83rd Annual Meeting of the American Thyroid Association San Juan, Puerto Rico

Randomized Double-Blind Placebo-controlled Trial of Rituximab for Treatment of Graves' Ophthalmopathy

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PRESENTATION FROM THE 83rd ANNUAL MEETING OF THE AMERICAN THYROID ASSOCIATION, OCTOBER 16-20, 2013 (Marius Stan)

DISCLOSURE

Relevant Financial Relationships

None

Off Label Usage

Rituximab (Genentech)

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Learning Objectives

- Discuss the results of a trial of rituximab for moderate-to-severe Graves' ophthalmopathy (GO)

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Background

- Moderate-to-severe GO does not have a therapy with consistently good long-term results
- Studies support an important role for B cells, TSHR and TSHR antibodies in the pathophysiology of GO
- Case series have suggested rituximab (RTX) therapy could be beneficial
- No previous randomized controlled trials have evaluated the role of RTX in GO

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What is rituximab (RTX)?

RTX –

- anti-CD20 chimeric monoclonal antibody (found on pre-B cells and mature B lymphocytes)
- induces transient B-cell depletion
- blocks early B cell activation and differentiation
- decreases cytokine secretion, antigen presentation and T cell activation.

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CAS

1) Spontaneous retrobulbar pain
2) Pain with eye movement
3) Redness of the eyelids
4) Redness of the conjunctiva
5) Swelling of the eyelids
6) Inflammation of the caruncle
7) Conjunctival edema

Clinical Activity Score (CAS) = sum of all items present

- Exclusion criteria:
  - Corticosteroids within last 4 weeks
  - Orbital decompression surgery within last year.
  - Orbital radiotherapy within last 18 months

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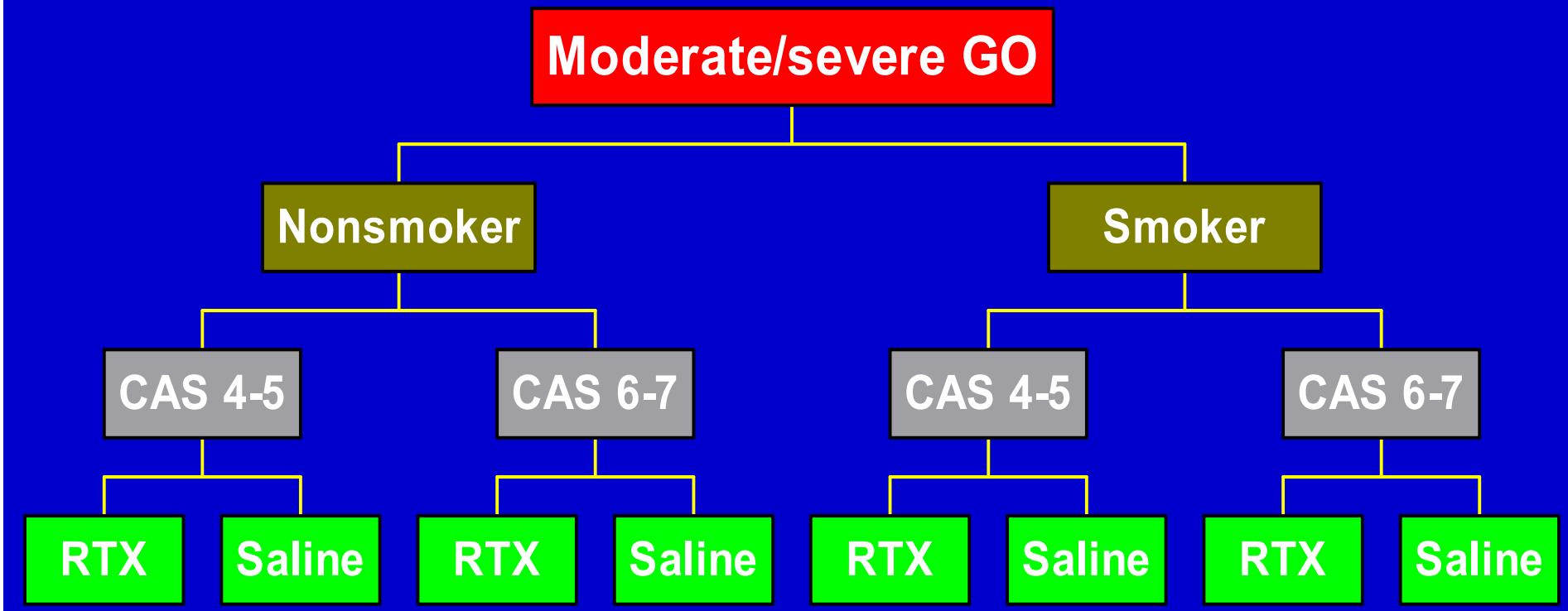
Study Design



