Graves' Ophthalmopathy Treatments

Number: 0419

Policy

*Please see amendment for Pennsylvania Medicaid at the end of this CPB.

Note: REQUIRES PRECERTIFICATION

Precertification of Tepezza (teprotumumab-trbw) is required of all Aetna participating providers and members in applicable plan designs. For precertification, call (866) 752-7021 (Commercial), (866) 503-0857 (Medicare), or fax (866) 267-3277.


I. Surgery
Aetna considers orbital decompression surgery, and eye muscle surgery or eyelid surgery (e.g., marginal myotomy of levator palpebrae muscle, lateral tarsal canthoplasty, mullerectomy (resection of the Müller muscle), eyelid spacer grafts, and recession of the lower eyelid retractors) medically necessary for members with severe Graves' ophthalmopathy (especially individuals with marked proptosis and optic neuropathy) when both of the following measures have not been successful:

A. A trial of conservative measures, such as elevating the head at night, cool compresses, sunglasses, lubricating eyedrops, and if the member has strabismus, prisms for glasses; and

B. A trial of medications, such as diuretics, methimazole, prednisone, and propylthiouracil.

**Note:** According to available literature, surgical treatment should not be undertaken until stability of the thyroid-related orbitopathy (TRO) has been demonstrated. One of the advantages of waiting for stability of TRO is that some cosmetic problems may resolve or improve without intervention. Fat pad removal is commonly requested with surgery for exophthalmos and is generally cosmetic in nature, and therefore, is considered not medically necessary.

**II. Radiotherapy**

Aetna considers orbital radiotherapy medically necessary for the treatment of members with severe Graves' ophthalmopathy when both of the afore-mentioned criteria are met.

**III. Allograft**
Aetna considers the use of banked human tissue graft (e.g., Alloderm) to elevate the lower eyelids in members with lower eyelid retraction associated with Graves ophthalmopathy experimental and investigational because there is insufficient evidence to support this approach.

IV. Teprotumumab (Tepezza)

Aetna considers the use of teprotumumab (Tepezza) medically necessary for the treatment of thyroid eye disease (TED) when all of the following criteria are met:

A. Member is 18 years of age or older; and
B. Member has active disease with a CAS greater than or equal to 4 (see Appendix A); and
C. Member has moderate-to-severe disease (see Appendix B); and
D. Tepezza is prescribed by or in consultation with an ophthalmologist.

V. Experimental Treatments

Aetna considers Tepezza to be experimental and investigational for a repeat course of treatment. Repeat infusions within the first treatment course are considered medically necessary

Aetna considers Tepezza to be experimental and investigational for all other indications.

Aetna considers the following interventions experimental and investigational for the treatment of Graves’ ophthalmopathy because their effectiveness for this indication has not been established.

- Celecoxib
- Intravenous immunoglobulins
- Phosphorus-32 brachytherapy
- Pioglitazone
- Rituximab
- Somatostatin analogs (e.g., lanreotide and octreotide)
- Tocilizumab
- Tumor necrosis factor-alpha inhibitors (e.g., etanercept and infliximab).

**Dosing Recommendations**

**Teprotumumab (Tepezza)**

Tepezza is available as a 500 mg lyophilized powder in a single-dose vial for reconstitution.

The recommended dose is an intravenous infusion of 10 mg/kg for the initial dose followed by an intravenous infusion of 20 mg/kg every three weeks for 7 additional infusions. Administer Tepezza by intravenous infusion over 60 to 90 minutes.

Source: Horizon Therapeutics 2020.

**Background**

Graves' disease (also known as Parry's or Basedow's disease) is a complex disease whose pathogenesis is believed to be autoimmune. It is a disorder that affects mainly females, and although it may occur at any age, has a peak incidence in the 3rd and 4th decades. Graves' disease has 3 principal manifestations: (i) hyperthyroidism with diffuse goiter, (ii) ophthalmopathy, and (iii) dermopathy; however, they do not necessarily appear simultaneously.
Graves' ophthalmopathy, also known as thyroid-associated ophthalmopathy (TAO), occurs in 2 to 7% of patients with Graves' disease with the major manifestations being proptosis, ophthalmoplegia, optic neuropathy, and/or eyelid retraction. Thyroid-associated ophthalmopathy is the commonest cause of proptosis in adults. The term exophthalmos is used exclusively to describe the proptosis of TAO; exophthalmos may be unilateral early but usually becomes bilateral with time. The term exophthalmic ophthalmoplegia refers to the ocular muscle weakness that results in impaired upward gaze and convergence and strabismus with varying degree of diplopia.

Physicians recommend treatment of Graves' ophthalmopathy according to each patient's symptoms. Sometimes combinations of the following procedures are used:

- Elevating the head at night, cool compresses, sunglasses, lubricating eyedrops, or prisms for glasses;
- Eye muscle surgery, eyelid surgery, or both;
- Medications or radiation to shrink tissue;
- Orbital decompression surgery.

An assessment by the National Institute for Health and Clinical Excellence (2005) found that retrobulbar irradiation to be an effective procedure in patients for whom other treatments are inadequate or are associated with significant side effects.

Orbital Decompression Surgery

In orbital decompression surgery, the bone between the orbit and the sinuses is removed. A successful procedure improves vision and provides room for the eye to slip back into the orbit's protection. Orbital decompression is indicated in patients with severe ophthalmopathy refractory to medications and radiotherapy, especially in the presence of marked proptosis and optic neuropathy.
Eye Muscle Surgery

Diplopia often occurs because the eyes are misaligned. Usually, misalignment is caused by 1 or more eye muscles that are too short or “tight” due to scar tissue from Graves' ophthalmopathy. This scar tissue results from changes surrounding the eye because of swelling. The goal of eye muscle surgery is to attain single vision when looking straight ahead and looking down when reading. During eye muscle surgery, the muscle is cut from its attachment to the eyeball and re-attached further back on the eye. Usually eye muscle surgery does not require an over-night stay in the hospital. The physician evaluates the final results about 2 months later. More than 1 operation is sometimes required.

If orbital decompression and eye muscle surgery are to be performed, the orbital decompression surgery generally is carried out first.

Eyelid Surgery

Graves' ophthalmopathy generally causes the eyelids to open more widely. The front surface of the eyeball becomes exposed beyond the eyelid and causes excessive tearing and discomfort. Lid retraction may be improved by orbital decompression, especially the lower lid. However, the backward and downward movement of the globe following decompression may accentuate upper lid retraction. Surgical re-positioning (recession) of the upper lid retractors may have to be performed as an adjunct.

If orbital decompression, eye muscle, and eyelid surgery are required, the eyelid procedure is generally performed as the final operation in a series.
Acellular human dermis is being investigated for elevating the lower eyelids in lower eyelid retraction associated with Graves ophthalmopathy. However, current evidence in the peer-reviewed medical literature is limited to case reports and small, retrospective case series.

Repositioning of the canthus may be necessary for orbital decompression when surgery is being done for lid retraction and lid lengthening by myotomy of the lid retractors is insufficient.

Leone (1984) noted that from a series of 124 consecutive patients, parameters were developed in the management of Graves' disease. Patients who were stable with symptomatic treatment were observed and followed. Oral steroids, 40 to 80 mg prednisone daily, were moderately effective in reducing progressive soft tissue inflammatory signs, but were less effective in controlling myopathy and lid retraction. Radiotherapy, 1,000 rad from each lateral port, was most effective in halting the progressive inflammatory component, particularly in those who had a recent rapid rate of change. Dysthyroid optic neuropathy required high dose steroids; if it was not effective, decompression of the orbit was carried out. Once the disease became stable, myopathy, lid retraction, and exophthalmos were surgically treated on an elective basis. The techniques utilized were tarsorrhaphy, lateral canthoplasty, upper and lower eyelid retractor release, and 1- to 3-wall orbital decompression.

A Wikipedia review on “Graves' ophthalmopathy” (Last modified July 20, 2015) states that “Eyelid surgery is the most common surgery performed on Graves ophthalmopathy patients. Lid-lengthening surgeries can be done on upper and lower eyelid to correct the patient’s appearance and the ocular surface exposure symptoms. Marginal myotomy of levator palpebrae muscle can reduce the palpebral fissure height by 2 to 3 mm. When there is a more severe upper lid retraction or exposure keratitis, marginal myotomy of levator palpebrae
associated with lateral tarsal canthoplasty is recommended. This procedure can lower the upper eyelid by as much as 8 mm. Other approaches include mullerectomy (resection of the Müller muscle), eyelid spacer grafts, and recession of the lower eyelid retractors”.

