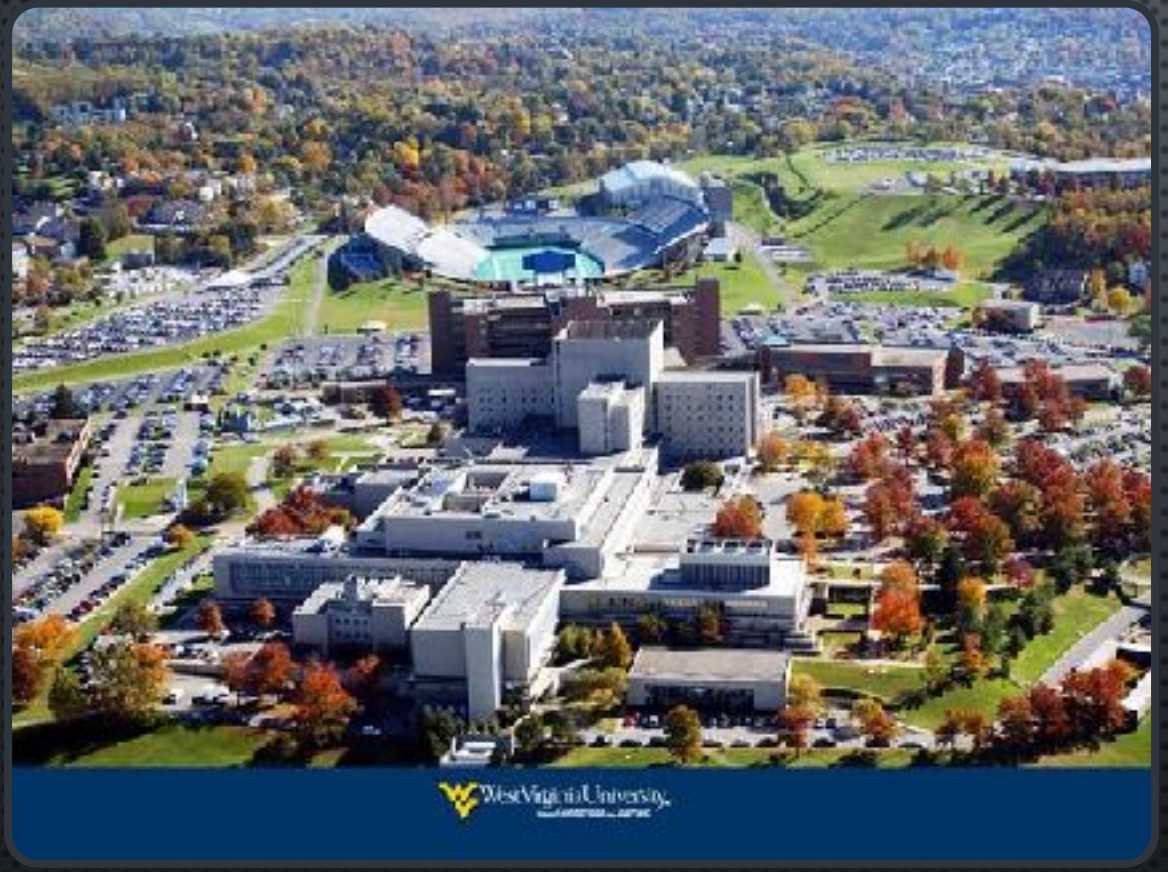


UPDATES ON THYROID EYE DISEASE

JOHN NGUYEN, MD

DISCLOSURE

- No financial interest or relationship to disclose

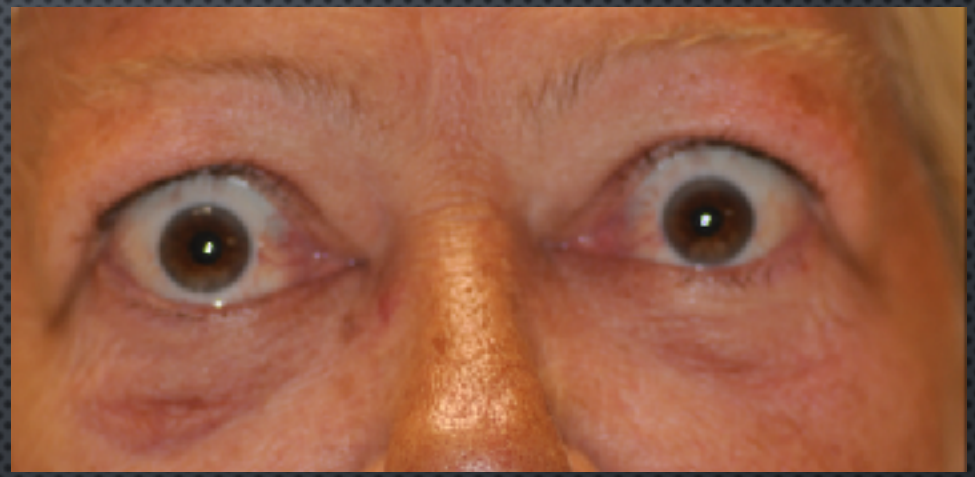
EPIDEMIOLOGY

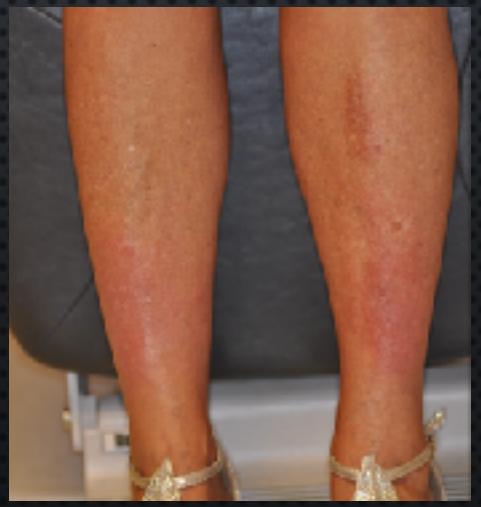
- Most common autoimmune orbital disease
- Annual incidence
  - 16/100K women
  - 3/100K men
- Caucasian>Asian
- 30-50 yo
  - Older age (male)
- Thyroid status
  - Hyperthyroidism (90%)
  - Hashimoto thyroiditis (3%)
  - Hypthyroidism (1%)
  - Normal thyroid function (6%)

Smith TJ and Hegedus L. Graves' Disease. N Engl J Med 2016;375:1552-65. DOI: 10.1056/NEJMra1510030

