

**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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DISCLOSURE

Relevant Financial Relationships

None

Off Label Usage

Rituximab (Genentech)

Learning Objectives

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

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**

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.**

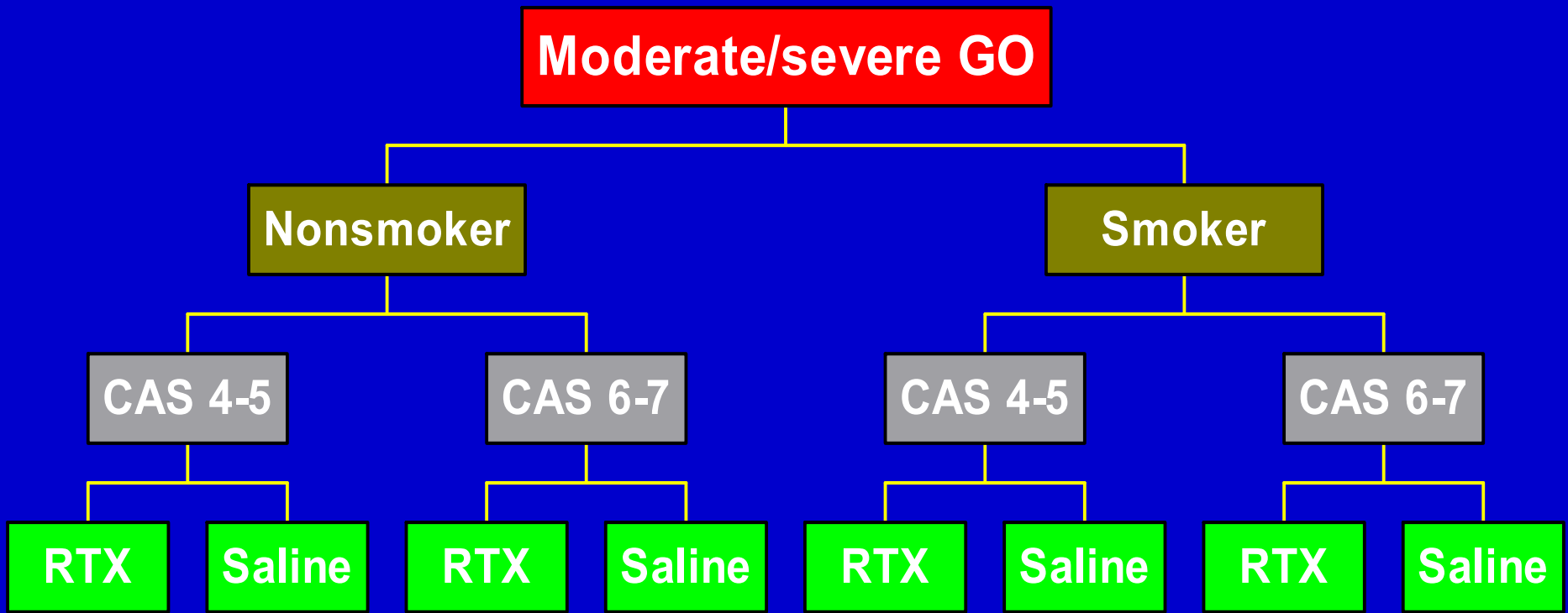
CAS

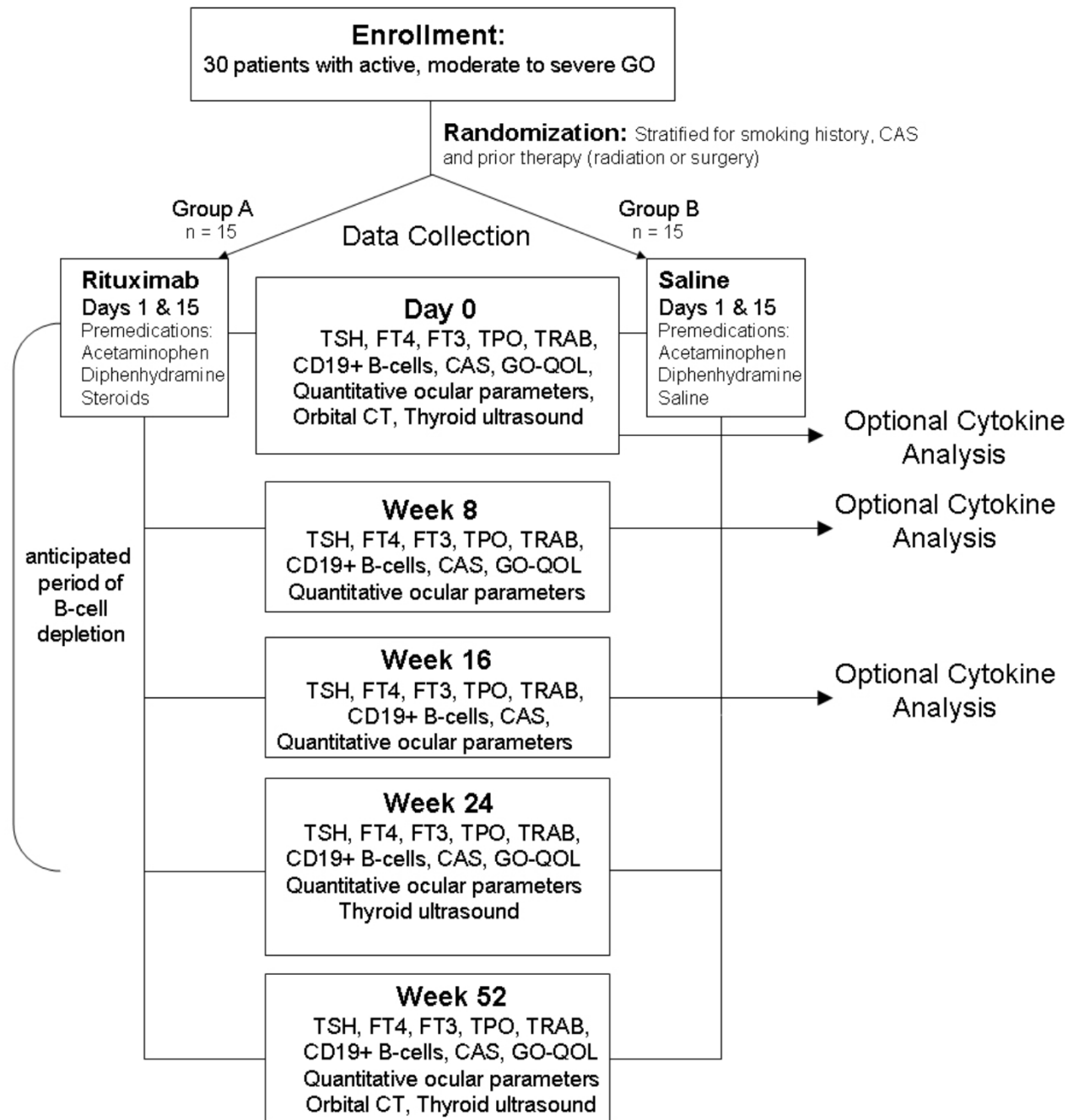
- 1) Spontaneous retrobulbar pain
- 2) Pain with eye movement
- 3) Redness of the eyelids
- 4) Redness of the conjunctiva
- 5) Swelling of the eyelids
- 6) Inflammation of the caruncle
- 7) Conjunctival edema