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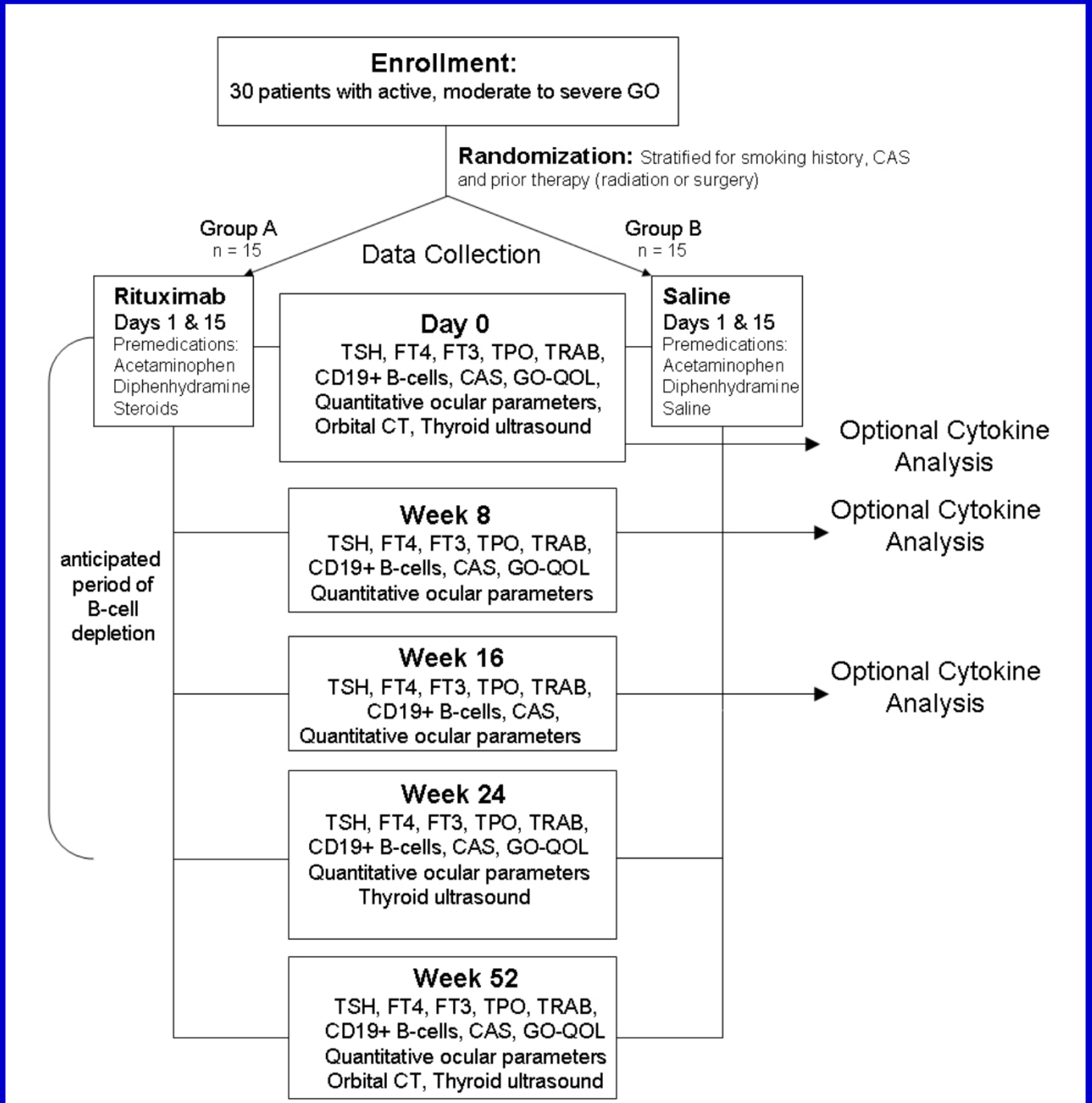
Enrollment:
30 patients with active, moderate to severe GO
Randomization: Stratified for smoking history, CAS and prior therapy (radiation or surgery)
Group A
n = 15
Data Collection
Group B
n = 15
Rituximab
Days 1 & 15
Premedications:
Acetaminophen
Diphenhydramine
Steroids
Saline
Days 1 & 15
Premedications:
Acetaminophen
Diphenhydramine
Saline
Day 0
TSH, FT4, FT3, TPO, TRAB, CD19+ B-cells, CAS, GO-QOL, Quantitative ocular parameters, Orbital CT, Thyroid ultrasound
Optional Cytokine Analysis
Week 8
TSH, FT4, FT3, TPO, TRAB, CD19+ B-cells, CAS, GO-QOL Quantitative ocular parameters
Optional Cytokine Analysis
anticipated period of B-cell depletion
Week 16
TSH, FT4, FT3, TPO, TRAB, CD19+ B-cells, CAS, Quantitative ocular parameters
Optional Cytokine Analysis
Week 24
TSH, FT4, FT3, TPO, TRAB, CD19+ B-cells, CAS, GO-QOL Quantitative ocular parameters Thyroid ultrasound
Week 52
TSH, FT4, FT3, TPO, TRAB, CD19+ B-cells, CAS, GO-QOL Quantitative ocular parameters Orbital CT, Thyroid ultrasound

