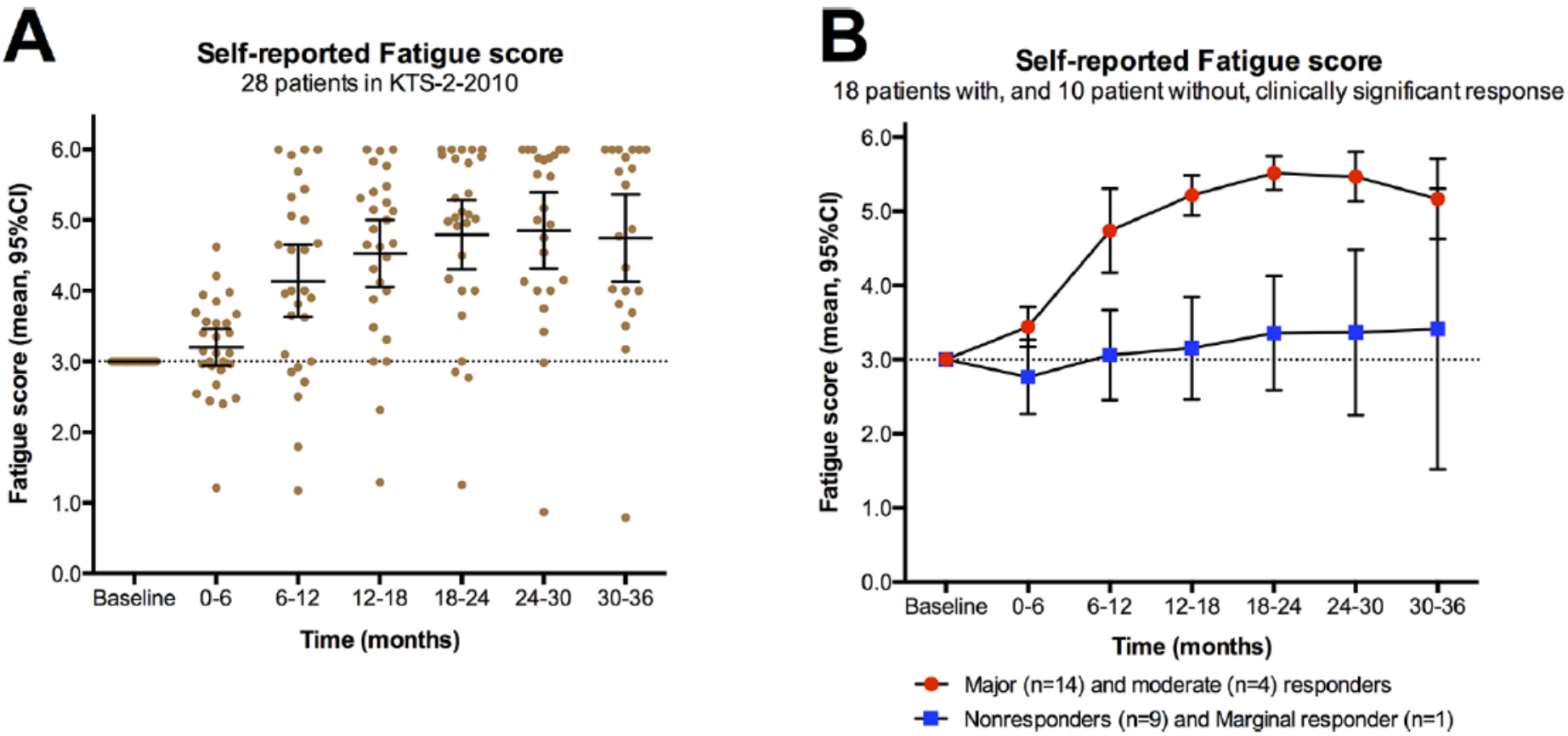

Figure: Self-reported Fatigue scores for 28 patients receiving rituximab induction and maintenance treatment. Fatigue score was recorded every second week, always compared to baseline, as the mean of four fatigue-related symptoms (scale 0–6; 3: no change from baseline; 4, 5, 6: slight, moderate, major improvement, respectively; 2, 1, 0: slight, moderate, major worsening, respectively). Panel A shows Fatigue scores for the time intervals, with means and 95% CI for each time interval. In panel B the corresponding Fatigue scores are shown for each time interval during follow-up, divided between 18 patients with clinically significant responses, and 10 patients with either marginal response or no response.

