Efficacy of Corticosteroids and External Beam Radiation in the Management of Moderate to Severe Thyroid Eye Disease

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Abstract: 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 (XRT) have traditionally been believed to provide benefit in active inflammation. Our 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 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. Our 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 (NANOS), American Society of Ophthalmic Plastic and Reconstructive Surgery (ASOPRS) and the Orbital Society, in conjunction with Neuro-Ophthalmology Research and Development Consortium (NORDIC), will investigate the design and funding of a multi-center controlled trial.

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Thyroid eye disease (TED, Graves ophthalmopathy, thyroid orbitopathy), which is associated with Graves disease (GD) in over 80% of cases, is an autoimmune disorder characterized by inflammation and expansion of the orbital fat and extraocular muscles. Although it has been identified in all age groups, it primarily affects adults in the fourth and fifth decades. TED can profoundly impair a patient's ability to work and perform activities of daily living. Multiple scoring systems exist to grade the activity and severity of TED. There is, however, no consensus on the most accurate system, nor is there correlation between the currently available scoring systems (1–3).

The pathophysiology of TED is not completely understood, but there is evidence for both humoral and cell-mediated immune processes (4–7). Active phase TED results from lymphocytic infiltration of the orbital and periorbital fat and muscles. The active phase generally persists for six months to three years, and is typically longer in smokers and those with prolonged hypothyroidism (8–10). The duration and severity of disease in an individual case, however, is unpredictable. After the inflammatory process ends, fibrosis and the associated disabling symptoms persist in the chronic, inactive phase.

Immunomodulatory agents are believed to affect the activity of orbital lymphocytes and fibroblasts (9,11,12).

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TABLE 1. ***Studies evaluating corticosteroid treatment of TED***

Authors	Patients	Study inclusion criteria	Pretreatment patient profile	Treatment study type
Bartalena et al (1983)[21]	48 (36 PO steroids and XRT, 12 only PO steroids)	Mild to moderate active TED	Not clearly stated	Prospective case series in 36 pts that received combined PO steroids (70–80 mg tapered over 6 months) and XRT. 12 pts that received only PO steroids were part of a prospective randomized study
Bartalena et al (1998)[31]	75	Needed to meet major categories (variations in 2 mm of proptosis and lid width, diplopia, change in vision) and minor categories (CAS, self assessment)	Pts with pre-existing TED given iodine and started on PO steroids 2 days after RAI	Prospective, randomized study. PO steroids (0.5 mg/kg/day prednisone × 1 month then with 8 wk PO taper
Baschieri et al[34]	55 (30 PO steroids, 25 IVIg)	Grades II–V NOSPECS (not VI)	Not clearly stated	Prospective, randomized, blinded study. 80 mg/day PO steroids × 2 wks then tapered over 5 months
Chang et al[42]	22	Grades II–IV NOSPECS (not V and VI)	Not clearly stated	Prospective case series. IV steroids 0.5 g/day × 3 then 5 month PO steroid taper (starting at 40 mg PO/day then tapered)
Dandona et al[41]	37	Not stated	Not clearly stated	Case series, (IV steroids 1 gm or 0.5 gm/day × 3 with three week PO oral taper
Hiromatsu et al[44]	23	Grades II–V NOSPECS (not VI)	Not clearly stated	Prospective case series. 1 gm/day IV steroids × 3, repeat 3–5 times over 5 weeks (total 9–12 gm) followed by 30 mg/day PO steroids × 1 month, then taper
Kahaly et al[33]	70 (35 IV steroids and 35 PO steroids)	Defined as untreated, active, moderate TED	Not clearly stated	Randomized, single blind study. 35 received IV steroids 0.5 gm/day × 6 wks (once weekly), then down to 0.25 gm/pulse IV steroids × 6 wks (once weekly); 35 received PO steroids 0.1 gm/day then taper for 12 wks by 0.01 g/wk (cumulative dose of 4.5 gm and 4.0 gm, respectively)
Kazim et al[43]	30	Not clearly stated	Not clearly stated	Retrospective case series. 80–120 mg/day PO steroids tapered "over many months"
Kendall-Taylor et al[38]	11	Not clearly stated	2 had prior immunosuppressive treatments for TED	Prospective case series. IV steroid (500 mg /day × 2) then with 40 mg PO steroid taper × 4 wks
Koshiyama et al[36]	8	Mod to severe TED	2 of 8 already had prior IV pulse steroids	Prospective case series. IV steroids 1gm/day × 3 then tapered to 30–40 mg/day PO steroids with variable tapered length (6–14 wks)