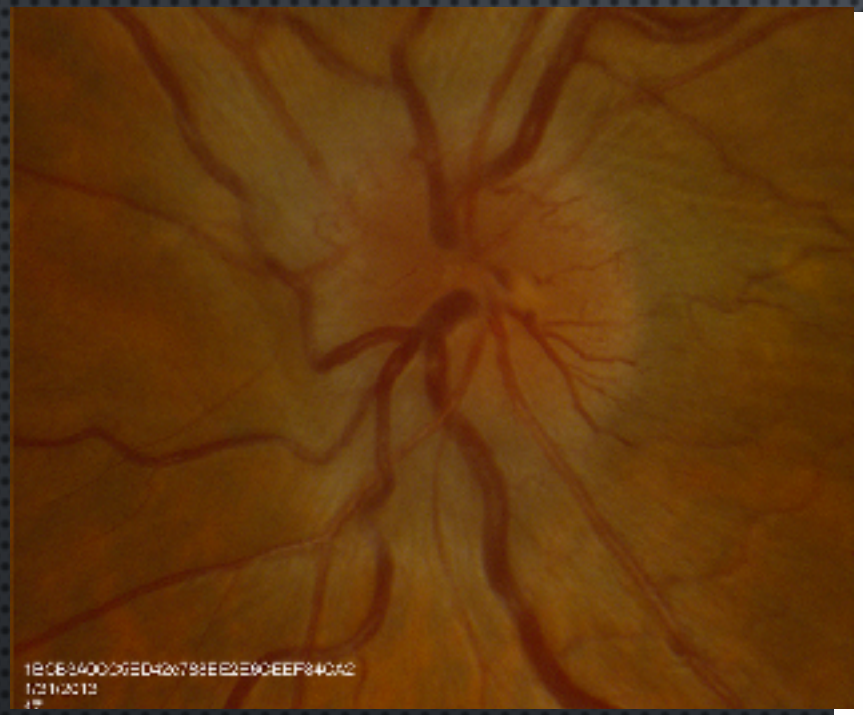
SYMPTOMS & SIGNS

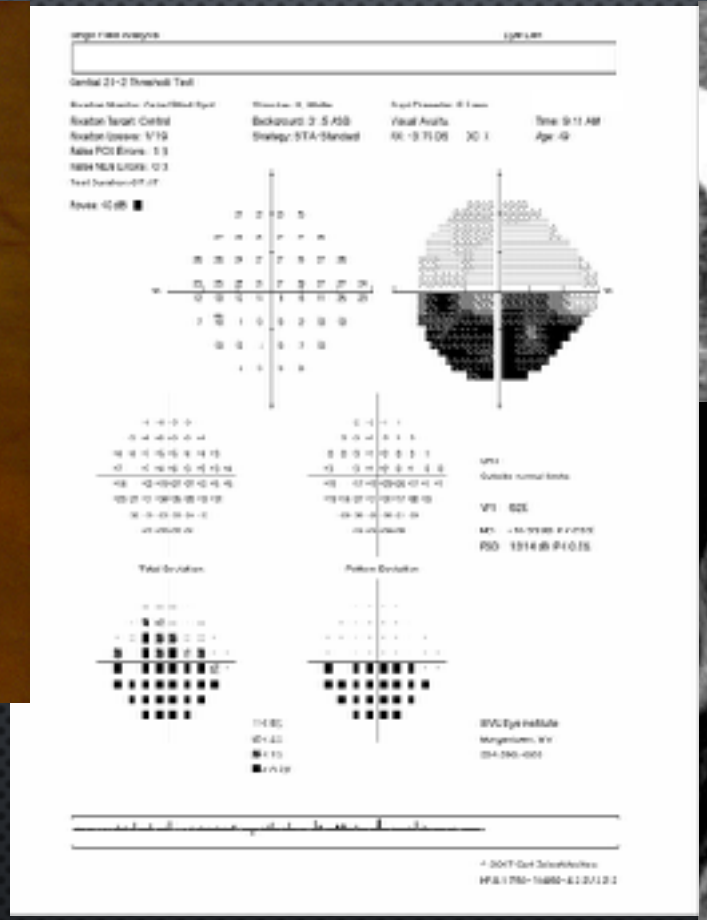
- Clinical signs in 50% of graves' pt
  - Eyelid retraction – 75-90%
  - Proptosis – 40-70%
  - Motility disturbances – 42%
  - Pain -30%
  - Tearing – 23%
  - Optic Neuropathy - <5%
- Subtle changes in orbital imaging seen in 70% with graves

