Graves' Ophthalmopathy Treatments

Policy

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

I. 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

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Definitions

Additional

Clinical Policy Bulletin Notes

Information
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. 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. 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. 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
- Pioglitazone
- Rituximab
- Somatostatin analogs (e.g., lanreotide and octreotide)
- Teprotumumab
- Tocilizumab
- Tumor necrosis factor-alpha inhibitors (e.g., etanercept and infliximab).

**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,
mis-alignment 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
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. Extraocular 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 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 glucocorticoid 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 toproctumumab. 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 ($I^2 = 91 %$) and the
RRs were 0.61 or 0.06 with non-overlapping CIs. Adverse events other than development of worsening of Graves' ophthalmopathy for radiiodine 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 radiiodine 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 radiiodine treatment US$ 1,862. Costs for patients with relapse and methimazole treatment were US$ 2,284/1,972 (young/older methimazole group) and for radiiodine 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 radiiodine treatment is associated with an increased risk of Graves' ophthalmopathy. They noted that these findings suggested some benefit from radiiodine treatment for recurrence of hyperthyroidism (relapse) but there is uncertainty about the magnitude of the effect size.

**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 clinical activity score (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.

Celecoxib and Pioglitazone:

Cheng and colleagues (2016) examined the role of extra-ocular 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:_

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

**CPT codes covered if selection criteria are met:**

<table>
<thead>
<tr>
<th>Code</th>
<th>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>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>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>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>Code</td>
<td>Description</td>
</tr>
<tr>
<td>--------</td>
<td>-----------------------------------------------------------------------------</td>
</tr>
<tr>
<td>90284</td>
<td>Immune globulin (SClg), human, for use in subcutaneous infusions, 100 mg, each</td>
</tr>
</tbody>
</table>

**HCPCS codes covered if selection criteria are met:**

<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>V2710</td>
<td>Slab off prism, glass or plastic, per lens [for members with strabismus]</td>
</tr>
<tr>
<td>V2715</td>
<td>Prism, per lens [for members with strabismus]</td>
</tr>
<tr>
<td>V2718</td>
<td>Press-on lens, Fresnel prism, per lens [for members with strabismus]</td>
</tr>
</tbody>
</table>

**HCPCS codes not covered for indications listed in the CPB:**

<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>J0135</td>
<td>Injections, adalimumab, 20 mg</td>
</tr>
<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>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>J9310</td>
<td>Injection, rituximab, 100 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>
<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>

**Other HCPCS codes related to the CPB:**

<table>
<thead>
<tr>
<th>Code</th>
<th>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>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>H05.89</td>
<td>Other disorders of orbit [thyrotoxic exophtalmos, exophthalmicophthalmoplegia]</td>
</tr>
</tbody>
</table>

**The above policy is based on the following references:**

29. Sherman J, Thompson GB, Lteif A, et al. Surgical management of Graves disease in childhood and


52. Bhatti MT, Dutton JJ. Thyroid eye disease: Therapy in the
54. Davies TF. Treatment of Graves' orbitopathy (ophthalmopathy). UpToDate [online serial]. Waltham, MA: UpToDate; reviewed February 2015.
64. Wiersinga WM. Advances in treatment of active, moderate-to-severe Graves' ophthalmopathy. Lancet Diabetes
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Amendment to
Aetna Clinical Policy Bulletin Number:
0419 Graves' Ophthalmopathy Treatments

There are no amendments for Medicaid.