Orbital Radiation

Zoumalan and colleagues (2007) noted that thyroid eye disease (TED, Graves’ ophthalmopathy, thyroid ophthalmopathy) is the most common cause of orbital inflammation and proptosis in adults. There is no agreement on its management although corticosteroids and external beam orbital radiation have traditionally been believed to provide benefit in active inflammation. A review of the published literature in English disclosed an overall corticosteroid-mediated treatment response of 66.9 % in a total of 834 treated patients who had moderate or severe TED. Intravenous (IV) corticosteroids used in repeated weekly pulses were more effective (overall favorable response = 74.6 %, n = 177) and had fewer side effects than daily oral corticosteroids (overall favorable response = 55.5 %, n = 265). A combination of corticosteroid and radiation therapy seemed to be more effective than corticosteroids alone. However, the authors stated that these conclusions are tempered by a notable lack of standardization within and between study designs, treatment protocols, and outcome measures. Accordingly, the North American Neuro-Ophthalmology Society, American Society of Ophthalmic Plastic and Reconstructive Surgery and the Orbital Society, in conjunction with Neuro-Ophthalmology Research and Development Consortium, will investigate the design and funding of a multi-center controlled trial.

A technology assessment on orbital radiation for Graves ophthalmopathy by the American Academy of Ophthalmology (Bradley et al, 2008) examined if orbital radiation offers effective and safe treatment for Graves ophthalmopathy.
Medical literature databases were searched to identify all published reports relating to orbital radiation treatment for Graves ophthalmopathy. To be included in the technology assessment, reports had to provide original data, to report on a case series or uncontrolled trial of at least 100 subjects or a randomized clinical trial (RCT) of any size, to focus on orbital radiation for the treatment of Graves ophthalmopathy, and to follow-up patients for at least 3 months. Abstracted data included study characteristics, patient characteristics, treatment response, and safety information. A total of 14 studies were included in the technology assessment: 5 observational studies and 9 RCTs. Three of the observational studies reported on treatment response, with overall favorable outcomes for 40% to 97% of patients. Three of the observational studies provided intermediate-term safety data. The risk of definite radiation retinopathy is 1% to 2% within 10 years after treatment. Patients treated with orbital radiation did not have an increased risk of secondary malignancy or premature death. The 9 RCTs were qualitatively heterogeneous. Patients with optic neuropathy generally were excluded from participating in the RCTs. Three of the RCTs were sham-controlled. None of these studies showed that orbital radiation was more effective than sham irradiation for improving proptosis, lid fissure, or soft tissue changes such as eyelid swelling. Two of the 3 sham-controlled RCTs demonstrated improved vertical range of motion in radiation-treated subjects compared with controls. The authors concluded that systematic review of the effect of orbital radiation on Graves ophthalmopathy is limited by the lack of standardization and variable quality of published reports. Extra-ocular motility impairment may improve with radiotherapy, although the evidence of a treatment effect is mixed in clinical trials. Future studies are needed to determine if a potentially beneficial motility effect results in improved patient function and quality of life. Level I evidence indicates that proptosis, eyelid retraction, and soft tissue changes do not improve with radiation treatment. The effectiveness of orbital radiation for compressive optic neuropathy resulting from
Graves' ophthalmopathy has not been investigated in clinical trials and merits further study. Radiation retinopathy, although rare, is a risk of orbital radiation, even in patients without diabetes who receive appropriate radiation dose and delivery.

Guidance on retrobulbar irradiation for thyroid eye disease from the National Institute for Health and Clinical Excellence (NICE, 2005) concluded: "Current evidence on the safety and efficacy of retrobulbar irradiation for thyroid eye disease appears adequate to support the use of this procedure in patients for whom other treatments are inadequate or associated with significant side effects."

Other Treatments

Bartalena and Tanda (2009) noted that RCT have not shown a benefit of somatostatin analogs (e.g., lanreotide and octreotide) for Graves' ophthalmopathy. They stated that there are also few data to support the use of intravenous immune globulin for this condition. This is in agreement with the consensus statement of the European Group on Graves' orbitopathy on the management of Graves' orbitopathy (Bartalena et al, 2008), which stated that treatments of marginal or unproven value include somatostatin analogs and intravenous immunoglobulins.

In a systematic review and meta-analysis on treatment modalities for Graves' ophthalmopathy, Stiebel-Kalish et al (2009) concluded that current evidence demonstrates the effectiveness of intravenous corticosteroids in decreasing clinical activity score (CAS) in patients with moderate-to-severe Graves' ophthalmopathy. Intravenous pulse corticosteroids therapy has a small but statistically significant advantage oral therapy and causes significantly fewer adverse events. Somatostatin analogs have marginal clinical efficacy. The efficacy of orbital radiotherapy as single therapy remains unclear, whereas the combination of radiotherapy with corticosteroids has better efficacy than either
radiotherapy or oral corticosteroids alone. Rituximab is not listed as a therapeutic option. Furthermore, Hegedus (2009) stated that no data as yet support the routine use of biological therapies (e.g., rituximab). The author stated that prospective, randomized trials comparing available and any novel therapeutic options for Graves' disease are needed.

Bartalena et al (2010) stated that non-surgical treatments for moderate to severe and active Graves' orbitopathy (systemic glucocorticoids with or without orbital radiotherapy) have limited effects on the underlying autoimmune process causing the disease. Although the clinical responses to treatment are often good, at least one-third of patients with Graves' orbitopathy are eventually dissatisfied with the treatment outcome. Advent in the understanding of the autoimmune basis of Graves' orbitopathy (although still incomplete) made it possible, similar to other autoimmune disorders, to envision the use of novel immunomodulating drugs. Among the currently available biologic agents, the CD20+ B cell-depleting agent, rituximab, and tumor necrosis factor-alpha inhibitors (e.g., etanercept and infliximab) are presently the drugs that have the best chance of being employed in the future for the treatment of Graves' orbitopathy. However, the authors noted that RCTs to support their use are needed.

Viani et al (2012) evaluated the effectiveness of radiotherapy (RT) with total dose of 20 Gy (RT 20 Gy) in the treatment of Graves' ophthalmopathy. A systematic review and meta-analysis of RCTs was performed comparing RT 20 Gy with or without glucocorticoid to clinical treatments for Graves' ophthalmopathy. The MEDLINE, EMBASE, Cochrane Library databases and recent relevant journals were searched. Relevant reports were reviewed by 2 reviewers. Response to radiotherapy was defined as clinical success according to each trial. These investigators also evaluated the quality of life and whether RT to produce fewer side effects than other treatments. A total of 8 RCTs (439 patients) were identified. In the subgroup analysis, the overall response to treatment
rates was better for: RT 20 Gy plus glucocorticoids versus glucocorticoids alone, OR = 17.5 (95% confidence interval [CI]: 1.85 to 250, \( p = 0.04 \)), RT 20 Gy versus sham RT, OR = 3.15 (95% CI: 1.59 to 6.23, \( p = 0.003 \)) and RT 20Gy plus intravenous glucocorticoid versus RT 20Gy plus oral glucocorticoid, OR = 4.15 (95% CI: 1.34 to 12.87, \( p = 0.01 \)).

There were no differences between RT 20 Gy versus other fractionations and RT 20 Gy versus glucocorticoid alone.

Radiotherapy 20 Gy with or without glucocorticoids showed an improvement in diplopia grade, visual acuity, optic neuropathy, lid width, proptosis and ocular motility. No difference was seen for costs, intra-ocular pressure and quality of life. The authors concluded that these findings showed that RT 20 Gy should be offered as a valid therapeutic option to patients with moderate-to-severe ophthalmopathy. The effectiveness of orbital radiotherapy can be increased by the synergistic interaction with glucocorticoids. Moreover, RT 20 Gy is useful to improve a lot of ocular symptoms, excluding intra-ocular pressure, without any difference in quality of life and costs.

