B-Lymphocyte Depletion in Patients With Myalgic Encephalomyelitis/Chronic Fatigue Syndrome. A Randomized, Double-Blind, Placebo-Controlled Trial

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25.04.2025

About the paper

- **Title**: „*B-Lymphocyte Depletion in Patients With Myalgic Encephalomyelitis/Chronic Fatigue Syndrome. A Randomized, Double-Blind, Placebo-Controlled Trial*".
- **Authors**: Øystein Fluge et al.
- The study lasted 24 months.
- Study performed at 4 university hospitals and 1 general hospital in Norway.
- Phase 3 trial.
- **Work goals**: To determine whether 6 infusions of rituximab given at certain intervals mitigate symptoms of Chronic Fatigue Syndrome.

Beginnings

- Firstly, a small, randomized, placebo-controlled, phase 2 trial was conducted.
- 30 patients with CFS received 2 infusions (rituximab or placebo) 2 weeks apart with 12 months of follow-up.
- The groups did not differ in the primary end point of self-reported fatigue score at 4 months of follow-up.
- The secondary end points favored the rituximab group at 6 to 12 months.

Inclusion criteria

1. Age between 18 and 65
2. Had ME/CFS for at least 2 years, but less than 15 years
3. Disease is not very severe
4. Signed informed consent

Statistical Analysis

A sample size was set to 152 patients using presumed overall response rates:

- 50% in the rituximab group,
- 25% in the placebo group.

Additionally, we have allowance for 5% withdrawal.

Primary and secondary outcome measures were analyzed according to treatment group allocation by the intention-to-treat principle.

Missing data were replaced by multiple imputation.

Study population

1. 1150 referrals received
2. 491 referrals with adequate medical information
3. 204 patients randomly selected and invited
4. 195 patients agreed to participate
5. 152 patients met inclusion criteria and went through random assignment
6. 73 patients in rituximab group received and 66 patients in placebo group received all infusions
7. Full data received from 76 patients from rituximab group and 73 patients from placebo group (in two more cases, missing data was imputed)

Details about outcomes

Primary outcome:

- score ≥ 4.5 for ≥ 8 consecutive weeks,
- repeated measurements of fatigue score over 24 months.

Secondary outcomes:

- repeated measurements of self-reported function over 24 months,
- components of the Short Form-36 Health Survey and Fatigue Severity Scale over 24 months,
- changes from baseline to 18 months in these measures and physical activity level.

Primary outcome results

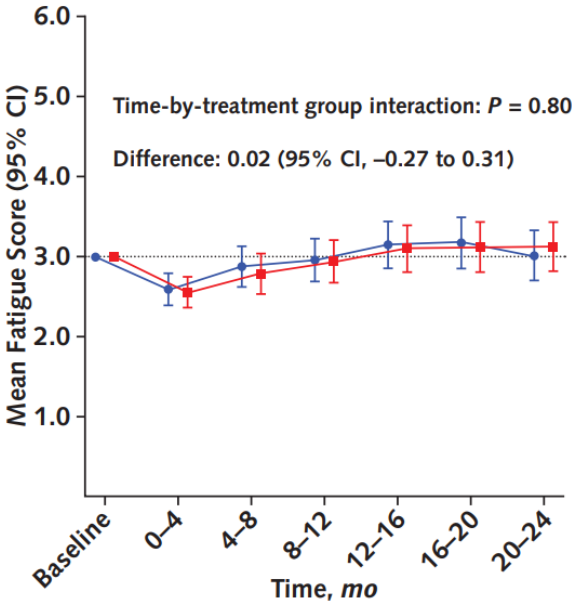
Preliminary Breslow-Day test to test homogeneity of the odds ratios across study centers:

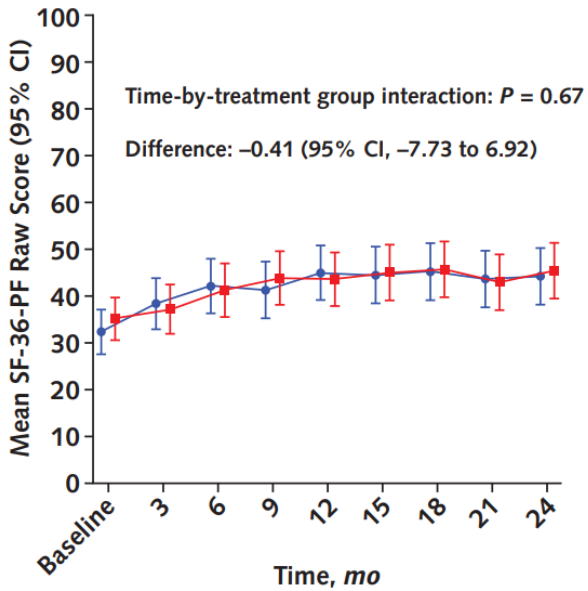
- p-value: 0.54,
- no evidences to say that effect of the treatment depends on a center.