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Comparison of groups at baseline

No differences in:

- Quantitative ocular evaluations
- CAS
- Age/sex/smoking prevalence
- GO duration
- Prior use of systemic steroids
- TRAb levels

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Baseline evaluation

Variable	Placebo (n=12)	Rituximab (n=13)	P value
Age – mean (SD)	61.8 (11.0)	57.6 (12.7)	0.31
Female gender – n (%)	8 (66.7)	9 (69.2)	0.89
Caucasian race – n (%)	12 (100)	13 (100)	
CAS (SD)	5.3 (1.0)	4.9 (1.0)	0.36
Smoking – n (%)	2 (16.7)	2 (15.4)	0.93
GO duration, days – median (IQR)	299 (253-595)	373 (240-1080)	0.79
TRAb, IU/L – median (IQR)	19.5 (2.2-28.8)	20 (9-60)	0.44
Dermopathy/Acropachy – n(%)	1 (8.3%)	2 (15.4)	0.59
Prior steroid therapy – n (%)	6/11	2/12	0.09
Progressive GO – n (%)	12 (100)	12 (92.3%)	0.33

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Baseline evaluation

Variable	Placebo (n=12)	Rituximab (n=13)	P value
Proptosis left (Ophthalmology) mm – mean (SD)	23.0 (2.4)	24.2 (3.3)	0.36
Proptosis right (Ophthalmology) mm – mean (SD)	23.3 (3.8)	24.6 (3.0)	0.32
Proptosis left (CT) mm – mean (SD)	17.3 (2.6)	18.2 (2.7)	0.34
Proptosis right (CT) mm – mean (SD)	17.2 (3.3)	19.0 (2.6)	0.24
Lid fissures left (mm) – mean (SD)	9.8 (2.0)	11.1 (2.8)	0.30
Lid fissures right (mm) – mean (SD)	9.0 (2.7)	10.9 (1.5)	0.06

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Results

- 25 patients were randomized (12 to placebo and 13 to RTX)
- 24/25 received both infusions; 1 received only one infusion → severe reaction.
- 21/25 patients completed the study to 6 months (primary end point analysis)
  - 1 dropped out for personal reasons
  - 1 due to medication reaction
  - 2 due to disease progression
- 19/21 patients completed additional 6 months follow-up
  - 1 dropped out for personal reasons
  - 1 due to disease progression