Tanda and Bartalena (2012) examined the safety and effectiveness of orbital radiotherapy (OR) for graves’ orbitopathy (GO). The major source of data acquisition included PubMed strategies. Original articles, systemic reviews and meta-analyses, and other relevant citations were screened. Randomized clinical trials evaluating the effectiveness of OR are limited. However, available data suggest that OR is a safe treatment, which seems to be effective particularly on ocular motility impairment, especially if it is of recent onset. Orbital radiotherapy seems to be effective also on soft tissue changes, whereas exophthalmos and long-standing extra-ocular muscle dysfunction are poorly affected. The effectiveness of OR on dysthyroid optic neuropathy is uncertain. The combination of OR and oral glucocorticoids (GCs) is more effective than either treatment alone, suggesting a synergistic effect of the 2 treatments. There is no available evidence that the addition of OR to intravenous GCs provides an advantage over intravenous GCs alone. The authors
concluded that OR can be considered a safe second-line treatment for patients with moderate-to-severe and active GO but less effective than GCs. A possible strategy may include its use in combination with intravenous GCs in patients whose GO has only partially responded to a first-course of intravenous GCs alone and is still active.

Melcescu et al (2014) noted that GO often remains a major diagnostic and therapeutic challenge. It has become increasingly important to classify patients into categories based on disease activity at initial presentation. A Hertel exophthalmometer measurement of greater than 2 mm above normal for race usually categorizes a patient as having moderate-to-severe GO. Encouraging smoking cessation and achieving euthyroidism in the individual patient are important. Simple treatment measures such as lubricants for lid retraction, nocturnal ointments for incomplete eye closure, prisms in diplopia, or botulinum toxin injections for upper-lid retraction can be effective in mild cases of GO. Glucocorticoids, orbital radiotherapy, and decompression/rehabilitative surgery are generally indicated for moderate-to-severe GO and for sight-threatening optic neuropathy. Future therapies, including rituximab aimed at treating the molecular and immunological basis of GO, are under investigation and hold promise for the future.

Salvi (2014) noted that in recent years, immunosuppressive therapy, as an alternative to corticosteroids, has been proposed as novel agents that target the various antigens involved in the pathogenesis of Graves’ ophthalmopathy. Although the lack of randomized and controlled studies suggests caution in generalizing results, some data show interesting results. Potential targets for immune therapy in Graves’ ophthalmopathy are the antigens expressed on the target organ of inflammation, namely the receptor and the insulin growth factor 1 (IGF-1) receptor on fibroblasts, inflammatory cytokines, and B and T cells. The most promising results are observed with small thyroid stimulating
hormone receptor molecules interacting with the receptor on thyrocytes and fibroblasts and with the anti-IGF-1 receptor antibody teprotumumab. A recent open study with tocilizumab, an anti-soluble interleukin-6 receptor, has shown inactivation of Graves’ ophthalmopathy. Consistent reports on the efficacy of rituximab will have to be confirmed by RCTs, which are now in progress. The author concluded that current clinical practice for Graves' ophthalmopathy will greatly benefit from the availability of immunosuppressors that act as disease-modifying drugs, as compared to steroids, the current standard treatment for Graves' ophthalmopathy. Rituximab seems to be a good candidate, as preliminary results from ongoing randomized trials suggest good efficacy with a relative well-tolerated profile.

In a prospective, interventional, non-randomized study, Perez-Moreiras et al (2014) examined the effectiveness of tocilizumab in thyroid eye disease patients who were refractory to multiple intravenous steroids. This study enrolled active GO (defined by CAS greater than or equal to 4) patients resistant to previous intravenous steroids treated with tocilizumab. Snellen visual acuity, Hertel exophthalmometry, CAS evaluation, TSI levels, ocular motility, and side effects were registered at a 4-week interval. A total of 18 patients were included with a mean age of 47.9 ± 8.63 years. All patients had a significant progressive CAS improvement (mean CAS score reduction 5.89 ± 1.41 points, p < 0.00027). Mean TSI levels were significantly lower at the end of the treatment (mean of -76.18 % ± 17.80 %, p = 0.00007). Thirteen patients (72.22 %) reduced proptosis a mean of -3.92 ± 1.54 mm (p = 0.002); 15 patients (83.33 %) had an improvement in extra-ocular motility, and 7 patients of 13 resolved their diplopia (53.85 %). No severe side effects or relapse of active GO were observed at the end of follow-up. The authors concluded that the findings of this study suggested that intravenous tocilizumab may be effective on reducing activity in patients.
with thyroid eye disease refractory to intravenous steroids. These preliminary findings need to be validated by well-designed studies.

Radioiodine Therapy

Ren et al (2015) integrated the evidence to provide hierarchies of the comparative effectiveness of 4 treatments (radioiodine, radioiodine+prednisone, anti-thyroid drugs and surgery). These researchers conducted a Bayesian-framework network meta-analysis of RCTs to compare 4 treatments in patients with Graves' disease. The eligible RCTs were identified by searching Amed, the British Nursing Index, Embase, PubMed, the Cochrane Central Register of Controlled Trials (CENTRAL), Google scholar, SIGLE, the National Technical Information Service, the National Research Register (UK) and the Current Controlled Trials databases. The data for 2 outcomes (e.g., ophthalmopathy and recurrence) were independently extracted by 2 authors. A total of 4 RCTs were ultimately included. Radioiodine+prednisone therapy showed statistical significance in reducing the incidence of new or deteriorative ophthalmopathy comparing with the other 3 therapies. Compared with radioiodine, therapy with anti-thyroid drugs therapy as well as surgery significantly decreased the incidence of new or deteriorative ophthalmopathy. Radioiodine therapy significantly reduced the rate of recurrence when compared to therapy with anti-thyroid drugs or surgery. For decreasing the incidence of new or deteriorative ophthalmopathy, the 4 treatments were ranked as follows: radioiodine+prednisone therapy, therapy with anti-thyroid drugs, surgery and radioiodine therapy. For reducing the rate of recurrence, 3 treatments were ranked as follows: radioiodine therapy, therapy with anti-thyroid drugs and surgery. The authors concluded that radioiodine+prednisone therapy might have the least probability of leading to an exacerbation or new appearance of ophthalmopathy, and radioiodine therapy might have the least probability of causing a recurrence.
In a Cochrane review, Ma and colleagues (2016) evaluated the effects of radioiodine therapy versus anti-thyroid medications for Graves' disease. These researchers performed a systematic literature search in the Cochrane Library, MEDLINE and EMBASE and the trials registers ICTRP Search Portal and ClinicalTrials.gov. The date of the last search was September 2015 for all databases. Randomized controlled trials comparing the effects of radioiodine therapy versus anti-thyroid medications for Graves' disease with at least 2 years follow-up were selected for analysis. Two authors independently screened titles and abstracts for relevance. One author carried out screening for inclusion, data extraction and "Risk of bias" assessment and a second author checked this. They presented data not suitable for meta-analysis as descriptive data, and analyzed the overall quality of evidence utilizing the GRADE instrument. These investigators included 2 RCTs involving 425 adult participants with Graves' disease in this review. Altogether 204 participants were randomized to radioiodine therapy and 221 to methimazole therapy. A single dose of radioiodine was administered. The duration of methimazole medication was 18 months. The period of follow-up was at least 2 years, depending on the outcome measured. For most outcome measures risk of bias was low; for the outcomes health-related quality of life as well as development and worsening of Graves' ophthalmopathy risks of performance bias and detection bias were high in at least 1 of the 2 RCTs. Health-related quality of life appeared to be similar in the radioiodine and methimazole treatment groups, however no quantitative data were reported (425 participants; 2 trials; low quality evidence). The development and worsening of Graves' ophthalmopathy was observed in 76 of 202 radioiodine-treated participants (38 %) and in 40 of 215 methimazole-treated participants (19 %): risk ratio (RR) 1.94 (95 % CI: 1.40 to 2.70); 417 participants; 2 trials; low quality evidence. A total of 35 % to 56 % of radioiodine-treated participants and 42 % of participants treated with methimazole were smokers, which is associated with the risk of worsening or development of Graves'
ophthalmopathy. Euthyroidism was not achieved by any participant being treated with radioiodine compared with 64/68 (94%) of participants after methimazole treatment (112 participants; 1 trial). In this trial thyroxine therapy was not introduced early in both treatment arms to avoid hypothyroidism. Recurrence of hyperthyroidism (relapse) in favor of radioiodine treatment showed a RR of 0.20 (95% CI: 0.01 to 2.66); p = 0.22; 417 participants; 2 trials; very low quality evidence. Heterogeneity was high (I² = 91%) and the RRs were 0.61 or 0.06 with non-overlapping CIs. Adverse events other than development of worsening of Graves' ophthalmopathy for radioiodine therapy were hypothyroidism (39 of 41 participants (95%) compared with 0% of participants receiving methimazole, however thyroxine treatment to avoid hypothyroidism was not introduced early in the radioiodine group -- 104 participants; 1 trial; very low quality evidence) and drug-related adverse events for methimazole treatment (23 of 215 participants (11%) reported adverse effects likely related to methimazole therapy -- 215 participants; 2 trials; very low quality evidence). The outcome measures all-cause mortality and bone mineral density were not reported in the included trials. One trial (174 participants) reported socio-economic effects: costs based on the official hospital reimbursement system in Sweden for patients without relapse and methimazole treatment were US$ 1,126/1,164 (young/older methimazole group) and for radioiodine treatment US$ 1,862. Costs for patients with relapse and methimazole treatment were US$ 2,284/1,972 (young/older methimazole group) and for radioiodine treatment US$ 2,760. The authors concluded that the only anti-thyroid drug investigated in the 2 included trials was methimazole, which might limit the applicability of these findings with regard to other compounds such as propylthiouracil. Results from 2 RCTs suggested that radioiodine treatment is associated with an increased risk of Graves' ophthalmopathy. They noted that these findings suggested some benefit from radioiodine treatment for recurrence of hyperthyroidism (relapse) but there is uncertainty about the magnitude of the effect size.
In a pilot study, Leo and colleagues (2018) examined if a low-dose of radioiodine can be used to ablate thyroid remnants in patients with GO, following thyroidectomy. The study was performed in 2 small groups of consecutive thyroidectomized patients (6 patients per group) with Graves' hyperthyroidism and GO. Patients underwent ablation with either 15 or 30 mCi of I-131 following treatment with recombinant human TSH (rhTSH). The primary outcome was rhTSH-stimulated serum thyroglobulin (Tg) at 6 months; the secondary outcome was baseline Tg at 6 months. Baseline Tg and rhTSH-stimulated Tg after at 6 months did not differ between 2 groups, suggesting a similar extent of ablation. rhTSH-stimulated Tg was reduced significantly compared with rhTSH-stimulated Tg at ablation in both groups; GO outcome following treatment with intravenous glucocorticoids did not differ between the 2 groups. The authors concluded that the findings of this pilot trial may provide a preliminary basis for the use of a 15 mCi dose of radioiodine upon rhTSH stimulation in thyroidectomized patients with Graves' hyperthyroidism and GO.