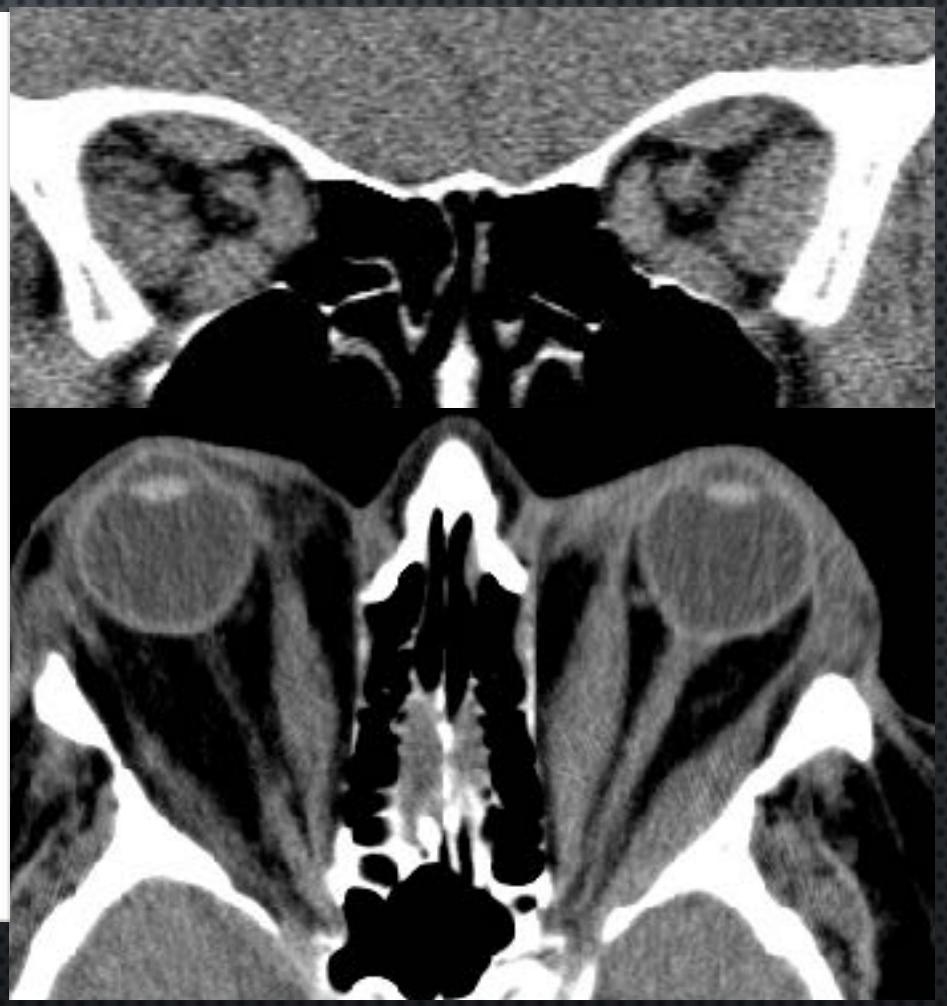


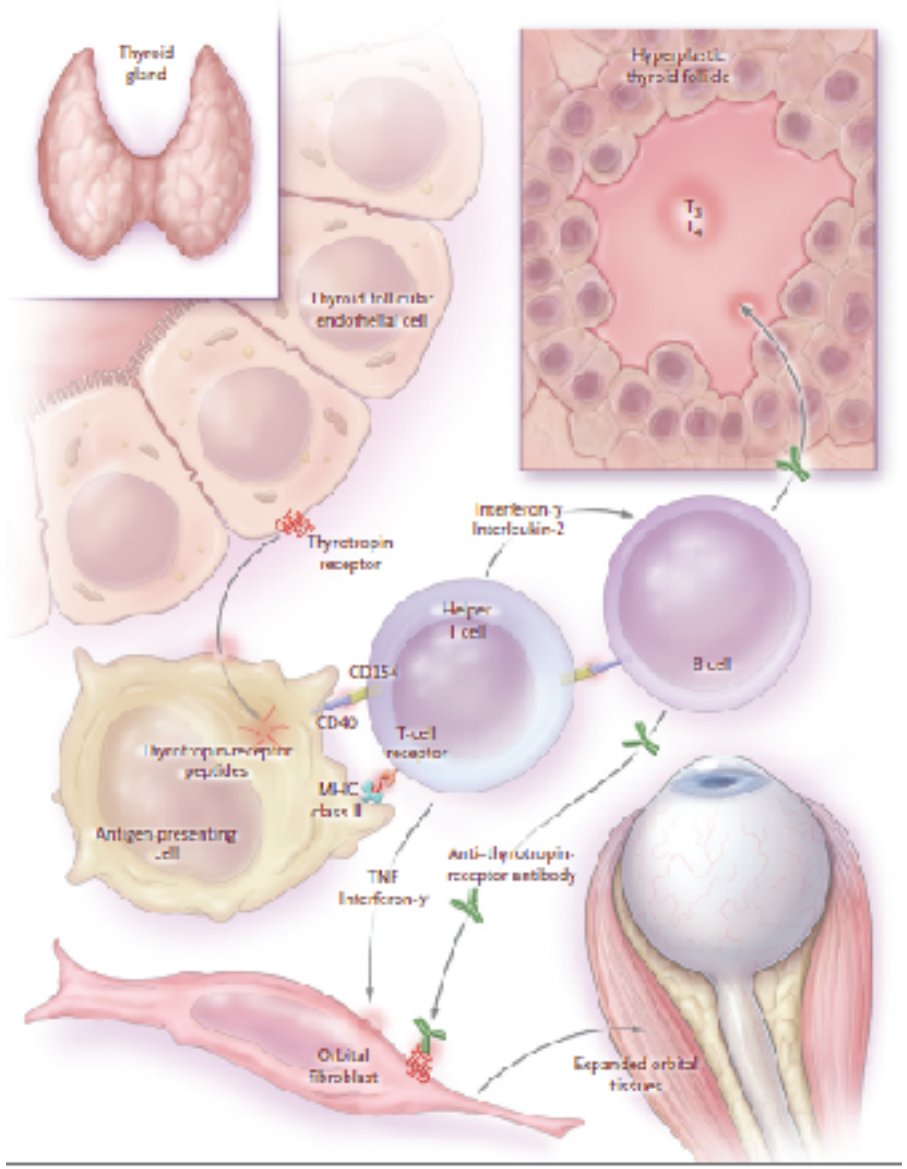


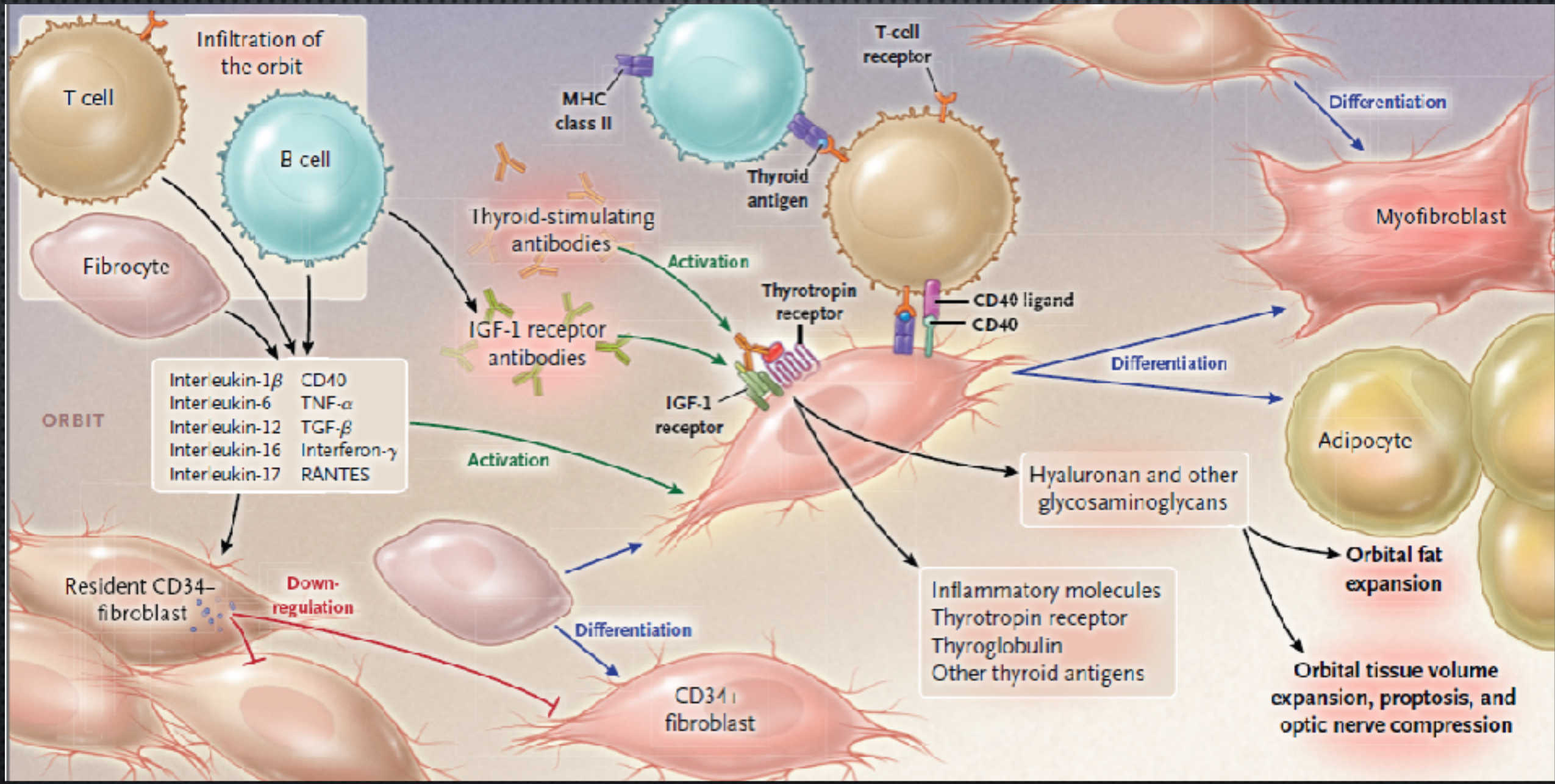
Bartelena L. Graves' orbitopathy: Imperfect treatment for a rare disease. European Thyroid Journal 2013; 2:259-269.