Adjunctive treatment	Outcome measures	Duration of follow up (wks)	Comment/Conclusions
36 combined PO steroids and XRT (20 Gy × 2 wks)	Clinical activity index, clinical assessment	12	26/36 (72%) excellent or good response in combined group, 12/12 that received only PO steroids had regression or improvement in soft tissue changes, but only 33% had overall good results (no excellent results reported). Proptosis improved in 19/36 (56%) of combined group while 5/11 (45%) improved with PO alone. 5/12 (41.7%) had improvement in EOM thickness in PO group. Recurrence occurred in 4/36 (11.1%) patients in combined group
	CAS and patient's impression	52	50/75 (67%) improved/regressed by CAS. Study showed PO steroids reduced the worsening of TED seen with RAI treatment
	Soft tissue changes, CT, proptosis, NOSPECS	24	24/30 (80%) improved diplopia with PO steroids, 18/25 (75%) with IVIG; 76% response to NOSPECS with IVIG, 66% response with PO steroids, used CT to evaluate EOM size and found an average improvement in EOM thickness in both PO and IVIG groups
	NOSPECS, CAS, CT	17	12/22 (55%) good response esp lacrimation, soreness, soft tissue swelling, proptosis; 4/10 poor responders got worse when steroids tapered to 20 mg or 10 mg/day, found that improvement in CAS correlated well with improvement seen in EOM size on CT
	Self assessment, eye exam, muscle size on CT	Not clearly stated	32/37 (86.5%) improved with reduction in proptosis, 6/6 that were imaged had reduction in EOM
	NOSPECS class, MRI muscle size	24	12/23 (52.2%) improved diplopia and soft tissue swelling, decrease in mean proptosis values, 13/23 (56.5%) decrease muscle size on MRI
	Proptosis and lid width, visual acuity, IOP in upgaze, diplopia, B-U/S, CAS, self assessment survey	12	Favorable response in 27/35 (77%) of patients receiving IV steroids vs 18/35 (51%) with PO steroids on CAS; rapid improvement seen in IV group, diplopia improved or resolved in 44% (16/35) with IV steroids, only in 4/35 (11.4%) in PO, improved motility in 16/35 (46%) in IV and 9/35 (26%) in PO. Proptosis improved in 21/35 (61%) in IV group and 14/35 (30%) in PO group. Survey: 80% satisfied with IV vs 54% in PO. No PO steroid taper used for IV pulse steroids. Found a more significant improvement in EOM thickness via B-U/S in patients that received IV than PO steroids
	Subjective improvement, improved fusion, proptosis, clinical exam	24	10/30 (33%) improved in some way. Proptosis and diplopia improved in 10/30 (30%); 6/16 with optic neuropathy improved, though 9 underwent additional treatment (XRT of surgical decompression). One patient noted to have recurrence
	Eye exam with IOP, CT EOM size, photos	24	6/7 (85.7%) with optic neuropathy improved, 9/11 (81.8%) improved soft tissue swelling, proptosis persisted in all patients, 8/9 (88.9%) improved EOM size on CT; of note, the 3 poor responders had TED > 1 year, 9 had CT's performed and 8 had a reduction of EOM size, though variable
XRT (20 Gy × 2 wks) given after completion of pulse IV steroids	Diplopia, muscle size on MRI, NOSPECS	3 yr (156 wks)	5/8 (62.5%) with eliminated diplopia, NOSPECS index improved on average, 6/8 (75%) decreased EOM size on MRI (EOM size compared with optic nerve thickness), 7/8 (88%) excellent result, no recurrence seen