Rituximab

In a retrospective, interventional case series, Khanna and colleagues (2010) examined the effectiveness of rituximab in patients with severe, corticosteroid (CS)-resistant TAO. Responses to rituximab therapy were graded using standard clinical assessment and flow cytometric analysis of peripheral lymphocytes. Main outcome measures were CAS, proptosis, strabismus, treatment side effects, and quantification of regulatory T cells; 6 patients were studied. Systemic CS failed to alter clinical activity in all patients (mean CAS +/- standard deviation, 5.3 +/- 1.0 before versus 5.5 +/- 0.8 during therapy for 7.5 +/- 6.4 months; p = 1.0). However, after rituximab therapy, CAS improved from 5.5 +/- 0.8 to 1.3 +/- 0.5 at 2 months after treatment (p < 0.03) and remained quiescent in all patients (CAS, 0.7 +/- 0.8; p < 0.0001) at a mean follow-up of 6.2 +/- 4.5 months. Vision improved bilaterally in all 4
patients with dysthyroid optic neuropathy (DON). None of the 6 patients experienced disease relapse after rituximab infusion, and proptosis remained stable (Hertel measurement, 24 +/- 3.7 mm before therapy and 23.6 +/- 3.7 mm after therapy; p = 0.17). The abundance of T regulatory cells, assessed in 1 patient, increased within 1 week of rituximab and remained elevated at 18 months of follow-up. The authors concluded that in progressive, CS-resistant TAO, rapid and sustained resolution of orbital inflammation and DON followed treatment with rituximab.

In a Cochrane review, Minakaran and Ezra (2013) examined the effectiveness and safety of rituximab for the treatment of TAO. These investigators searched CENTRAL (which contains the Cochrane Eyes and Vision Group Trials Register) (the Cochrane Library 2013, Issue 3), Ovid MEDLINE, Ovid MEDLINE In-Process and Other Non-Indexed Citations, Ovid MEDLINE Daily, Ovid OLDMEDLINE, (January 1950 to April 2013), EMBASE (January 1980 to April 2013), Latin American and Caribbean Literature on Health Sciences (LILACS) (January 1982 to April 2013), OpenGrey (System for Information on Grey Literature in Europe) (www.opengrey.eu/), the metaRegister of Controlled Trials (mRCT) (www.controlled-trials.com), ClinicalTrials.gov (www.clinicaltrials.gov), the WHO International Clinical Trials Registry Platform (ICTRP) (www.who.int/ictrp/search/en) and the EU Clinical Trials Register (www.clinicaltrialsregister.eu). They did not use any date or language restrictions in the electronic searches for trials. They last searched the electronic databases on April 15, 2013. These researchers manually searched references of review articles and used the Science Citation Index to identify additional studies citing trials. They contacted the lead investigators of relevant trials on ClinicalTrials.gov and the WHO ICTRP for information and data from as yet unpublished clinical trials. They contacted experts in the field for information about any ongoing trials; and contacted the manufacturers of rituximab for details of any sponsored trials. These researchers included RCTs of rituximab treatment by
intravenous infusion for the treatment of patients with TAO, compared with placebo or intravenous glucocorticoid treatment. Two review authors independently scanned titles and abstracts, as well as independently screened the full reports of the potentially relevant studies. At each stage, the results were compared and disagreements were solved by discussion. No studies were identified that met the inclusion criteria. There are 3 ongoing studies that are likely to meet inclusion criteria once published, and thus be included in future updates of this review. The authors concluded that there is currently insufficient evidence to support the use of rituximab in patients with TAO. There is a need for large RCTs, investigating rituximab versus placebo or corticosteroids in patients with active TAO to make adequate judgment on the safety and effectiveness of this novel therapy for this condition.

An UpToDate review on “Treatment of Graves’ orbitopathy (ophthalmopathy)” (Davies, 2015) states that “Rituximab -- A number of reports have indicated that some patients with severe Graves’ orbitopathy may respond dramatically to B cell depletion induced by rituximab, which is a monoclonal antibody directed against the B cell CD20 molecule. Rituximab induces a fall in TSH receptor antibody levels and depletion of B cells in the retro-orbital tissues, not just the periphery. Although high doses of this antibody may be associated with severe side effects from the profound immunosuppression that ensues, it is likely that much lower doses may be effective in Graves’ orbitopathy and allow such effects to be avoided. This approach to the treatment of severe eye disease is currently undergoing larger trials; preliminary results from these trials have been mixed and are not yet published …. Somatostatin analogs -- Somatostatin analogs have been explored as a potential therapy for Graves’ ophthalmopathy, based upon the observations that orbital fibroblasts have somatostatin receptors and the activity of orbitopathy correlates with activity on octreotide scintigrams. One randomized, placebo-controlled trial of a long-acting
octreotide preparation reported improvement in clinical activity scores and median lid fissure width with octreotide compared with placebo. In contrast, two other similar trials reported limited benefit with octreotide. In a meta-analysis of four trials, somatostatin analogs resulted in a slightly lower clinical activity score than placebo, but had no advantages for other important outcomes (diplopia, proptosis, lid aperture). Octreotide has no role in the routine treatment of Graves' ophthalmopathy”.

Furthermore, this review does not mention tocilizumab as a therapeutic option.