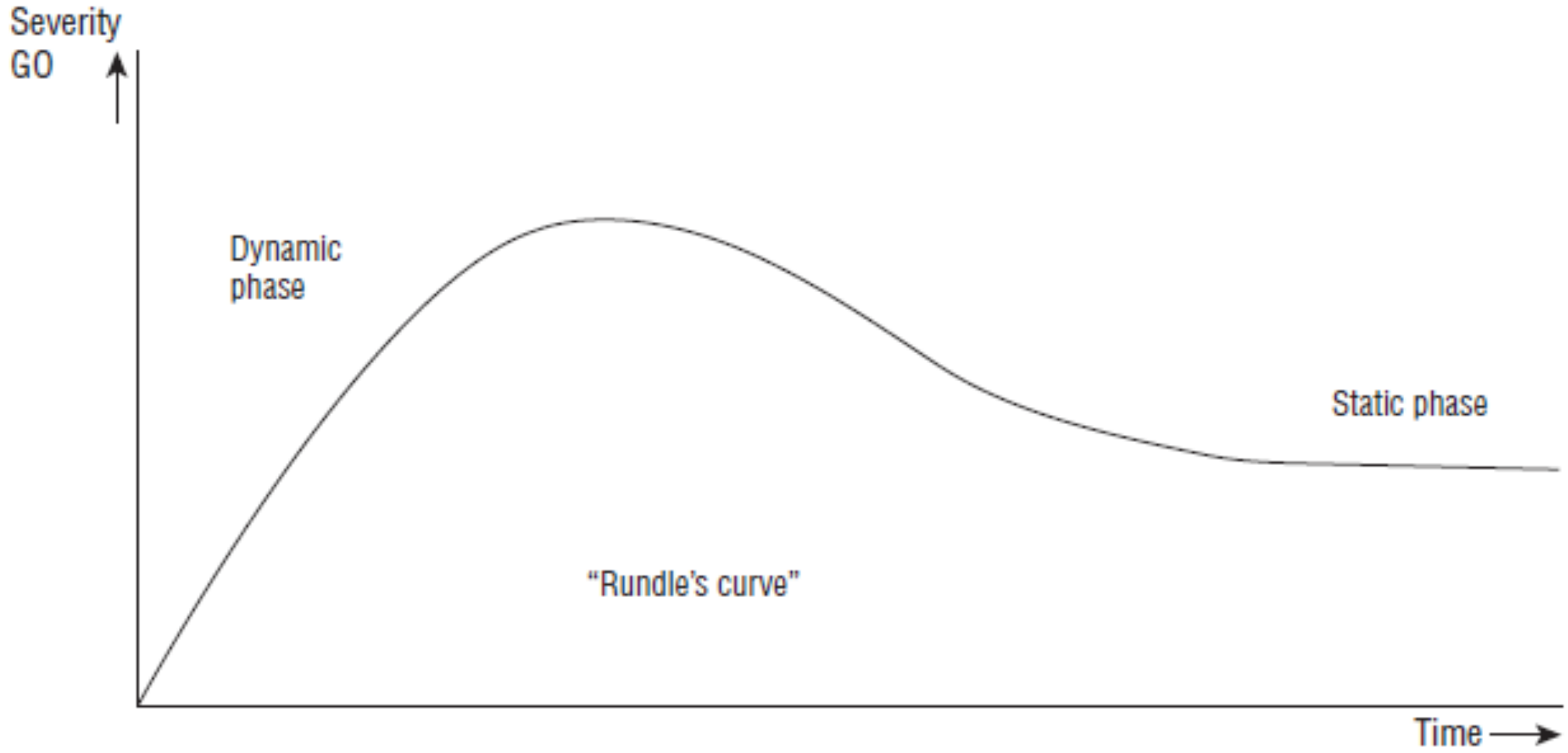


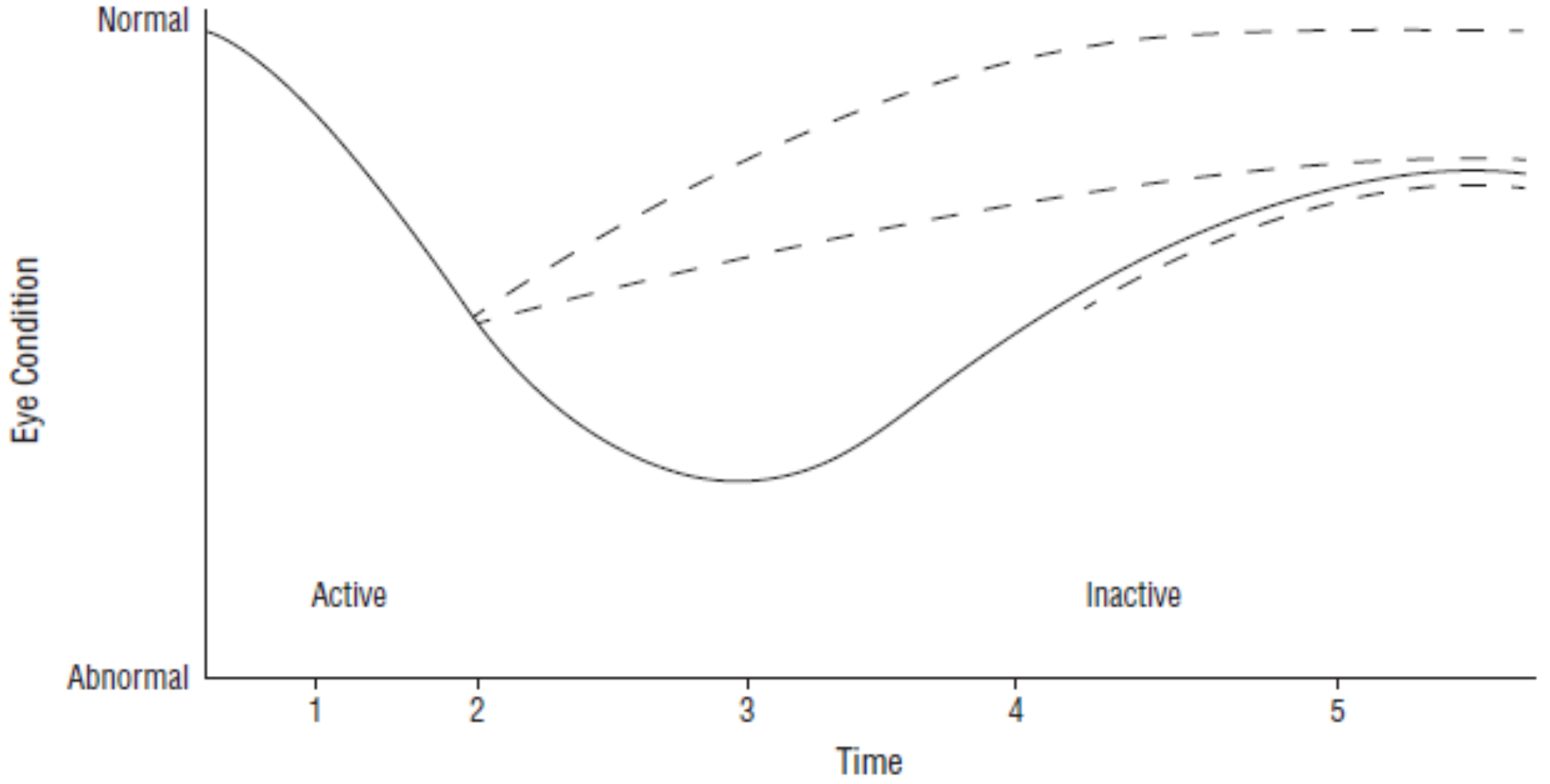





Thyroid gland
Hyperplastic thyroid follicle
Thyroid follicular endothelial cell
Thyrotropin receptor
Interferon-γ
Interleukin-2
Helper T cell
B cell
CD154
CD40
T-cell receptor
Thyrotropin-receptor peptides
MHC class II
Antigen presenting cell
TNF
Interferon-γ
Anti–thyrotropin-receptor antibody
Orbital fibroblast
Expanded orbital tissues


Infiltration of the orbit
T cell
B cell
Fibrocyte
MHC class II
T-cell receptor
Thyroid antigen
Thyroid-stimulating antibodies
IGF-1 receptor antibodies
Activation
Thyrotropin receptor
CD40 ligand
CD40
IGF-1 receptor
Differentiation
Myofibroblast
Adipocyte
Interleukin-1β
Interleukin-6
Interleukin-12
Interleukin-16
Interleukin-17
CD40
TNF-α
TGF-β
Interferon-γ
RANTES
ORBIT
Activation
Hyaluronan and other glycosaminoglycans
Orbital fat expansion
Resident CD34– fibroblast
Down-regulation
Differentiation
Inflammatory molecules
Thyrotropin receptor
Thyroglobulin
Other thyroid antigens
CD34+ fibroblast
Orbital tissue volume expansion, proptosis, and optic nerve compression


Severity
GO
Dynamic
phase
Static phase
"Rundle's curve"
Time


Normal
Eye Condition
Abnormal
Active
Inactive
1
2
3
4
5
Time

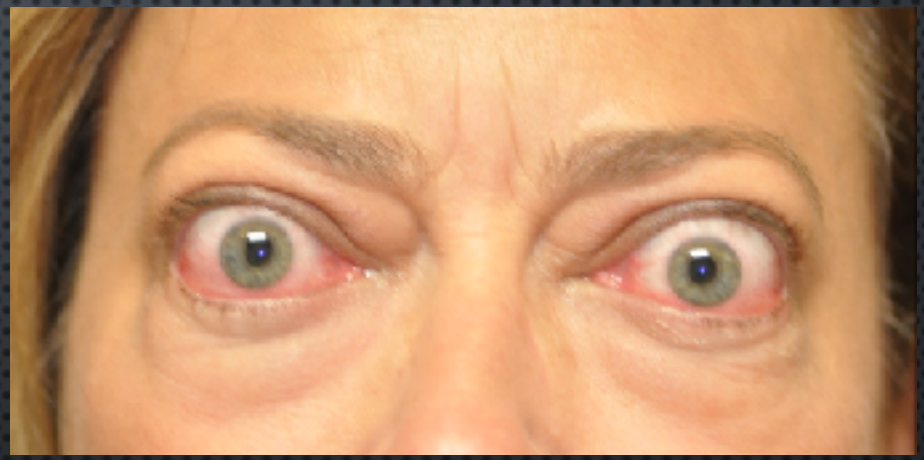
Sign or symptom	Score
Caruncular edema	0: absent 1: present
Chemosis	0: absent 1: conjunctiva lies behind the grey line of the lid 2: conjunctiva extends anterior to the grey line of the lid
Conjunctival redness	0: absent 1: present
Lid redness	0: absent 1: present
Lid edema	0: absent 1: present but without redundant tissues 2: present and causing bulging in the palpebral skin, including lower lid festoon
Retrobulbar ache	
At rest	0: absent; 1: present
With Gaze	0: absent; 1: present
Diurnal variation	0: absent; 1: present

Soft tissues	*Eyelid swelling* i) Absent ii) Mild: none o' the features defining moderate/over severe swelling are present iii) Moderate: definite swelling but no lower eyelid festoons and in the upper eyelid the skin fold becomes angled on a 45° downgaze iv) Severe: lower eyelid festoons OR upper lid fold remains rounded on a 45° downgaze *Eyelid erythema* i) Absent ii) Present *Conjunctival redness* i) Absent ii) Mild: equivocal or minimal redness iii) Moderate: >50% of definite conjunctival redness iv) Severe: >50% of definite conjunctiva redness *Conjunctival edema* i) Absent ii) Present: separation of conjunctiva from sclera present in >1/3 of the total height of the subtarsal anterior conjunctiva prolapsing anterior to eyelids of eyelid *Inflammation of caruncle or plica semilunaris* i) Absent ii) Present: plica is prolapsed through closed eyelids or caruncle and/or plica are inflamed
Eyelid measurements	*Palpebral aperture (mm)* *Upper/lower lid retraction (mm)* *Levator function (mm)* *Lagophthalmos* i) Absent ii) Present *Bell's phenomenon* i) Absent ii) Present
Proptosis	Measurement with Hertel's exophthalmometer. Recording of intercanthal distance.
Ocular motility	*Prism cover test* *Binocular diplopia* *Head posture* *Torsion* *Field of binocular single vision*
Cornea	*Corneal integrity* i) Normal ii) Punctate keratopathy iii) Ulcer iv) Perforation
Optic neuropathy	i) Visual acuity (Logmar or Snellen) ii) Afferent pupil defect (present/absent) iii) Colour vision iv) Optic disc assessment: normal/atrophy/edema

CLINICAL EVALUATION

VISA

- Vision
- Inflammation (10 points scale)
  - Conjunctival injection (0-1)
  - Chemosis (0-2)
  - Caruncular edema (0-1)
  - Eyelid edema (0-2)
  - Eyelid erythema (0-1)
  - Retrobulbar ache (0-2)
  - Diurnal variation (0-1)
- Strabismus
- Appearance