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TABLE 1. ***(Continued)***

Authors	Patients	Study inclusion criteria	Pretreatment patient profile	Treatment study type
Macchia et al[32]	51 (26 PO steroids and 25 IV steroids)	Not clearly stated	None received prior treatment for TED	Randomized, prospective study 60–80 mg PO steroids with 4–6 month taper. IV group received 1000 mg/day for two consecutive days each week for total of 6 weeks
Marcocci et al (1987)[14]	60 (30 XRT and PO steroids, 30 combined XRT and retrobulbar steroids	Not clearly stated	Not clearly stated	Prospective, randomized, controlled study. PO steroids group: 70–80 mg/day PO steroids × 3 wks then tapered over 5–6 months, Retrobulbar steroids group: 14 injections (methylprednisolone, 40 mg/1.5 mL) q20–30 days × 9 months
Marcocci et al (2001)[30]	82 (41 PO steroids, 41 IV steroids)	Not clearly stated	12 received prior immunosuppressive treatment, 1 with prior orbital decompression	Prospective, single blind, r andomized study.100 mg/day PO steroid with taper over 22 wks, (total dose 6 g) vs IV steroids 15 mg/kg/day × 2 days every 2 weeks for 4 cycles, repeat with 7.5 mg/kg IV steroids × 2 every 2 wks for 4 cycles (total dose 9–12 gm)
Matejka et al[37]	8	Ophthalmology Index > 8 on NOSPECS	Not clearly stated	Prospective case series. IV 12.5 mg/kg q 1 mo), then repeated 3–6 times monthly, given PO steroids interpulse (0.5 mg/kg/day) then 4 wk PO steroid taper after last pulse IV dose
Noth et al[35]	19	Not clearly stated	No clearly stated	Prospective case series. 20–60 mg/day PO steroids × 3 months
Prummel et al (1989)[28]	18	Severe NOSPECS (Grade II–VI)	Not clearly stated	Prospective, single blind, randomized study. 60 mg PO steroids/day vs cyclosporine × 12 wks
Prummel et al (1993)[12]	56 (28 PO steroids, 28 XRT)	Severe NOSPECS (Grade II–VI)	None received prior treatment for TED	Prospective, double blind randomized trial. 60 mg PO steorids/day for 4 wks then taper down over 20 wks
Staar et al[39]	225	NOSPECS 2–6, and orbitopathy index	187 received prior immunosuppressive (steroid) treatment	Partly retrospective and prospective case series. 60 mg PO steroids simultaneously started with onset of XRT, PO steroids tapered over 6 wks
Tagami et al[40]	27 (11 XRT and IV steroids, 16 only IV steroids)	Not clearly stated	Not clearly stated	Prospective case series. 1 gm/pulse IV steroids × 3, repeat q1 week × 4 (if clinically indicated), then followed by 40–50 mg/day PO steroids, tapered over next 3–12 months

CAS, clinical activity score; RAI, radioactive iodine treatment; XRT, external beam orbital radiation; TED, thyroid eye disease; PO, oral; (grade 1), soft tissue involvement with symptoms and signs (grade 2), proptosis (grade 3), extraocular muscle involvement (grade 4), corneal