Ladsous (2016) stated that the use of rituximab in GO is appealing but its exact role in the therapeutic arsenal remains to be clarified, and its safety profile also needs to be confirmed on a larger scale.

In a systematic review and meta-analysis of 4 RCTs Shen and colleagues (2018) evaluated the safety and efficacy of rituximab in patients with GO. A total of 293 patients with GO who received rituximab or control (either glucocorticoids, the established 1st-line therapy [3 trials], or saline [1 trial]). Relevant studies published before February 2018 were identified from the PubMed, Embase, Cochrane Library, and Scopus databases and the ClinicalTrials.gov registry. Individual effect sizes were standardized, and a meta-analysis was conducted to calculate the pooled effect size by using a random-effects model. Treatment efficacy was assessed by measuring the following outcomes: CAS, sight visual acuity reduction (NOSPECS) score, proptosis, diplopia, changes in eye volume, QOL, and adverse events (AEs). In the 4 included trials, 113 patients in the rituximab group and 108 patients in the control group were evaluated. Compared with the control group, CAS (weighted mean difference [WMD] 0.57, 95% CI: 0.25 to 0.89) was significantly reduced at 24 weeks in the rituximab group. Compared with the control group, considerable proptosis reduction was also observed in the rituximab group; however, the difference was not significant. The proportion of AEs in the rituximab group was
not significantly higher than that in the glucocorticoid control group, but one of the included trials indicated that the rituximab group had more serious AEs than the saline control group. The authors concluded that rituximab was a relatively safe and viable treatment that is superior to glucocorticoids or saline for patients with moderate-to-severe GO. However, these researchers stated that the incidence of serious AEs was disparate among the included trials. They stated that additional studies involving a larger sample size and examining the optimal rituximab dosage, frequency, and method of administration are needed.

Celecoxib and Pioglitazone

Cheng and colleagues (2016) examined the role of extraocular muscles (EOM) myoblasts in GO pathology and the effect of a cyclooxygenase (COX)-2 inhibitor and a peroxisome proliferator-activated receptor (PPAR)-γ agonist in its treatment. Myoblasts were isolated and cultured from EOM of 10 patients with GO and 4 without (non-GO). The cultured myoblasts were treated with interferon-gamma (IFN-γ), insulin-like growth factor (IGF)-1, interleukin (IL)-1β, and tumor-necrosis-factor-alpha (TNF-α), and the effect on PPAR-γ, COX-2, TGF-β, and thyroid stimulating hormone receptor (TSHR) expressions were assessed using real-time polymerase chain reaction (RT-PCR), enzyme-linked immunosorbent assay (ELISA), and Western blot. The effect of a COX-2 inhibitor and a PPAR-γ agonist on the expression of TGF-β, hyaluronan synthases (HAS)-1, -2, and -3, and hyaluronan (HA) were further evaluated. Real-time PCR showed significant up-regulation in PPAR-γ, COX-2, TGF-β, and TSHR messenger RNA (mRNA) expression in GO myoblasts when treated with TNF-α but not in the non-GO. While IFN-γ and IGF-1 had no significant effect, IL-1β did up-regulate COX-2 expression. These results were further confirmed by ELISA and Western blotting. Tumor necrosis factor α-induced TGF-β in turn significantly increased HA expression and HAS3 level, but not HAS1 and HAS2. The
cyclooxygenase 2 inhibitor and PPAR-γ agonist substantially diminished this TNF-α-induced TGF-β, HA, and HAS3 expression. The authors concluded that these findings showed the role of EOM myoblasts in the pathogenesis of GO. They stated that the cyclooxygenase 2 inhibitor and PPAR-γ agonist in this study are potential treatments for GO due to their ability to suppress TNF-α-induced TGF-β, HAS, and HA up-regulation.

Teprotumumab

Thyroid eye disease (TED) is a rare autoimmune condition caused by antibodies directed against receptors present in the thyroid cells and extraocular muscles and soft tissue of the orbit. The fatty and connective tissues behind the eye become inflamed, causing the eyes to be pushed forward and bulge outwards (proptosis). The outward bulging of the eye can cause a variety of symptoms such as eye pain, double vision, light sensitivity or difficulty closing the eye, and can impair activities of daily living (e.g., driving). TED typically has a progressive inflammatory phase followed by a stable post-inflammatory phase and is also known as thyroid associated ophthalmopathy (TAO), Grave’s orbitopathy, Graves’ Ophthalmopathy, or Graves’ eye disease. About 90% of patients with TED have Graves’ disease, the most common form of hyperthyroidism; however about 10% of patients with TED have either a normal-functioning (euthyroid) or under-functioning thyroid (hypothyroidism e.g. Hashimoto's thyroiditis). Although maintaining strict control of thyroid function is crucial in patients with TED, the course and severity of ocular manifestation does not always correlate with thyroid hormone levels. Therefore, treatment of thyroid dysfunction does not necessarily affect course of Grave’s ophthalmopathy (Durairaj 2019).

Conservative options to help prevent exacerbation and decrease the duration of active thyroid eye disease include smoking cessation and maintaining a euthyroid (i.e., a normal-
functioning thyroid). Lubricants, taping and protective shields can be tried for corneal exposure, and tarsorrhaphy can be done if necessary. For diplopia, Fresnel prisms or occlusion therapy should be considered. Other lifestyle modifications include sodium restriction to reduce water retention and tissue edema, and sleeping with the head of the bed elevated to decrease orbital edema. Oral NSAIDs can be used for periocular pain. Selenium has also shown significant benefit in European patients with mild, non-inflammatory orbitopathy (Durairaj 2019).

Systemic glucocorticoids to decrease orbital inflammation are the current mainstay among medical therapies for treatment of moderate to severe TED symptoms. Oral prednisone in a dose of 1-1.5-mg/kg can be given for a suggested maximum period of 2 months. Intravenous (IV) corticosteroids pulse methyl prednisolone can be considered as an alternative. In patients with severe disease, surgical procedures including strabismus correction, eyelid repair, and orbital decompression may be needed. Orbital Radiation can be used alone or in conjunction with corticosteroids, to improves vertical motility. However, radiation retinopathy can occur as a side effect. Orbital decompression enlarges the existing space by partial removal of bony walls and periosteum. In cases of significant strabismus, strabismus surgery may be required and should be done with adjustable sutures since the muscles typically do not respond as normal muscles would to strabismus surgery. Strabismus surgery should be considered only after orbital decompression is complete and muscle alignment has stabilized (Durairaj 2019).

Smith and Janssen (2017) noted that the pathogenesis of orbital Graves' disease (GD), a process known as TAO, remains incompletely understood. The TSHR represents the central autoantigen involved in GD and has been proposed as the thyroid antigen shared with the orbit that could explain the infiltration of immune cells into tissues surrounding the eye. Another cell surface protein, IGF-I receptor (IGF-IR), has
recently been proposed as a second antigen that participates in TAO by virtue of its interactions with anti-IGF-IR antibodies generated in GD, its apparent physical and functional complex formation with TSHR, and its necessary involvement in TSHR post-receptor signaling. The proposal that IGF-IR is involved in TAO has provoked substantial debate. Furthermore, several studies from different laboratory groups, each using different experimental models, have yielded conflicting results. These researchers summarized the biological characteristics of IGF-IR and TSHR. They also reviewed the evidence supporting and refuting the postulate that IGF-IR is a self-antigen in GD and that it plays a potentially important role in TAO. The putative involvement of IGF-IR in disease pathogenesis carries substantial clinical implications.

Specifically, blocking this receptor with monoclonal antibodies can dramatically attenuate the induction by TSH and pathogenic antibodies generated in GD of pro-inflammatory genes in cultured orbital fibroblasts and fibrocytes. These cell types appear critical to the development of TAO. The authors stated that these observations have led to the conduct of a now-completed multi-center therapeutic trial of a fully human monoclonal anti-IGF-IR blocking antibody (teprotumumab or RV001) in moderate-to-severe, active TAO.