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**

Study Design





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

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

Baseline evaluation

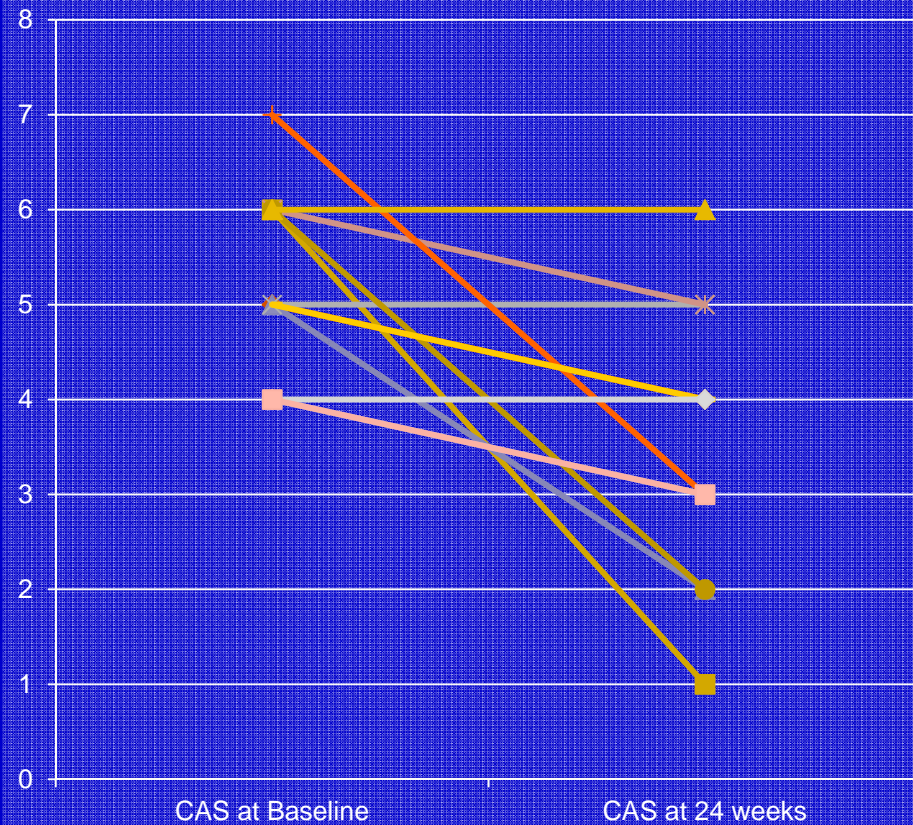
Variable	Placebo (n=12)	Rituximab (n=13)	P value
Proptosis left (Ophthalmology) mm – mean (SD)	23.0 (2.4)	24.2 (3.3)	0.36
Proptosis right (Ophthalmology) mm – mean (SD)	23.3 (3.8)	24.6 (3.0)	0.32
Proptosis left (CT) mm – mean (SD)	17.3 (2.6)	18.2 (2.7)	0.34
Proptosis right (CT) mm – mean (SD)	17.2 (3.3)	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

Results

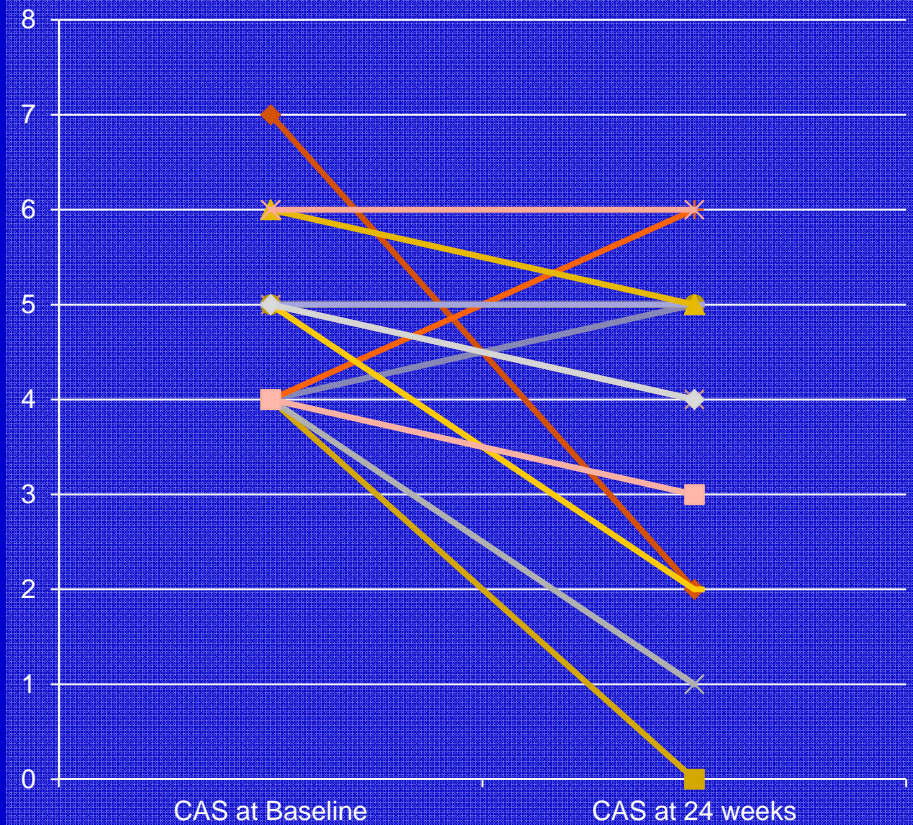
- **25 patients were randomized (12 to placebo and 13 to RTX)**
- **24/25 received both infusions; 1 received only one infusion → severe reaction.**
- **21/25 patients completed the study to 6 months (primary end point analysis)**
 - **1 dropped out for personal reasons**
 - **1 due to medication reaction**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

CAS Data

Placebo



Rituximab



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 (Δ CAS < 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

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

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, diarrhea)	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.

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

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**

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

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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