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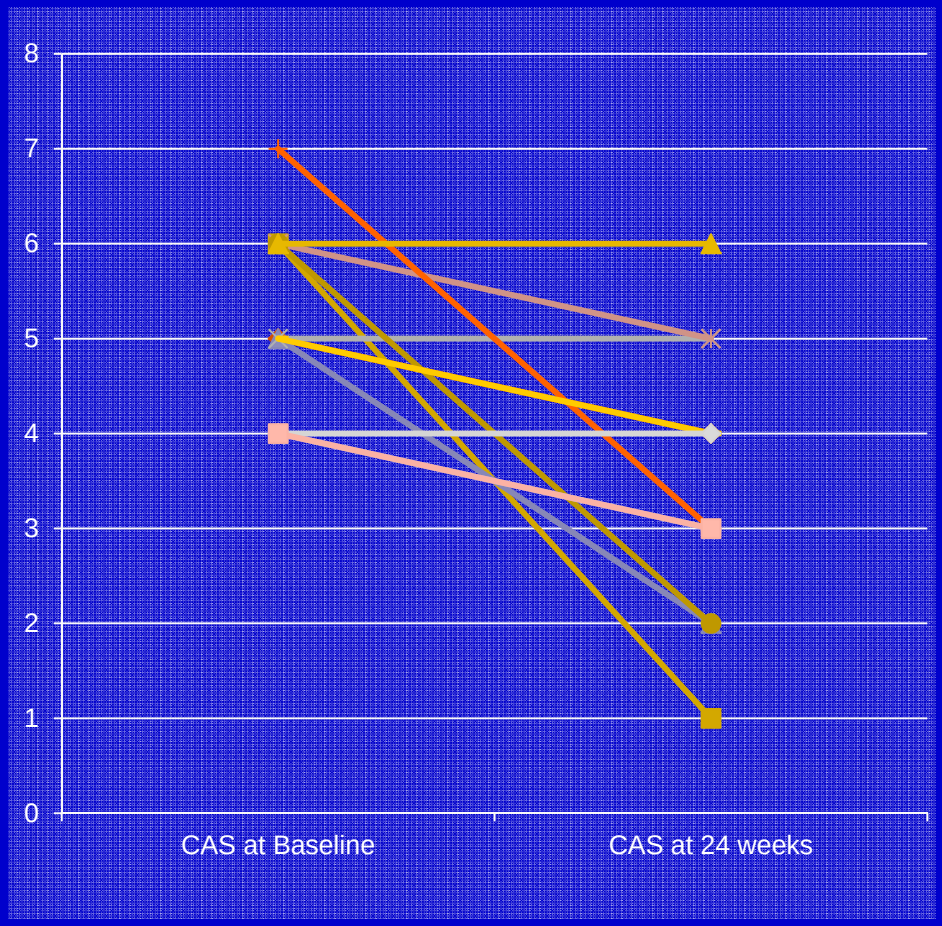
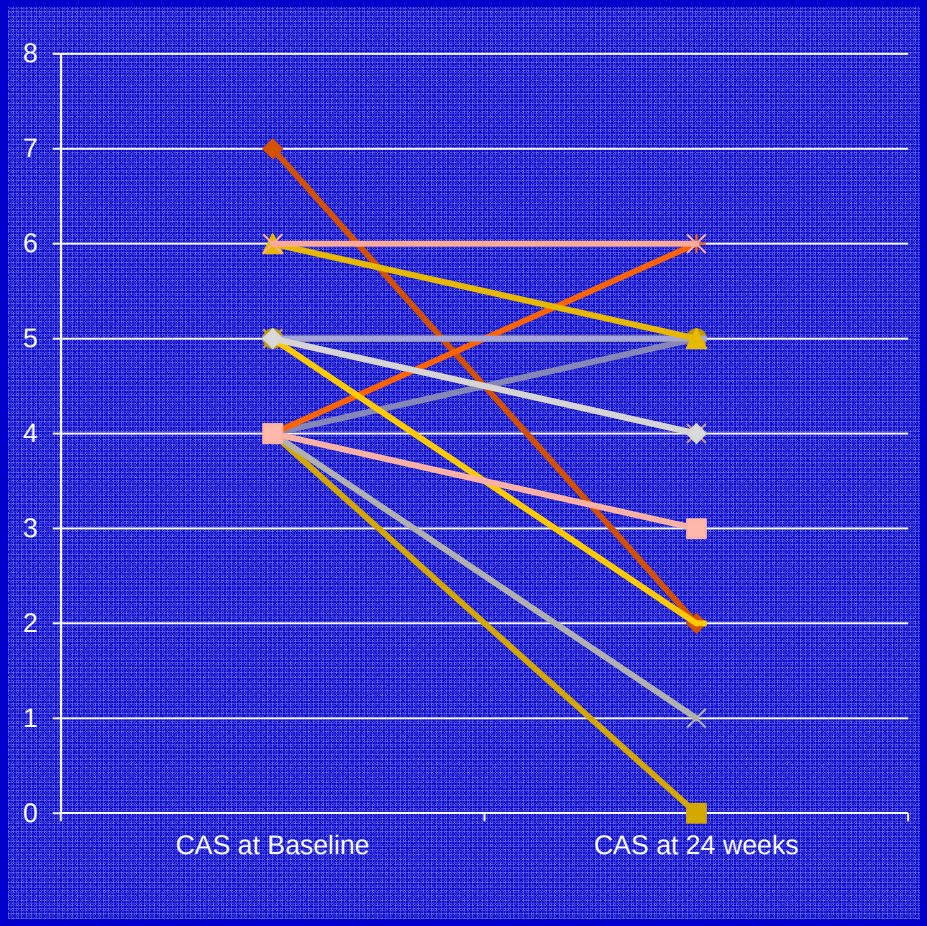
CAS Data