Wiersinga (2017) stated that corticosteroids have been the mainstay of treatment for GO, but new evidence about immune mechanisms has provided a basis to explore other drug classes; IV methylprednisolone pulses are more effective and better tolerated than oral prednisone in the treatment of active, moderate-to-severe GO. Rituximab has also been suggested as a possible replacement for IV corticosteroids. Two RCTs of rituximab reached seemingly contradictory conclusions -- rituximab was not better with respect to the primary outcome (clinical activity score) than placebo in 1 trial (which, however, was confounded by rather long GO duration), but was slightly better than IV methylprednisolone pulses in the other (disease flare-ups occurred only in the latter group). The author stated that on the basis of evidence published so far, rituximab
cannot replace IV methylprednisolone pulses, but could have a role in corticosteroid-resistant cases. Open-label studies of TNF-α blockade had limited efficacy, but other studies showed that interleukin (IL)-6 receptor antibodies were effective. Results of RCTs investigating the effectiveness of the IGF-1 receptor antibody teprotumumab and the IL-6 receptor antibody tocilizumab are expected shortly. Approaches that target the causal mechanism of GO (antibodies or antagonists that block TSHRs) also look promising.

Smith (2017) reviewed the fundamental characteristics of the TSHR, its role in GD and TAO, and its relationship to IGF-IR. Strong evidence supports the concept that the 2 receptors form a physical and functional complex and that IGF-IR activity is needed for some of the down-stream signaling initiated through TSHR. The author also reviewed recently developed small molecules and monoclonal antibodies that block TSHR and IGF-IR signaling in the narrow context of their potential utility as therapeutics in GD and TAO. The PubMed database was searched from its inception for relevant publications. The author concluded that agents that can interrupt the TSHR and IGF-IR pathways possess the potential for offering more specific and better tolerated treatments of both hyperthyroidism and TAO.

On January 21, 2020, the U.S. Food and Drug Administration (FDA) approved Tepezza (teprotumumab-trbw; Horizon Therapeutics) for the treatment of adults with thyroid eye disease. Tepezza, a fully human monoclonal antibody of the insulin-like growth factor type-1 receptor (IGF-1R), binds to IGF-1R and blocks its activation and signaling. Tepezza is the first drug approved for the treatment of thyroid eye disease. The underlying mechanism of action of thyroid eye disease is not completely understood, but is thought to be caused by the activation of orbital fibroblasts by Graves' disease-related autoantibodies. This activation then leads to the release of T cell chemoattractants and ultimately results in fibroblasts expressing extracellular matrix molecules, biologic
materials proliferating and differentiating into myofibroblasts or lipofibroblasts and deposition of glycosaminoglycans which bind water that lead to swelling, congestion in addition to connective tissue remodeling. This results in extraocular muscle enlargement and orbital fat expansion (Durairaj 2019).

Tepezza was approved based on the results of two studies (Smith 2017 and Douglas 2020) stated thyroid-associated ophthalmopathy (TAO), a condition commonly associated with Graves' disease, remains inadequately treated. Current medical therapies, which primarily consist of glucocorticoids, have limited efficacy and present safety concerns. Inhibition of the insulin-like growth factor I receptor (IGF-IR) is a new therapeutic strategy to attenuate the underlying autoimmune pathogenesis of ophthalmopathy. The authors conducted a multicenter, double-masked, randomized, placebo-controlled trial to determine the efficacy and safety of teprotumumab, a human monoclonal antibody inhibitor of IGF-IR, in patients with active, moderate-to-severe ophthalmopathy. A total of 88 patients were randomly assigned to receive placebo or active drug administered intravenously once every 3 weeks for a total of eight infusions. The primary end point was the response in the study eye. This response was defined as a reduction of 2 points or more in the Clinical Activity Score (scores range from 0 to 7, with a score of ≥3 indicating active thyroid-associated ophthalmopathy) and a reduction of 2 mm or more in proptosis at week 24. Secondary end points, measured as continuous variables, included proptosis, the Clinical Activity Score, and results on the Graves' ophthalmopathy-specific quality-of-life questionnaire. Adverse events were assessed. In the intention-to-treat population, 29 of 42 patients who received teprotumumab (69%), as compared with 9 of 45 patients who received placebo (20%), had a response at week 24 (P<0.001). Therapeutic effects were rapid; at week 6, a total of 18 of 42 patients in the teprotumumab group (43%) and 2 of 45 patients in the placebo group (4%) had a response (P<0.001). Differences between the groups increased at subsequent time points. The only drug-related adverse event
was hyperglycemia in patients with diabetes; this event was controlled by adjusting medication for diabetes. The authors concluded that in patients with active ophthalmopathy, teprotumumab was more effective than placebo in reducing proptosis and the Clinical Activity Score. (NCT01868997.)

consisting of a total of 170 patients with active thyroid eye disease who were randomized to either receive Tepezza or a placebo. Of the patients who were administered Tepezza, 71% in Study 1 and 83% in Study 2 demonstrated a greater than 2 millimeter reduction in proptosis (eye protrusion) as compared to 20% and 10% of subjects who received placebo, respectively.

Smith et al (2017) stated thyroid-associated ophthalmopathy (TAO), a condition commonly associated with Graves' disease, remains inadequately treated. Current medical therapies, which primarily consist of glucocorticoids, have limited efficacy and present safety concerns. Inhibition of the insulin-like growth factor I receptor (IGF-IR) is a new therapeutic strategy to attenuate the underlying autoimmune pathogenesis of ophthalmopathy. The authors conducted a multicenter, double-masked, randomized, placebo-controlled trial to determine the efficacy and safety of teprotumumab, a human monoclonal antibody inhibitor of IGF-IR, in patients with active, moderate-to-severe ophthalmopathy. Major inclusion criteria were the following: patients were 18 to 75 years of age, with ophthalmopathy that had been diagnosed no more than 9 months after the onset of symptoms, had a Clinical Activity Score of 4 or more on a 7-point scale (with a score of ≥3 indicating active thyroid-associated ophthalmopathy) in the more severely affected (study) eye, were euthyroid before taking study medication, and had not received surgical or medical treatment, with the exception of oral glucocorticoids (a cumulative dose of ≤1 g of methylprednisolone or equivalent, with a 6-week washout period). Serum glucose levels in patients with diabetes were well controlled. Female patients had negative pregnancy tests and used approved contraception. Patients with optic neuropathy, severe ocular
surface damage, or an improved Clinical Activity Score of 2 points or more between screening and baseline visits were excluded. A total of 88 patients were randomly assigned to receive placebo or active drug administered intravenously once every 3 weeks for a total of eight infusions. The primary end point was the response in the study eye, defined as a reduction of 2 points or more in the Clinical Activity Score (scores range from 0 to 7, with a score of ≥3 indicating active thyroid-associated ophthalmopathy) and a reduction of 2 mm or more in proptosis in the study eye at week 24, in the absence of a corresponding amount of worsening in the nonstudy eye. Secondary end points, measured as continuous variables, included proptosis, the Clinical Activity Score, and results on the Graves' ophthalmopathy-specific quality-of-life questionnaire. Adverse events were assessed. In the intention-to-treat population, 29 of 42 patients who received teprotumumab (69%), as compared with 9 of 45 patients who received placebo (20%), had a response at week 24 (P<0.001). Therapeutic effects were rapid; at week 6, a total of 18 of 42 patients in the teprotumumab group (43%) and 2 of 45 patients in the placebo group (4%) had a response (P<0.001). Differences between the groups increased at subsequent time points. The only drug-related adverse event was hyperglycemia in patients with diabetes; this event was controlled by adjusting medication for diabetes. The authors concluded that in patients with active ophthalmopathy, teprotumumab was more effective than placebo in reducing proptosis and the Clinical Activity Score. The authors cited the following limitations: the trial only enrolled patients with active disease of recent onset, with a Clinical Activity Score of 4 or more. Thus, the potential of teprotumumab in benefiting patients with milder, less active, or stable disease was not assessed. Longer-term observation in the ongoing 1-year follow-up trial phase is necessary for assessing the durability of the response. No orbital imaging was performed; thus, it remains uncertain which orbital tissues were primarily affected by teprotumumab therapy (NCT01868997).
Douglas et al (2020) stated thyroid eye disease is a debilitating, disfiguring, and potentially blinding periocular condition for which no Food and Drug Administration-approved medical therapy is available. Strong evidence has implicated the insulin-like growth factor I receptor (IGF-IR) in the pathogenesis of this disease. In a randomized, double-masked, placebo-controlled, phase 3 multicenter trial, the authors assigned patients with active thyroid eye disease in a 1:1 ratio to receive intravenous infusions of the IGF-IR inhibitor teprotumumab (10 mg per kilogram of body weight for the first infusion and 20 mg per kilogram for subsequent infusions) or placebo once every 3 weeks for 21 weeks; the last trial visit for this analysis was at week 24. The primary outcome was a proptosis response (a reduction in proptosis of ≥2 mm) at week 24. Prespecified secondary outcomes at week 24 were an overall response (a reduction of ≥2 points in the Clinical Activity Score plus a reduction in proptosis of ≥2 mm), a Clinical Activity Score of 0 or 1 (indicating no or minimal inflammation), the mean change in proptosis across trial visits (from baseline through week 24), a diplopia response (a reduction in diplopia of ≥1 grade), and the mean change in overall score on the Graves' ophthalmopathy-specific quality-of-life (GO-QOL) questionnaire across trial visits (from baseline through week 24; a mean change of ≥6 points is considered clinically meaningful). A total of 41 patients were assigned to the teprotumumab group and 42 to the placebo group. At week 24, the percentage of patients with a proptosis response was higher with teprotumumab than with placebo (83% [34 patients] vs. 10% [4 patients], P<0.001), with a number needed to treat of 1.36. All secondary outcomes were significantly better with teprotumumab than with placebo, including overall response (78% of patients [32] vs. 7% [3]), Clinical Activity Score of 0 or 1 (59% [24] vs. 21% [9]), the mean change in proptosis (-2.82 mm vs. -0.54 mm), diplopia response (68% [19 of 28] vs. 29% [8 of 28]), and the mean change in GO-QOL overall score (13.79 points vs. 4.43 points) (P≤0.001 for all). Reductions in extraocular muscle, orbital fat volume, or both were observed in 6 patients in the
teprotumumab group who underwent orbital imaging. Most adverse events were mild or moderate in severity; two serious events occurred in the teprotumumab group, of which one (an infusion reaction) led to treatment discontinuation. The authors concluded that among patients with active thyroid eye disease, teprotumumab resulted in better outcomes with respect to proptosis, Clinical Activity Score, diplopia, and quality of life than placebo; serious adverse events were uncommon (NCT03298867).