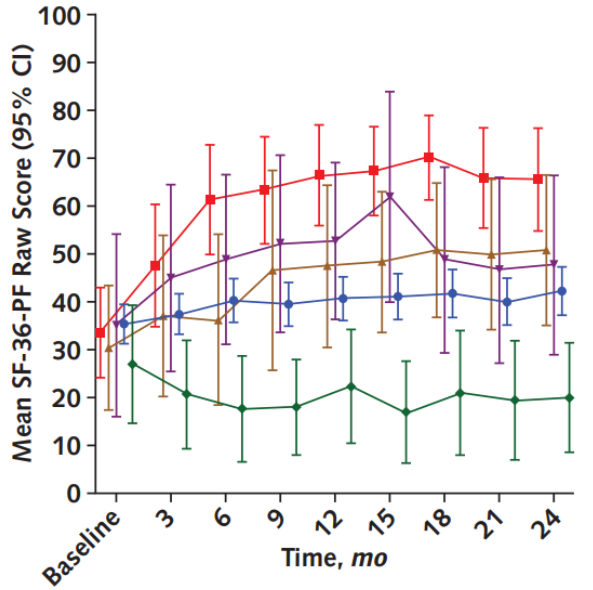
People with Fatigue score ≥ 4.5 for ≥ 8 consecutive weeks:

- (total) Placebo group: $26/74 \approx 35.1\%$,
- (total) rituximab group: $20/75 \approx 26.0\%$,
- the difference $\approx 9.2\%$,
- p-value of Mantel-Haenszel test: 0.22.

Primary outcome results







Placebo (n = 74)
Rituximab (n = 77)

Stable symptoms during follow-up (n = 90: 39 placebo, 51 rituximab)
Improvement ≥30 wk (n = 25: 14 placebo, 11 rituximab)
Improvement 14–28 wk (n = 12: 7 placebo, 5 rituximab)
Improvement 8–12 wk (n = 9: 5 placebo, 4 rituximab)
Worsening ≥12 wk (n = 15: 9 placebo, 6 rituximab)

Secondary outcome results

Secondary Outcome Measure*	Mean in Rituximab Group (n = 77)	Mean in Placebo Group (n = 74)	Mean Difference (95% CI)	P Value for Interaction†
Fatigue score‡				
Baseline	3.0	3.0		
16-20 mo	3.12	3.18	−0.06 (−0.51 to 0.39)	0.79
Function level, %§				
Baseline	20.14	18.37	1.77 (−1.50 to 5.05)	
16-20 mo	25.25	25.93	−0.68 (−5.90 to 4.54)	0.31
SF-36-PF score‖				
Baseline	35.24	32.45	2.79 (−3.79 to 9.36)	
18 mo	45.67	45.25	0.42 (−8.12 to 8.96)	0.52
SF-36-PCS score¶				
Baseline	24.80	23.61	1.19 (−0.92 to 3.32)	
18 mo	28.79	29.00	−0.21 (−3.18 to 2.77)	0.27
Fatigue Severity Scale score**				
Baseline	59.10	59.88	−0.78 (−2.47 to 0.92)	
18 mo	55.98	56.05	−0.07 (−3.21 to 3.08)	0.68
Mean steps per 24 h, n††				
Baseline	3297	3233	64 (−599 to 727)	
17-21 mo	3777	3904	−127 (−1004 to 749)	0.58

Figure 1: Secondary outcomes – Fluge et al. (2019)

Summary of the results

The randomized, double-blind, placebo-controlled trial did not detect a benefit from rituximab treatment in patients with ME/CFS during 24 months of follow-up.

Differences between placebo and experimental groups, regarding both primary and secondary outcomes were not statistically significant.

Potential limitation:
A lot of outcomes measures were self-reported. Wellbeing of patients is a subjective measure and everybody could feel it different.

Bibliography

- Henriques dos Santos de Sepúlveda, N. (2025). Lectures on Clinical Trials.
- Fluge Ø, Rekeland IG, Lien K, Thürmer H, Borchgrevink PC, Schäfer C, Sørland K, Aßmus J, Ktoridou-Valen I, Herder I, Gotaas ME, Kvammen Ø, Baranowska KA, Bohnen LMLJ, Martinsen SS, Lonar AE, Solvang AH, Gya AES, Bruland O, Risa K, Alme K, Dahl O, Mella O. *B-Lymphocyte Depletion in Patients With Myalgic Encephalomyelitis/Chronic Fatigue Syndrome: A Randomized, Double-Blind, Placebo-Controlled Trial*. Ann Intern Med. 2019 May 7;170(9):585-593. doi: 10.7326/M18-1451. Epub 2019 Apr 2. PMID: 30934066.

Thank You!