TABLE e5. ALTERNATIVE TREATMENTS FOR ACTIVE THYROID EYE DISEASE (TED)

Pharmacological Agent/Intervention	***Classification of Treatment/Mechanism of Action***	***Study Design(s)***	***Results of Randomized Study (if performed)***	***Comments***
Rituximab	Monoclonal antibody targeting CD20+ B-cells	7 Case reports[123-129] 4 Case series[121, 122, 130, 131] 2 open label studies[131,132]	None	5 patients were treated with intraorbital injection of rituximab[120] In open label study of rituximab and iv methylprednisolone, rituximab decreased mean CAS from 4.7 +/- 0.5 before treatment to 1.8 +/-0.8 after treatment. (Dose of rituximab used: 1000 mg twice over a 2 week interval). In comparison, the mean CAS decreased from 4.1 to 2.0 in the iv methylprednisolone group.[131] In open label study, the median decrease in CAS was -4.5 (dose of rituximab used: 1000 mg twice in 15 days)[132]
Cyclosporine	Immunosuppressant (humoral and cell-mediated immunity): inhibition of cytotoxic T cell activation.	3 Case reports [134-136] Randomized controlled trial: cyclosporine+ oral prednisone vs oral prednisone[137]	Response to therapy: greater for proptosis and diplopia in the cyclosporine+ prednisone group[136]	Prednisone alone group had a greater number of patients with relapses compared to cyclosporine+prednisone group (8/20 vs 1/20, respectively)[136]
		Randomized controlled trial: cyclosporine vs oral prednisone[138]	Response to therapy: 61% oral prednisone group vs 22% cyclosporine group.[137]	Non-responders in each group received combination treatment with improvement in 56% of the initial prednisone group and 62% in the initial cyclosporine group.[137]

Pentoxifylline	Anti-inflammatory	1 Prospective study [174] 1 Open label study [173]		In the open label study the pentoxifylline group should significant reduction in proptosis compared to placebo group.[172]
		Randomized controlled trial: Selenium vs placebo and pentoxifylline vs placebo [86]	At 12 months CAS change was -1.4 +/-1.6 in pentoxifylline group compared to -1.0+/-2.3 in placebo group ($p<0.30$)[85]	The randomized controlled trial enrolled mild TED patients.[85]
Octreotide or Lanreotide	Somatostatin analog	2 Case series [139, 140]		

		4 open label studies [141-144]		
		Randomized controlled trial: octreotide vs prednisone [145]	At end of treatment median CAS was lower in the prednisone group (2.5) vs octretotide group (3.5), p<0.05 [145]	No significant reduction in proptosis in either group. Corticosteroids reduced extraocular muscle thickness [145]
		Randomized controlled trial: octretotide (long-acting release) vs placebo [146]	After 16 weeks the OI reduced by -1.12 in octreotide group vs -0.23 in the placebo group, p=0.043 [146]	After 32 weeks treatment (all patients were treated with octreotide from week 16-32) there was no difference in the change in OI in either group [146]
		Randomized controlled trial: octreotide (long-acting release) vs placebo [147]	At 16 weeks composite success was 28% in octreotide group vs 44% in placebo group and composite failure was 72% in octreotide group vs 56% in placebo group. [147]	Proptosis reduction was seen in octreotide group but not in placebo group [147]
		Randomized controlled trial: octreotide (long-acting release) vs placebo [148]	Median change in CAS was 2.5 in octreotide group vs 1.0 in placebo group (p=0.02) [148]	Baseline CAS was higher in octreotide group. Small number of patients in placebo group.[148]
Diclofenac	COX-2 selective inhibitor and Anti-PPAR γ	1 Open label study [149]	None	13 patients were treated at a dose of 50 mg every 12 hours: CAS score decreased from

				3.61 +/-1.44 pre-treatment to 2.30 +/-1.03 post- treatment. There was also improvement in ocular pain (5/6), diplopia (4/5) and amount of proptosis.
Celecoxib	COX-2 selective inhibitor	1 Case report [150]	None	
Allopurinol and nicotinamide	Anti-oxidant	1 Open label study[174]	None	9/11 (82%) patients demonstrated improvement with allopurinol/nicotinamide. 3/11 (27%) patients demonstrated improvement with placebo
Tocilizumab	Monoclonal antibody targeting interleukin-6 receptor	1 Case report [151]	None	
Inliximab	Monoclonal antibody targeting TNF α	1 Case report [152]	None	
Etanercept	Monoclonal antibody targeting TNF α	1 Open label study [153]	None	Ten patients received 25 mg etanercept twice weekly for 12 weeks. After 12 weeks of treatment mean CAS decreased from 4.0 to 1.6 and 60% of patients reported moderate to marked improvement.

PLEX		2 Case reports [154, 155] 7 Case Series [156, 162] Randomized controlled trial: iv methylprednisolone + PLEX vs iv methylprednisolone 163	At 1 month CAS score dropped from 3.6 before treatment to 0.6 in iv methylprednisolone + PLEX group compared to 4.0 before treatment to 2.0 after treatment in iv methylprednisolone alone group (p=0.027). At 3 and 6 months there was no difference in the CAS for the two groups. [163]	Six of 12 patients received PLEX and azathioprine concomitantly [160] All 3 patient received concurrent immunosuppression (prednisone or prednisone + cyclophosphamide)[160] Thirteen of 18 patients received concurrent azathioprine [162] All patient received an immunosuppressive agent after PLEX [156, 158, 159]
IVIG	Pooled polyvalent immunoglobulin G	1 Open label study [164] 1 Prospective, non-randomized study of IVIG and oral methylprednisolone [166] Randomized clinical trial: IVIG vs IVIG+ORT[165] Randomized clinical trial: IVIG vs oral prednisolone [167]	Excellent/good clinical response: 70% in IVIG group (not statistically different from IVIG+ORT group) [166] Successful outcome: 62% IVIG group vs 63% prednisolone group [167]	Open label study showed no benefit with IVIG [164] Prospective, non-randomized study showed 76% IVIG group responded and 66% of methylprednisolone group responded [166]
Bromocriptine	Dopamine agonist (ergoline derivative)	2 Case reports [168, 169]	None	

Metrodinazole	Nitroimidazole antibiotic	1 Case series [170]		Nine of 13 patients noted to have improvement in proptosis [170]
		Randomized controlled trial: metrodinazole vs placebo for 12 weeks followed by cross-over for additional 12 weeks. [171]	At 12 weeks 46.11mm proptosis in placebo group vs 45.83 mm in metrodinazole group. Both groups had increase in proptosis over the initial 12 weeks (+1.11mm in placebo group vs. +0.41 mm in metrodinazole group). [171]	
Ciamexone	Immunomodulator	Randomized controlled trial: ciamoxene (300mg/day) vs placebo [176]	At 1 and 6 months there was no clinical or radiological difference in the ciamoxene group vs placebo group	
Acupuncture	Unknown mechanism	Randomized controlled trial [172]	No treatment effect with acupuncture	

ABBREVIATIONS

PPAR γ: peroxisome proliferator activated receptor gamma (adipogenesis inhibitor)
TNF: tumor necrosis factor
COX: cyclooxygenase
IVIG: Intravenous immunoglobulin
CAS: clinical activity score
OI= ophthalmology index
ORT: orbital radiotherapy
PLEX: plasma exchange
iv: intravenous