The most common adverse reactions observed in patients treated with Tepezza are muscle spasm, nausea, alopecia (hair loss), diarrhea, fatigue, hyperglycemia (high blood sugar), hearing loss, dry skin, dysgeusia (altered sense of taste) and headache. Tepezza should not be used if pregnant, and women of child-bearing potential should have their pregnancy status verified prior to beginning treatment and should be counseled on pregnancy prevention during treatment and for 6 months following the last dose of Tepezza.

Extraocular Muscle Repositioning

Rau and colleagues (2018) noted that Graves' disease is a common autoimmune inflammatory condition of the thyroid. About 25% of affected patients also develop orbital symptoms like exophthalmos, proptosis and diplopia -- called Graves' Ophthalmopathy. Not all patients respond well to the standard therapy of systemic glucocorticoid administration. The inflammatory swelling of the intra-orbital muscles can lead to pressure-induced damage of the optic nerve. Orbital decompression surgery is a therapeutic option for these patients with varying success. Other symptoms like the extreme malposition of the ocular globe are poorly addressed by decompression surgery and demand for different therapeutic approaches. These researchers presented the case of a 46-year old patient with an acute exacerbation of Graves' ophthalmopathy. Clinically apparent was a convergent strabismus fixus with severe hypotropia of both
eyes. The patient suffered from attacks of heavy retro-bulbar pain and eyesight deteriorated dramatically. Since neither systemic glucocorticoid therapy nor orbital decompression surgery had helped to halt the progress of the disease, a decision was made in favor of the surgical release and repositioning of the inferior and medial rectus muscle as a final therapeutic option. Surgery of both eyes was performed consecutively within 1 week. Detailed descriptions and illustrations of the surgical steps and treatment outcome were provided and supplemented by a discussion of the current literature. The authors concluded that Graves' Ophthalmopathy is a variant and therapeutically challenging disease. Exceptional courses of the disease call for therapeutic approaches off the beaten track. Surgical extraocular muscle repositioning, which has not been described before in the context of Graves' Ophthalmopathy, proved to be effective in improving the patient's eyesight and quality of life (QOL). These preliminary findings need to be further investigated.

**Phosphorus-32 Brachytherapy**

Hao and colleagues (2017) examined the therapeutic effect of radiation delivered via a phosphorus-32 (P-32) source on 30 patients (13 males and 17 females) with Graves' ophthalmopathy. A P-32 solution was injected into a 10-ml vacuum flask held inside a lead container. A window was cut in the lead, generating a treatment beam. Radiation was given to 4 areas: The upper and lower orbit (covering approximately 1/3 of the eyelid) and the inner and outer canthus. Each site received 10 daily doses of 20 cGy. Proptosis was measured by an exophthalmometer and the palpebral aperture was determined with a ruler. Measurements were taken before and after the treatment. After 5 days of treatment, the patient displayed a significant improvement, and by 10 days, the average reduction of proptosis in Graves' ophthalmopathy was 3.36 ± 1.73 mm for the left and 3.05 ± 2.04 mm for the right eyes. The treatment was effective in all patients, who
uniformly reported rapid pain relief. Conjunctival congestion and eyelid edema also improved significantly. However, only 50% of patients showed improved diplopia after treatment, which was poor compared with other symptoms. No obvious side effects were found in the subsequent follow-up. The authors concluded that the findings of the present study demonstrated that P-32 brachytherapy was a simple procedure for Graves' ophthalmopathy arising from hyperthyroidism with a curative effect. Moreover, they stated that while it is a promising therapeutic method, it was only applied to a small group (n = 30) and issues of optimal dose and long-term morbidity need further research.

Appendix

Appendix A: TED Activity Assessment – CAS Elements

Table: TED Activity Assessment – CAS Elements

<table>
<thead>
<tr>
<th>Elements</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Painful feeling behind the globe over last 4 weeks</td>
<td>1</td>
</tr>
<tr>
<td>Pain with eye movement during last 4 weeks</td>
<td>1</td>
</tr>
<tr>
<td>Redness of the eyelids</td>
<td>1</td>
</tr>
<tr>
<td>Redness of the conjunctiva</td>
<td>1</td>
</tr>
<tr>
<td>Swelling of the eyelids</td>
<td>1</td>
</tr>
<tr>
<td>Chemosis (edema of the conjunctiva)</td>
<td>1</td>
</tr>
<tr>
<td>Swollen caruncle (flesh body at medial angle of eye)</td>
<td>1</td>
</tr>
</tbody>
</table>

*A 7-point scale with 1-point given for each element present*
Appendix B: Disease Severity Assessment

I. Mild disease, at least one of the following:

A. Minor lid retraction (<2 mm)
B. Mild soft-tissue involvement
C. Exophthalmos <3 mm above normal for race and gender
D. No or intermittent diplopia
E. Corneal exposure responsive to lubricants

II. Moderate-to-severe disease, at least one of the following:

A. Lid retraction ≥2 mm
B. Moderate or severe soft-tissue involvement
C. Exophthalmos ≥3 mm above normal for race and gender
D. Inconstant or constant diplopia

III. Sight-threatening disease, at least one of the following:

A. Dysthyroid optic neuropathy (DON)
B. Corneal breakdown.

CPT Codes / HCPCS Codes / ICD-10 Codes

Information in the [brackets] below has been added for clarification purposes. Codes requiring a 7th character are represented by "+":