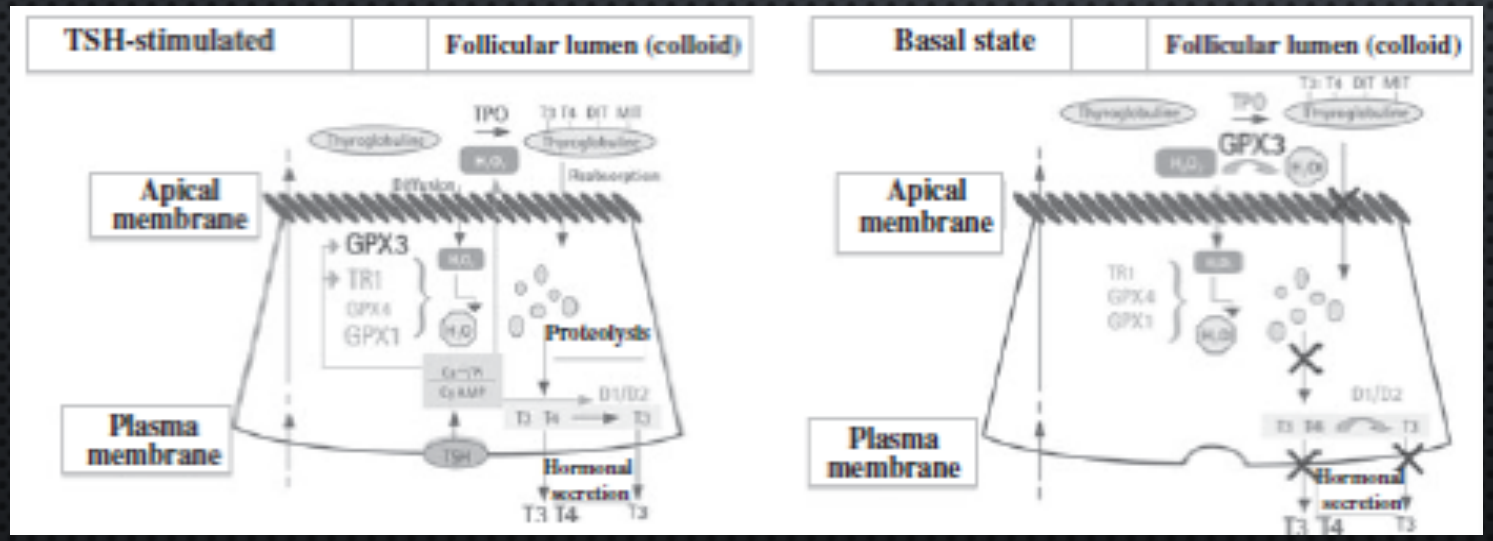
TREATMENT

Therapy	Mode of Action	Pros and Cons	Common Doses
Mild active disease			
Topical solutions			
Artificial tears	Maintain tear film	Rapid action, minimal side effects	
Glucocorticoids	Reduce inflammation	Rapid action, minimal side effects	
Avoidance of wind, light, dust, smoke	Reduces ocular surface desiccation, reduces irritation		
Elevation of head during sleep	Reduces orbital congestion		
Avoidance of eye cosmetics	Reduces irritation	Benefits not yet confirmed	
Selenium[55]	Uncertain	Benefits not yet confirmed	
Moderate or severe active disease			
Systemic glucocorticoids			
Oral	Reduce inflammation and orbital congestion	Hyperglycemia, hypertension, osteoporosis	Up to 100 mg of oral prednisone daily, followed by tapering of the dose[60]
Intravenous	Reduce inflammation and orbital congestion	Rapid onset of anti-inflammatory effect, fewer side effects than oral delivery, liver damage on rare occasions	Methylprednisolone, 500 mg/wk for 6 wk followed by 250 mg/wk for 6 wk[61,62]
Orbital irradiation	Reduces inflammation	Can induce retinopathy	2 Gy daily for 2 wk (20 Gy total)[63]
B-cell depletion*	Reduces autoreactive B cells	Very expensive; risks of infection, cancer, allergic reaction	Two 1000-mg doses of intravenous rituximab 2 wk apart
Emergency orbital decompression ‡	Reduces orbital volume		
Stable disease (inactive)			
Orbital decompression (fat removal)	Reduces orbital volume	Postoperative diplopia, pain	
Bony decompression of the lateral and medial walls	Reduces proptosis by enlarging orbital space	Postoperative diplopia, pain, sinus bleeding, cerebrospinal fluid leak	
Strabismus repair	Improves eye alignment, reduces diplopia		
Eyelid repair	Improves appearance, reduces lagophthalmos, and improves function		

Smith TJ and Hegedus L. Graves' Disease. N Engl J Med 2016;375:1552-65. DOI: 10.1056/NEJMra1510030

SELENIUM

- ESSENTIAL FOR SELENOCYTOSINE SYNTHESIS
- INCORPORATE INTO ENZYMES
- REDUCTION-OXIDATION FUNCTION



Selenoproteins	Proposed functions
Glutathione peroxidases (GPXs)	
GPX1	Cytosolic antioxidant, type of reserve?
GPX 2	Digestive tract antioxidant
GPX 3	Plasma and extracellular space antioxidant, significant thyroid expression
GPX 4	Mitochondrial membrane antioxidant, structural protein of sperm, apoptosis?
GPX 5	Unknown
GPX 6	GPX1 homologue?
Thioredoxin reductase (TRs)	Sustain the oxidation-reduction systems within the body, regulates certain transcription and cell growth factors
TR1	Principally cytosolic, ubiquitous
TR2	Testes expression
TR3	Principally mitochondrial, ubiquitous
Deiodinases	
Type 1 deiodinase (D1)	Conversion of T4 into T3 and rT3, and T3 into rT3 or T2 Localisation: liver, kidneys, thyroid gland, pituitary gland
Type 2 deiodinase (D2)	Conversion of T4 into T3, and T3 into T2 Localisation: thyroid gland, CNS, pituitary gland, skeletal and heart muscles
Type 3 deiodinase (D3)	Conversion of T4 and T3 into rT3 and T2 Localisation: gravid uterus, placenta, foetal liver, foetal and neonatal brain, skin of newborns
Other selenoproteins	
Selenoprotein P	Transportation of selenium, endothelial antioxidant
Selenoprotein W	Heart and skeletal muscle antioxidant
Selenophosphate synthetase	Synthesis of selenophosphate for selenoproteins
15-kDa selenoprotein	Protection against cancer?
Selenoproteins H, I, K, M, N, O, R, S, T, V	Function unknown

Claudio Marcocci, M.D., George J. Kahaly, M.D., Gerasimos E. Krassas, M.D., Luigi Bartalena, M.D., Mark Prummel, M.D.,* Matthias Stahl, M.D., Maria Antonietta Altea, M.D., Marco Nardi, M.D., Susanne Pitz, M.D., Kostas Boboridis, M.D., Paolo Sivelli, M.D., George von Arx, M.D., Maarten P. Mourits, M.D., Lelio Baldeschi, M.D., Walter Bencivelli, Ph.D., and Wilmar Wiersinga, M.D., for the European Group on Graves' Orbitopathy. Selenium and the Course of Mild Graves' Orbitopathy. N Engl J Med 2011;364:192031.

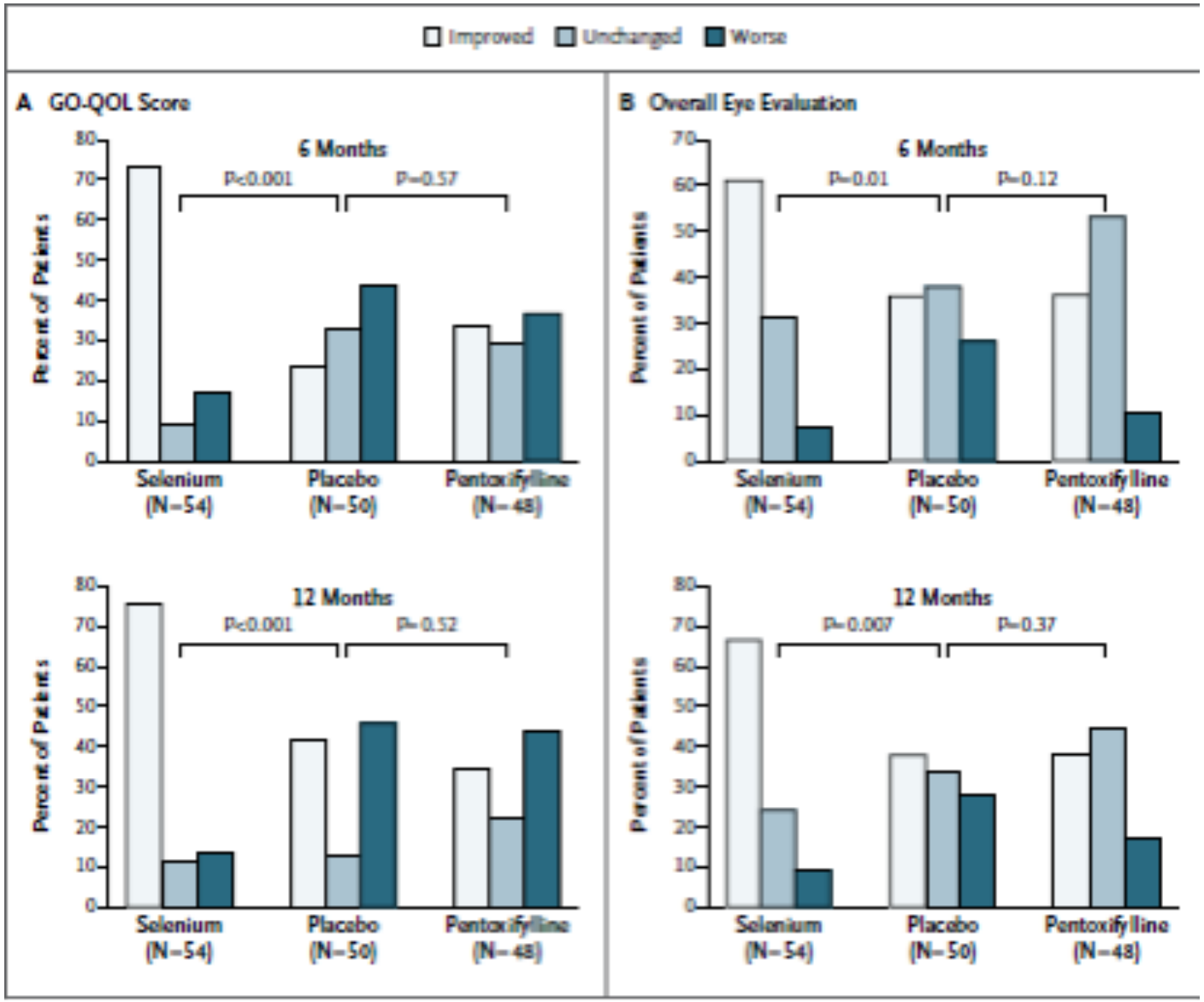
Selenium and the Course of Mild Graves' Orbitopathy