Placebo



Rituximab



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Results (24 wks)

- Change in CAS (primary endpoint) did not differ between groups
  - 0-24 we: 1.8 (1.8SD) vs. 1.2 (2.0)
  - 24 we: 3.5 (1.4) placebo vs. 3.7 (1.9) RTX
  - CAS increased in 2 patients – RTX group
- Failure (ΔCAS < 2 or need for surgery/steroids) equal between groups
  - 6 failed by 12 months in each group
  - 4 patients had progressive disease → decompression: 3 in RTX, 1 in placebo

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Results (24 weeks)

Variable	Placebo	Rituximab	P value
CAS 0-24 we – mean (SD)	-1.8 (1.8)	-1.2 (2.0)	0.47
CAS at 24 we – mean (SD)	3.5 (1.4)	3.7 (1.9)	0.62
Proptosis difference Ophthalmology left 0-24 we – mean (SD)	-0.4 (1.9)	0.3 (1.4)	0.28
Proptosis difference Ophthalmology right 0-24 we – mean (SD)	-0.3 (1.3)	0.3 (1.4)	0.36
Proptosis difference (CT) left 0-52 we – mm; mean (SD)	0.0 (1.9)	0.1 (1.2)	0.84
Proptosis difference (CT) right 0-52 we – mm; mean (SD)	-0.9 (1.3)	-0.8 (1.4)	0.87
Lid fissures difference 0-24 we (left) – mm; mean (SD)	-0.3 (1.4)	-0.5 (3.8)	0.49
Lid fissures difference 0-24 we (right) – mm; mean (SD)	0.0 (1.5)	0.0 (1.1)	0.98
Failure (%)	6 (50)	6 (46.2)	0.85

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Adverse Effects

Side-effect type	Placebo	Rituximab
Myalgias/arthralgias	2	2
Skin (rash, itching)	0	2
Infectious (bronchitis, conjunctivitis)	1	1
Vasculitis	0	1
Optic neuropathy	0	2
Severe eye tearing	0	1
GI (Tongue pain, abd pain, diarhea)	1	2
Moderate/Severe AEs	***1***	***5***

This table includes events possibly, probably/likely and definitely associated with therapy as well as those with unknown association.

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Quality of Life Data

	Placebo	RTX	P value
Baseline			
Indirect Q 2-19 - median (IQR)	17 (13-18)	17 (6-18)	0.84
Direct Q 20-25 - median (IQR)	6 (3-6)	5 (2-6)	0.14
SF-12 Physical - mean (SD)	39.9 (7.8)	47.7 (10.2)	0.052
SF-12 Mental - mean (SD)	44.3 (9.8)	41.8 (12.6)	0.71
24 Weeks			
Indirect Q 2-19 - median (IQR)	15 (10-18)	14.5 (6-18)	0.62
Direct Q 20-25 - median (IQR)	4 (3-6)	4 (1-6)	0.23
SF-12 Physical - mean (SD)	45.4 (9.8)	46.9 (8.4)	0.49
SF-12 Mental - mean (SD)	49.6 (11.4)	49 (11.2)	0.99
Difference 0-24 weeks			
Indirect Q 2-19	-1	-0.05	0.99
Direct Q 20-25	-0.05	-0.05	0.93
SF-12 Physical	4.5	-3.1	0.11
SF-12 Mental	7.34	2	0.49

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Results – ongoing work

- Other secondary endpoints and parameters currently being analyzed
  - Quality of life – specific Q, 52 weeks, EQ5D (functional impact)
  - Same 52 we data is currently being analyzed (plus perimetry, CAS 0-10)
  - Cytokines
  - CT data

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Summary

- In patients with active, moderately severe and progressive GO of ~ 1 year duration RTX does not offer a therapeutic benefit
- 50% of patients improved in both groups
- Decompression within 12 months of drug infusion more common in RTX group
- RTX side effects profile is significant, yet infections were not a major problem

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Conclusions

- Rituximab offers no therapeutic benefit and has a significant side effect profile in patients with active, moderate/severe and progressive GO of ~ 1 year duration
- Whether patients with active disease of shorter duration might benefit from this treatment is unknown

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