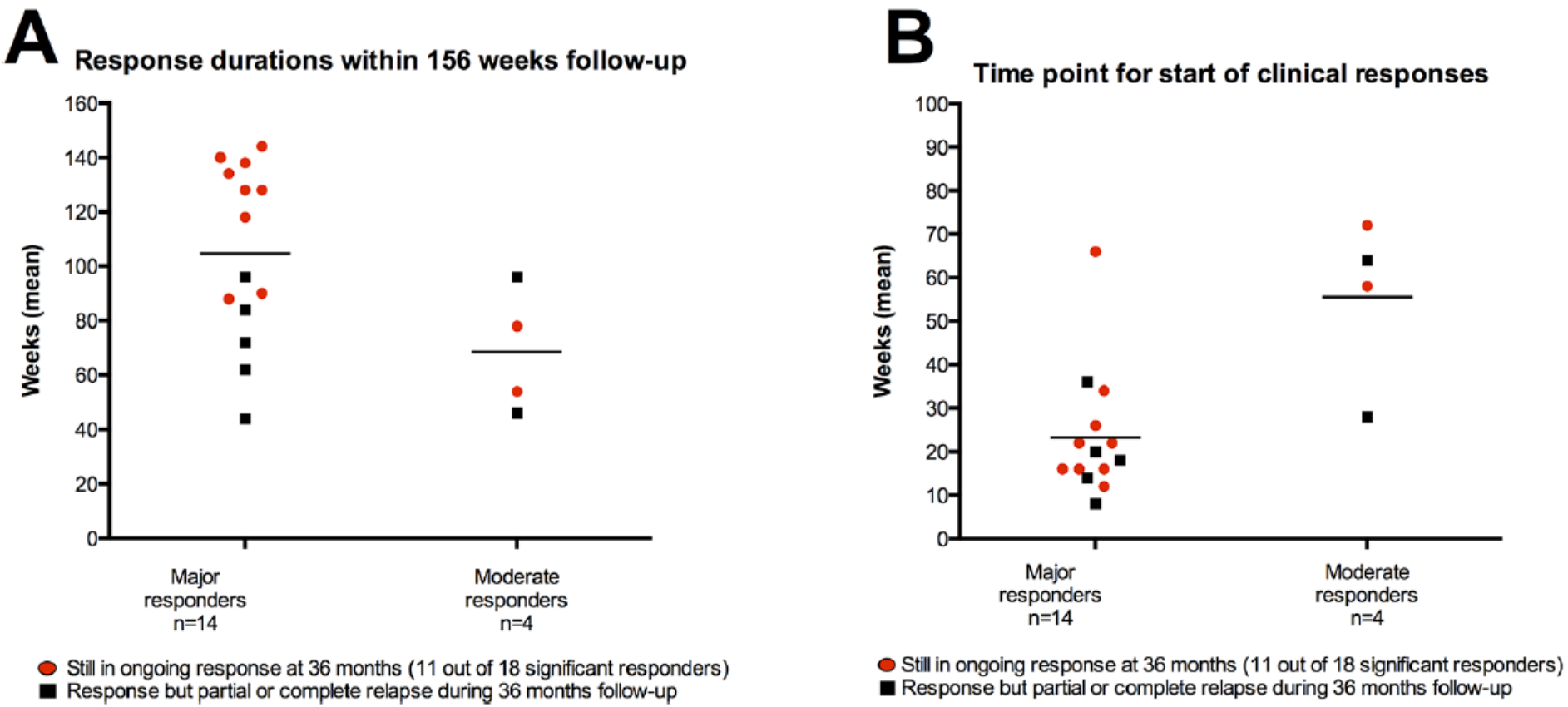

Figure: In panel A, response durations within the three years (156 weeks) follow-up are shown, for 14 major responders and four moderate responders. In panel B, time points for start of clinical responses are shown, for major and moderate responders. The overall response criterion was a Fatigue score 4.5 for a minimum of six consecutive weeks, which must include at least one recording of Fatigue score > 5.0 during the response period. Single response periods and the sum of response periods during follow-up were recorded as response duration.

Table: Comparison of SAT Issues (Dyachkova et al., 2024) with Rituximab Trial (Fluge et al., 2015)

SAT Issue (Dyachkova)	**Application to Rituximab Trial**
No control group	True - no placebo or active control arm. Limits causal inference.
Selection bias	Participants may have been more motivated. No randomization.
Time-related bias	Delayed responses (avg. 23 weeks) challenge timing interpretations.
Subjective outcomes	Fatigue and self-reported function are vulnerable to expectation bias.
Ethical justification	ME/CFS lacks effective treatments, making placebo potentially controversial.
Variable durations	Wide range of remission lengths (from a few weeks to years) raises questions about consistency and reproducibility of benefit.
Historic control use	Authors compared outcomes for nine patients against their own previous placebo data, but without formal weighting or matching.
Regulatory readiness	Phase II only — findings used to design a larger RCT, as appropriate.

Summary

1. **No Control Group:**
   Without a placebo or comparator, it's unclear if improvements in the Fluge trial were caused by rituximab or other factors (e.g., natural variation, psychological effects). Dyachkova et al. emphasize that without randomization and controls, SATs cannot reliably establish causality.
2. **Subjective Outcomes:**
   Reliance on self-reported fatigue and function scores introduces potential for bias. Expectation effects and lack of blinding further reduce the objectivity of results.
3. **Timing Bias and Delayed Response:**
   Clinical responses appeared after long delays (avg. 23 weeks), making it difficult to directly link outcomes to treatment timing and raising concerns about interpretability.
4. **Exploratory, Not Confirmatory:**
   While promising, the trial should be viewed as hypothesis-generating. It highlights areas for future study but does not provide definitive clinical or regulatory evidence.

Bibliography

[1] Dyachkova, Y., Dunger-Baldauf, C., Barbier, N., Devenport, J., Franzén, S., Kazeem, G., Künzel, T., Mancini, P., Mordenti, G., Richert, K., Ridolfi, A., & Saure, D. *Do You Want to Stay Single? Considerations on Single-Arm Trials in Drug Development and the Postregulatory Space.* Pharmaceutical Statistics, 23 (6), 1206–1217, (2024).

[2] Fluge, Ø., Risa, K., Lunde, S., Alme, K., Rekeland, I. G., Sapkota, D., Kristoffersen, E. K., Sørland, K., Bruland, O., Dahl, O., & Mella, O. *B-Lymphocyte Depletion in Myalgic Encephalopathy/Chronic Fatigue Syndrome. An Open-Label Phase II Study with Rituximab Maintenance Treatment.* PLOS ONE, 10 (7) (2015).

Thank you for your attention!