Claudio Marcocci, M.D., George J. Kahaly, M.D., Gerasimos E. Krassas, M.D., Luigi Bartalena, M.D., Mark Prummel, M.D.,* Matthias Stahl, M.D., Maria Antonietta Altea, M.D., Marco Nardi, M.D., Susanne Pitz, M.D., Kostas Boboridis, M.D., Paolo Sivelli, M.D., George von Arx, M.D., Maarten P. Mourits, M.D., Lelio Baldeschi, M.D., Walter Bencivelli, Ph.D., and Wilmar Wiersinga, M.D., for the European Group on Graves' Orbitopathy

Characteristic	Selenium (N=54)	Placebo (N=50)	Pentoxifylline (N=45)
Demographic and clinical characteristics			
Age — yr	43.0±11.0	44.6±10.7	43.7±12.4
Female sex — no. of patients (%)	48 (89)	41 (82)	37 (77)
Race — no. of patients (%)†			
White	52 (96)	50 (100)	48 (100)
Asian	1 (2)	0	0
Black	1 (2)	0	0
Thyroid disease — no. of patients (%)			
Graves' disease	51 (94)	43 (86)	46 (96)
Chronic autoimmune thyroiditis	2 (4)	3 (6)	2 (4)
Euthyroid Graves' disease	1 (2)	4 (8)	0
Previous thyroid treatment — no. of patients (%)			
Radioiodine	4 (7)	4 (8)	6 (13)
Thyroidectomy	4 (7)	9 (18)	6 (13)
Current thyroid treatment — no. of patients (%)			
Antithyroid drugs‡	41 (76)	34 (68)	35 (78)
Levothyroxine	9 (17)	9 (18)	11 (23)
NOS	4 (7)	7 (14)	2 (4)
Duration of eye symptoms or signs — mo	7.7±5.8	6.1±4.6	6.0±4.6
Current smoker — no. of patients (%)	23 (43)	25 (50)	17 (35)
Biochemical characteristics			
Thyrotropin — mU/liter			
Median	0.6	0.7	1.1
Interquartile range	0.3–2.1	0.3–2.0	0.5–2.2
Thyrotropin-receptor autoantibodies — U/liter			
Median	6.8	5.3	4.4
Interquartile range	3.3–23.0	2.0–13.0	1.3–11.0
Positive for thyrotropin-receptor autoantibodies — no. of patients/total no. (%)	32/47 (68)	30/41 (73)	27/41 (66)
Positive for thyroid peroxidase autoantibodies — no. of patients/total no. (%)	32/47 (68)	27/41 (66)	26/41 (63)

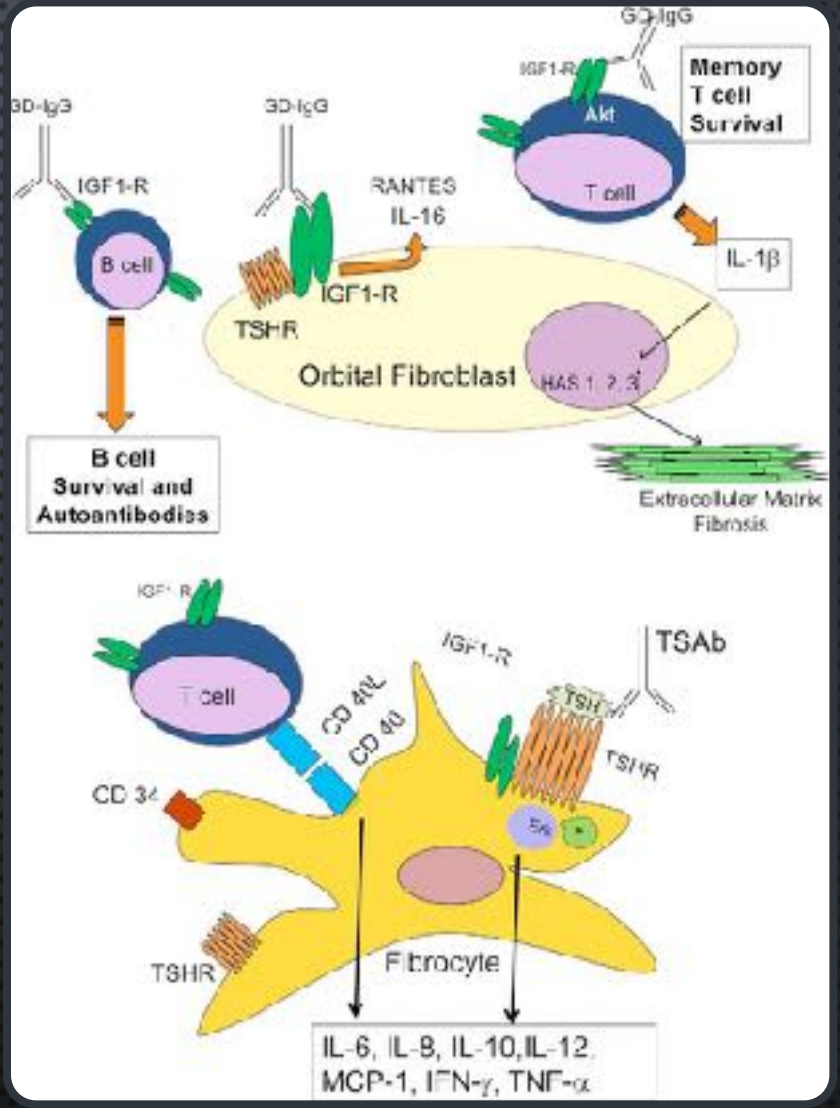
Characteristic	Selenium (N=54)	Placebo (N=50)	Pentoxifylline (N=48)
Eye symptoms and signs‖			
Proptosis — mm	19.7±2.7	19.8±2.3	20.0±2.5
Eyelid aperture — mm	11.5±1.9	11.3±1.7	11.6±2.1
Soft-tissue involvement — no. of eyes/total no. (%)			
Absent	5/108 (5)	5/100 (5)	0
Mild	64/108 (59)	65/100 (65)	52/96 (54)
Moderate	39/108 (36)	30/100 (30)	44/96 (46)
Diplopia — no. of patients (%)¶			
Absent	43 (80)	44 (88)	43 (90)
Intermittent	6 (11)	3 (6)	2 (4)
Inconstant	5 (9)	3 (6)	3 (6)
Clinical Activity Score‖			
Median	3.5	3.0	3.0
Interquartile range	3.0–4.0	2.0–4.0	2.0–5.0

Variable	Selenium (N=54)	Placebo (N=50)	Pentoxifylline (N=48)	P Value†	
				Selenium vs. Placebo	Pentoxifylline vs. Placebo
GO-QOL score‡					
Visual functioning					
At baseline	80.1±17.1	84.0±10.5	77.8±16.6	0.29	0.11
Change at 6 mo	8.73±17.7	−2.4±14.6	−0.21±18.0	0.001	0.52
Change at 12 mo	11.0±15.3	−1.7±18.7	−0.54±18.1	0.004	0.80
Appearance					
At baseline	74.0±19.8	79.5±18.1	75.0±18.3	0.15	0.24
Change at 6 mo	10.6±10.9	−2.6±11.7	−1.7±13.8	<0.001	0.73
Change at 12 mo	12.6±11.8	−1.6±17.1	−0.9±15.3	<0.001	0.85
Clinical Activity Score§					
Baseline				0.17	0.50
Median	3.5	3.0	3.0		
Interquartile range	3.0–4.0	2.0–4.0	2.0–5.0		
Change at 6 mo	−1.9±1.3	−0.6±1.9	−0.9±1.4	<0.001	0.24
Change at 12 mo	−2.2±1.3	−1.0±2.3	−1.4±1.6	<0.001	0.50
Eye evaluation¶					
Eyelid aperture — no. of patients (%)					
At 6 mo				0.01	0.79
Improved	20 (37)	6 (12)	7 (15)		
Unchanged	28 (52)	38 (76)	37 (77)		
Worse	6 (11)	6 (12)	4 (8)		
At 12 mo				0.03	0.54
Improved	21 (39)	10 (20)	9 (19)		
Unchanged	26 (48)	37 (74)	33 (69)		
Worse	7 (13)	3 (6)	6 (12)		
P value for 6 vs. 12 mo‖	0.92	0.55	0.64		
Soft-tissue signs — no. of patients (%)					
At 6 mo				0.04	0.02
Improved	23 (43)	16 (32)	20 (42)		
Unchanged	28 (52)	23 (46)	26 (54)		
Worse	3 (6)	11 (22)	2 (4)		
At 12 mo				0.005	0.22
Improved	31 (57)	16 (32)	20 (42)		
Unchanged	21 (39)	24 (48)	24 (50)		
Worse	2 (4)	10 (20)	4 (8)		
P value for 6 vs. 12 mo‖	0.30	0.07	0.68		


Improved
Unchanged
Worse
A GO-QOL Score
6 Months
P<0.001
P=0.57
12 Months
P<0.001
P=0.52
B Overall Eye Evaluation
6 Months
P=0.01
P=0.12
12 Months
P=0.007
P=0.37
Percent of Patients
Selenium (N=54)
Placebo (N=50)
Pentoxifylline (N=48)