<table>
<thead>
<tr>
<th>Code</th>
<th>Code Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>15820</td>
<td>Blepharoplasty, lower eyelid</td>
</tr>
<tr>
<td>15822</td>
<td>Blepharoplasty, upper eyelid</td>
</tr>
<tr>
<td>Code</td>
<td>Code Description</td>
</tr>
<tr>
<td>----------</td>
<td>-----------------------------------------------------------------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>61330</td>
<td>Decompression of orbit only, transcranial approach</td>
</tr>
<tr>
<td>67311 - 67343</td>
<td>Strabismus surgery</td>
</tr>
<tr>
<td>67414</td>
<td>Orbitotomy without bone flap (frontal or transconjunctival approach); with removal of bone for decompression</td>
</tr>
<tr>
<td>67445</td>
<td>Orbitotomy with bone flap or window, lateral approach (e.g., Kroenlein); with removal of bone for decompression</td>
</tr>
<tr>
<td>67901 - 67908</td>
<td>Repair of blepharoptosis</td>
</tr>
<tr>
<td>67950</td>
<td>Cathoplasty [lateral tarsal canthoplasty]</td>
</tr>
<tr>
<td>67961 - 67966</td>
<td>Excision and repair of eyelid, involving lid margin, tarsus, conjunctiva, canthus, or full thickness, may include preparation for skin graft or pedicle flap with adjacent tissue transfer or rearrangement [mullerectomy (resection of the Müller muscle), eyelid spacer grafts]</td>
</tr>
<tr>
<td>67909</td>
<td>Reduction of overcorrection of ptosis</td>
</tr>
<tr>
<td>67911</td>
<td>Correction of lid retraction</td>
</tr>
<tr>
<td>77789</td>
<td>Surface application of low dose rate radionuclide source</td>
</tr>
</tbody>
</table>

CPT codes not covered for indications listed in the CPB:

<table>
<thead>
<tr>
<th>Code</th>
<th>Code Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>15821</td>
<td>Blepharoplasty, lower eyelid; with extensive herniated fat pad</td>
</tr>
<tr>
<td>15823</td>
<td>Blepharoplasty, upper eyelid; excessive skin weighting down lid</td>
</tr>
<tr>
<td>Code</td>
<td>Code Description</td>
</tr>
<tr>
<td>--------</td>
<td>----------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>90281</td>
<td>Immune globulin (Ig), human, for intramuscular use</td>
</tr>
<tr>
<td>90283</td>
<td>Immune globulin (IgIV), human, for intravenous use</td>
</tr>
<tr>
<td>90284</td>
<td>Immune globulin (SClg), human, for use in subcutaneous infusions, 100 mg, each</td>
</tr>
</tbody>
</table>

**HCP CS codes covered if selection criteria are met:**

**Teprotumumab - No specific code:**

- V2710 Slab off prism, glass or plastic, per lens [for members with strabismus]
- V2715 Prism, per lens [for members with strabismus]
- V2718 Press-on lens, Fresnel prism, per lens [for members with strabismus]

**HCP CS codes not covered for indications listed in the CPB:**

**Celecoxib, Pioglitazone - No specific code:**

- C2698 Brachytherapy source, stranded, not otherwise specified, per source [phosphorus-32 brachytherapy]
- C2699 Brachytherapy source, non-stranded, not otherwise specified, per source [phosphorus-32 brachytherapy]
- G0069 Professional services for the administration of subcutaneous immunotherapy for each infusion drug administration calendar day in the individual's home, each 15 minutes
- J0135 Injections, adalimumab, 20 mg
<table>
<thead>
<tr>
<th>Code</th>
<th>Code Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>J0717</td>
<td>Injection, certolizumab pegol, 1 mg (code may be used for medicare when drug administered under the direct supervision of a physician, not for use when drug is self administered)</td>
</tr>
<tr>
<td>J1438</td>
<td>Injection, etanercept, 25 mg</td>
</tr>
<tr>
<td>J1459</td>
<td>Injection, immune globulin (Privigen), intravenous, nonlyophilized (e.g., liquid), 500 mg</td>
</tr>
<tr>
<td>J1561</td>
<td>Injection, immune globulin, (Gamunex-C/Gammaked), nonlyophilized (e.g. liquid), 500 mg</td>
</tr>
<tr>
<td>J1566</td>
<td>Injection, immune globulin, intravenous, lyophilized (e.g., powder), not otherwise specified, 500 mg</td>
</tr>
<tr>
<td>J1568</td>
<td>Injection, immune globulin, (Octagam), intravenous, nonlyophilized (e.g., liquid), 500 mg</td>
</tr>
<tr>
<td>J1569</td>
<td>Injection, immune globulin, (Gammagard liquid), nonlyophilized, (e.g. liquid), 500 mg</td>
</tr>
<tr>
<td>J1572</td>
<td>Injection, immune globulin, (Flebogamma/Flebogamma Dif), intravenous, nonlyophilized (e.g., liquid), 500 mg</td>
</tr>
<tr>
<td>J1745</td>
<td>Injection, infliximab, 10 mg</td>
</tr>
<tr>
<td>J1930</td>
<td>Injection, lanreotide, 1 mg</td>
</tr>
<tr>
<td>J2353</td>
<td>Injection, octreotide, depot form for intramuscular injection, 1 mg</td>
</tr>
<tr>
<td>J2354</td>
<td>Injection, octreotide, nondepot form for subcutaneous or intravenous injection, 25 mcg</td>
</tr>
<tr>
<td>Code</td>
<td>Code Description</td>
</tr>
<tr>
<td>--------</td>
<td>----------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>J2792</td>
<td>Injection, Rho D immune globulin, intravenous, human, solvent detergent, 100 IU</td>
</tr>
<tr>
<td>J3262</td>
<td>Injection, tocilizumab, 1 mg</td>
</tr>
<tr>
<td>J9312</td>
<td>Injection, rituximab, 10 mg</td>
</tr>
<tr>
<td>Q5103</td>
<td>Injection, infliximab-dyyb, biosimilar, (Inflectra), 10 mg</td>
</tr>
<tr>
<td>Q5104</td>
<td>Injection, infliximab-abda, biosimilar, (Renflexis), 10 mg</td>
</tr>
<tr>
<td>Q5109</td>
<td>Injection, infliximab-qbbx, biosimilar, (ixifi), 10 mg</td>
</tr>
<tr>
<td>S9338</td>
<td>Home infusion therapy, immunotherapy, administrative services, professional pharmacy services, care coordination, and all necessary supplies and equipment (drugs and nursing visits coded separately), per diem</td>
</tr>
</tbody>
</table>

Other HCPCS codes related to the CPB:

<table>
<thead>
<tr>
<th>Code</th>
<th>Code Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>S9338</td>
<td>Home infusion therapy, immunotherapy, administrative services, professional pharmacy services, care coordination, and all necessary supplies and equipment (drugs and nursing visits coded separately), per diem</td>
</tr>
<tr>
<td>S9359</td>
<td>Home infusion therapy, anti-tumor necrosis factor intravenous therapy, (e.g., Infliximab), administrative services, professional pharmacy services, care coordination, and all necessary supplies and equipment (drug and nursing visits coded separately), per diem</td>
</tr>
</tbody>
</table>

ICD-10 codes covered if selection criteria are met:

<table>
<thead>
<tr>
<th>Code</th>
<th>Code Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>E05.00 - E05.01</td>
<td>Thyrotoxicosis with diffuse goiter [with/without thyrotoxic crisis or storm]</td>
</tr>
<tr>
<td>Code</td>
<td>Code Description</td>
</tr>
<tr>
<td>--------</td>
<td>----------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>H05.89</td>
<td>Other disorders of orbit [thyrotoxic exophthalmos, exophthalmic ophthalmoplegia]</td>
</tr>
</tbody>
</table>

The above policy is based on the following references:


17. Davies TF. Treatment of Graves' orbitopathy (ophthalmopathy). UpToDate [online serial]. Waltham, MA: UpToDate; reviewed February 2015.


29. Hegedüs L, Smith TJ, Douglas RS, Nielsen CH. Targeted biological therapies for Graves' disease and thyroid-


32. Horizon Therapeutics USA, Inc. Tepezza (teprotumumab-trbw) for injection, for intravenous use. Prescribing Information. Lake Forest, IL: Horizon Therapeutics USA, Inc; revised January 2020.


39. Leong SC, White PS. Outcomes following surgical decompression for dysthyroid orbitopathy (Graves'


70. Viani GA, Boin AC, De Fendi LI, et al. Radiation therapy for Graves' ophthalmopathy: A systematic review and


AETNA BETTER HEALTH® OF PENNSYLVANIA

Amendment to
Aetna Clinical Policy Bulletin Number: 0419 Graves' Ophthalmopathy Treatments

There are no amendments for Medicaid.