TEPROTUMUMAB

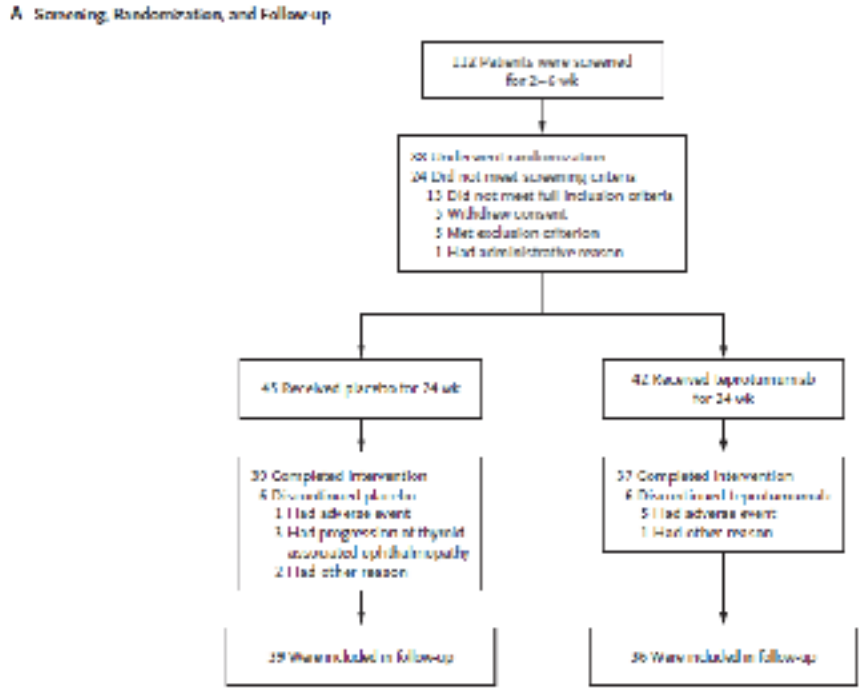
- TARGET IGF1-R
  - TYROSINE KINASE RECEPTOR
  - ENHANCES THYROTROPIN
  - OVER EXPRESSED IN FIBROBLASTS, T & B CELLS



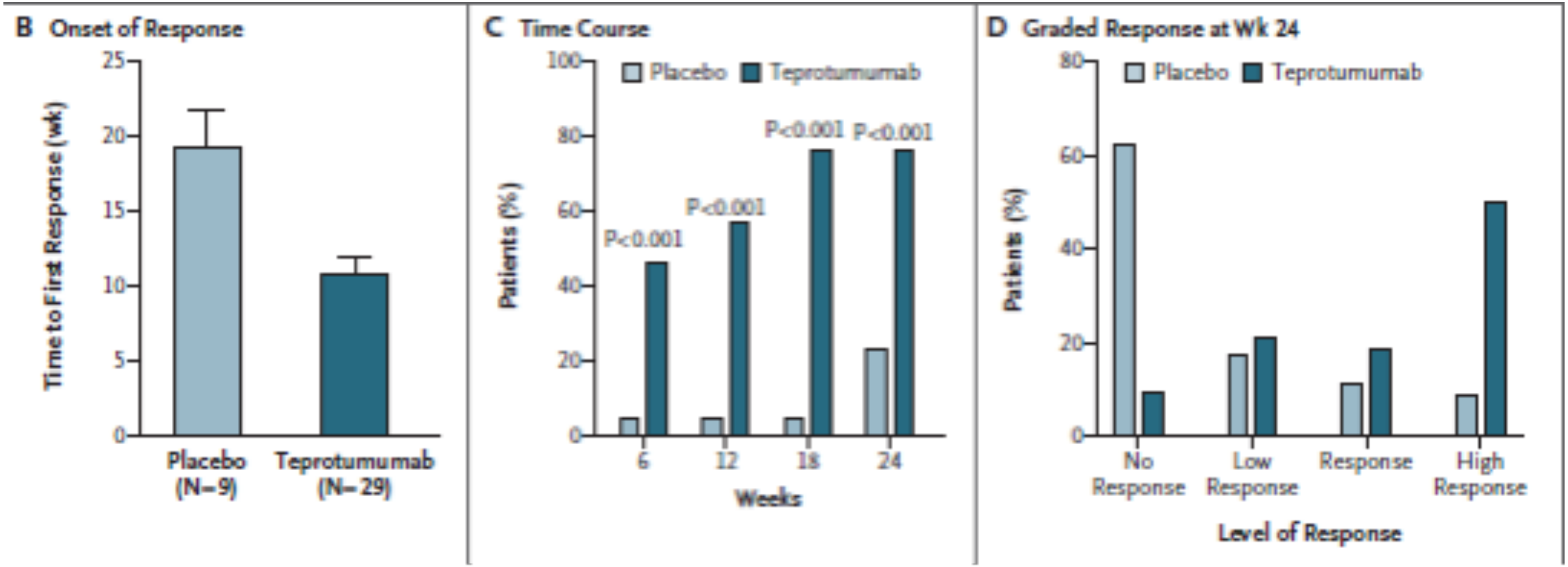
Terry J. Smith, M.D., George J. Kahaly, M.D., Ph.D., Daniel G. Ezra, M.D., James C. Fleming, M.D., Roger A. Dailey, M.D., Rosa A. Tang, M.D., Gerald J. Harris, M.D., Alessandro Antonelli, M.D., Mario Salvi, M.D., Robert A. Goldberg, M.D., James W. Gigantelli, M.D., Steven M. Couch, M.D., Erin M. Shriver, M.D., Brent R. Hayek, M.D., Eric M. Hink, M.D., Richard M. Woodward, Ph.D., Kathleen Gabriel, R.N., Guido Magni, M.D., Ph.D., and Raymond S. Douglas, M.D., Ph.D. Teprotumumab for Thyroid-Associated Ophthalmopathy. N Engl J Med 2017;376:1748-61. DOI: 10.1056/NEJMoa1614949

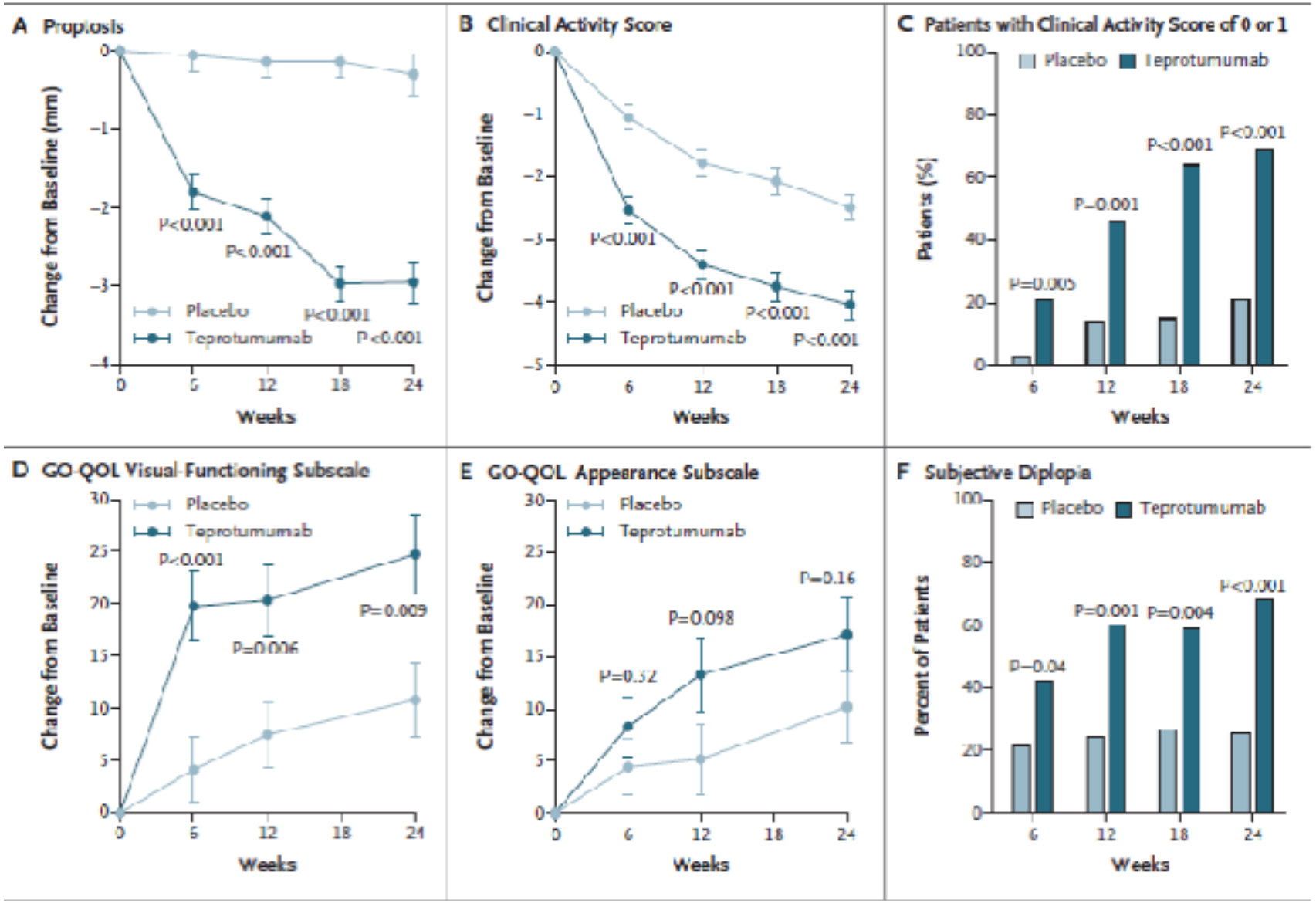
Teprotumumab for Thyroid-Associated Ophthalmopathy

Terry J. Smith, M.D., George J. Kahaly, M.D., Ph.D., Daniel G. Ezra, M.D., James C. Fleming, M.D., Roger A. Dailey, M.D., Rosa A. Tang, M.D., Gerald J. Harris, M.D., Alessandro Antonelli, M.D., Mario Salvi, M.D., Robert A. Goldberg, M.D., James W. Gigantelli, M.D., Steven M. Couch, M.D., Erin M. Shriver, M.D., Brent R. Hayek, M.D., Eric M. Hink, M.D., Richard M. Woodward, Ph.D., Kathleen Gabriel, R.N., Guido Magni, M.D., Ph.D., and Raymond S. Douglas, M.D., Ph.D.



Characteristic	Teprotumumab (N = 43)	Placebo (N = 44)
Demographic and clinical characteristics		
Age — yr	51.6±10.6	54.2±13.0
Female sex — no. of patients (%)	28 (65)	36 (82)
Time since initiation of treatment for thyroid disease — mo†		
Median	8	15
Range	2–154	3–189
Current treatment for thyroid disease — no. of patients (%)		
Antithyroid drug‡	15 (35)	20 (45)
Levothyroxine	26 (60)	23 (52)
Thyroid extract	1 (2)	3 (7)
Adjustment of medication at trial entry — no. of patients (%)		
Levothyroxine	8 (19)	5 (11)
Antithyroid drug	5 (12)	7 (16)
Duration of eye symptoms or signs — mo	4.7±2.1	5.2±2.3
Duration of Graves' disease — mo		
Median	10.7	10.8
Range	1.2–228.0	1.2–299.0
Smoking status — no. of patients (%)§		
Nonsmoker	32 (74)	26 (59)
Smoker	11 (26)	18 (41)
Biochemical characteristics		
Thyrotropin-binding inhibitory immunoglobulins — %	51.6±26.9	48.7±25.4
Thyroid-stimulating immunoglobulins — %	422.9±118.1	435.1±108.2
Mean thyroid hormone levels — pmol/liter¶		
Free triiodothyronine	4.8±1.4	4.9±1.7
Free thyroxine	16.3±4.8	16.3±3.6
Levels of free triiodothyronine and free thyroxine — no. of patients (%)		
Euthyroid at baseline and through intervention phase	20 (46)	13 (30)
Values occasionally outside normal range during intervention phase	18 (42)	25 (57)
Sustained out-of-range values during intervention phase	5 (12)	6 (14)


B Onset of Response
Time to First Response (wk)
25
20
15
10
5
0
Placebo (N=9)
Teprotumumab (N=29)
C Time Course
Placebo
Teprotumumab
Patients (%)
100
80
60
40
20
0
P<0.001
P<0.001
P<0.001
P<0.001
6
12
18
24
Weeks
D Graded Response at Wk 24
Placebo
Teprotumumab
Patients (%)
80
60
40
20
0
No Response
Low Response
Response
High Response
Level of Response


A Proptosis
Change from Baseline (mm)
0
−1
−2
−3
−4
P<0.001
P<0.001
P<0.001
P<0.001
Placebo
Teprotumumab
0
6
12
18
24
Weeks
B Clinical Activity Score
Change from Baseline
0
−1
−2
−3
−4
−5
P<0.001
P<0.001
P<0.001
P<0.001
Placebo
Teprotumumab
0
6
12
18
24
Weeks
C Patients with Clinical Activity Score of 0 or 1
Placebo
Teprotumumab
Patients (%)
100
80
60
40
20
0
P=0.005
P=0.001
P<0.001
P<0.001
6
12
18
24
Weeks
D GO-QOL Visual-Functioning Subscale
Placebo
Teprotumumab
Change from Baseline
30
25
20
15
10
5
0
P<0.001
P=0.006
P=0.009
0
6
12
18
24
Weeks
E GO-QOL Appearance Subscale
Placebo
Teprotumumab
Change from Baseline
30
25
20
15
10
5
0
P=0.32
P=0.098
P=0.16
0
6
12
18
24
Weeks
F Subjective Diplopia
Placebo
Teprotumumab
Percent of Patients
100
80
60
40
20
0
P=0.04
P=0.001
P=0.004
P<0.001
6
12
18
24
Weeks

Variable	Teprotumumab (N = 42)	Placebo (N = 45)	Odds Ratio (95% CI)	P Value
Response analysis				
Primary outcome measure: response in study eye at wk 24 — no. of patients/total no. (%)†				
Intention-to-treat population	29/42 (69)	9/45 (20)	8.86 (3.29–23.8)	<0.001
Per-protocol population	26/34 (76)	8/36 (22)	12.73 (4.01–40.4)	<0.001
Time to first response — wk	11.7±6.6	18.7±7.6		NC
Graded response — no. of patients (%)‡			11.80 (4.72–29.5)	<0.001
High response	21 (50)	4 (9)		
Response	8 (19)	5 (11)		
Low response	9 (22)	8 (18)		
No response or missing data	4 (10)	28 (62)		
Proptosis — mm				
Baseline	23.4±3.2	23.1±2.9		
Change from baseline	−2.46±0.20	−0.15±0.19		<0.001
Clinical Activity Score§				
Baseline	3.1±0.9	3.2±0.74		
Change from baseline	1.43±0.18	1.85±0.17		<0.001
GO-QOL score¶				
Combined visual-functioning and appearance subscales				
Baseline	34.5±7.3	34.5±6.8		
Change from baseline	17.7±2.4	6.8±2.3		<0.01
Visual-functioning subscale				
Baseline	16.9±4.4	17.8±4.3		
Change from baseline	11.4±2.9	4.5±2.7		<0.001
Appearance subscale				
Baseline	17.6±4.5	16.7±3.8		
Change from baseline	12.9±2.8	6.6±2.7		0.10
Subjective diplopia‖				
Baseline according to grade — no. of patients (%)			3.78 (1.68–8.54)**	0.001
No diplopia	4 (10)	14 (31)		
Intermittent	16 (38)	19 (42)		
Inconstant	7 (17)	8 (18)		
Constant	15 (35)	4 (9)		
Wk 24 according to grade — no. of patients (%)				
No diplopia	21 (50)	18 (40)		
Intermittent	4 (10)	8 (18)		
Inconstant	9 (21)	7 (16)		
Constant	4 (10)	6 (13)		
Wk 24 response — no. of patients/total no. (%)	26/38 (68)	10/39 (26)		<0.001

Variable	Teprotumumab (N=43)*	Placebo (N=44)*	Summary Details of Adverse Events in Teprotumumab Group
	number of patients (percent)		
Adverse event during intervention†			
Nausea	8 (19)	4 (9)	Generally mild and reported after first and second infusions
Muscle spasms	8 (19)	2 (5)	Intermittent, 2 of 8 patients had muscle spasms for >1 wk and received muscle relaxants
Diarrhea	6 (14)	2 (5)	Treatment occurred in 2 of 6 patients, 1 case designated as a serious adverse event (see below)
Hyperglycemia	5 (12)	2 (5)	Mechanism-based adverse event
Alopecia	3 (7)	2 (5)	All mild and no treatment necessary
Dry skin	3 (7)	0	All mild, 1 patient used topical dry-skin cream
Dysgeusia	3 (7)	0	In 2 of 3 patients, a transient "metallic" taste reported on days 1–2
Headache	3 (7)	2 (5)	Generally mild, 1 patient took paracetamol
Paresthesia	3 (7)	0	"Tingling" reported in nose, feet, or chest; variable onset and in 2 of 3 patients occurred on 1 day
Hearing impairment	3 (7)	0	Disparate symptoms, onset, and duration [i.e., one case of unilateral hearing impairment with onset 16 wk after end of therapy,‡ one case of mild bilateral hearing impairment that resolved, and one case of tinnitus in a patient with a history of tinnitus]
Weight loss	3 (7)	0	Variable timing, decreases ranged from 5–9 lb (11–20 kg)
Any adverse event during intervention	32 (74)	32 (73)	
Serious adverse event§			
Optic neuropathy¶	0	1 (2)	
Diarrhea	1 (2)	0	Severe diarrhea in 1 patient with a 6-mo history of ulcerative colitis
Inflammatory bowel disease	1 (2)	0	In 1 patient with recent diagnosis of Hellis and colitis, inflammatory bowel disease diagnosed and treated while patient received trial drug
Escherichia sepsis‖	1 (2)	0	*Escherichia coli* infection of unknown origin treated with intravenous antibiotics
Hashimoto's encephalopathy	1 (2)	0	Provisional diagnosis after episodic mental confusion with no other neurologic symptoms
Urinary retention	1 (2)	0	Diagnosed after patient had an inguinal herniorrhaphy
Any serious adverse event	5 (12)	1 (2)	

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