Adjunctive treatment	Outcome measures	Duration of follow up (wks)	Comment/Conclusions
None	NOSPECS, self assessment survey, proptosis	2 yrs	21/25 (84%) had improvement with IV steroids, and 15/26 (57%) had improvement with PO steroids. Proptosis improved similarly in both groups. Four patients that received PO steroids had to withdraw therapy due to severe side effects. No recurrences were seen in a two-year follow up
XRT (20 Gy × 2 wks), started at same time as steroids	Clinical exam, NOSPECS	78	19/30 (63%) improvement of EOM with PO steroids and XRT, overall excellent response in 18/30 (60%). Retrobulbar steroid and XRT group had overall improvement in 80%, 39% improvement in proptosis, and 17% improvement of EOM
XRT (20 Gy × 2 wks) started one week after onset of steroids	Proptosis, lid fissure width, diplopia, CAS	52	Overall improvement of 36/41 (88%) with IV steroids, (26/41) 63% with PO steroids; less side effects with IV (23/41 vs 35/41 in PO), CAS more improved with IV (36/41 vs 26/41 in PO); diplopia improved in 14/40 in IV, 12/40 in PO, optic neuropathy better result with IV (11/14 vs 3/9); no PO steroid taper used in IV steroids group
	Self assessment, NOSPECS, EOM and proptosis on CT	24	7/8 (87.5%) had improvement in all parameters, All eight had an improvement in proptosis on CT
+/− XRT (20 Gy × 2 wks)	Clinical exam, NOSPECS	~3 yrs (156 wks)	5/11 (45.5%) had good result with PO steroids only, 6 went on to have XRT and 1 went on to have XRT and decompressive surgery
Vs Cyclosporine	NOSPECS, proptosis, EOM size on CT	52	11/18 (61.1%) responded by EOM size on CT, clinical scores and proptosis at 12 wks; in non responders, combination with cyclosporine was helpful, followed for 52 wks but eventually 17/36 had surgery or XRT
Vs XRT (20 Gy × 2 wks)	Highest NOSPECS class, CT	24	14/28 (50%) responded to steroids, 13/28 (46%) responded to XRT, both had similar improvement in EOM size on CT, XRT seemed to improve motility more than PO steroids. Soft tissue swelling improved better with PO steroids than XRT
XRT (16–19 Gy over 6 wks)	Subjective impression, NOSPECS	52	Overall, 153/225 (68%) improved. Proptosis improved in 131/207 (64%), and diplopia impoved in 133/169 (78.7%). 72/225 (32%) eventually had orbital decompressive surgery over the course of the year follow up due to progression/ recurrence
12 pts received XRT (followed 2 wks after pulse IV steroids were completed)	Clinical score, CT or MRI of EOM, NOSPECS	2 yrs (104 wks)	21/27 (77.8%) diplopia improved (all pts had diplopia) or disappeared; overall 9/11 (81.8%) improved in XRT and IV steroids group, and 12/16 (75%) improved in IV steroids group, 15/27 (55.6%) improved proptosis; NOSPECS improved as average across the group; used CT to compare EOM size (by comparing the thickness to optic nerve) and found a correlation in EOM and NOSPECS improvement in responders

IV, intravenous; IVIg, intravenous immunoglobin therapy; EOM, extraocular muscles; NOSPECS, no signs or symptoms (grade 0), only signs involvement (grade 5), and sight involvement (grade 6).

The most commonly employed immunomodulators include corticosteroids with or without adjunctive external beam orbital radiation (XRT) in moderate to severe cases of TED. However, disease management varies widely (13). The goals of medical therapy are to shorten the duration and minimize the severity of the active phase, thereby reducing the chronic phase disfigurement and disability produced by irreversible fibrosis.

Corticosteroids are typically administered orally or intravenously (IV). Local injections of corticosteroids into the orbit have failed to provide an effect in improving orbitopathy (14,15). Some studies have shown that local injections can improve motility and extraocular muscle (EOM) size and can be a suitable alternative to patients with contraindications to systemic corticosteroids (16,17).

XRT was first used empirically to treat TED. While the mechanism for its action is not fully understood, radiation (XRT, typical total dose = 20 Gy) is biologically active against infiltrating lymphocytes, tissue-bound monocytes, and fibroblasts so as to alter the local cellular matrix and interrupt the inflammatory process in a more permanent fashion than can be achieved with corticosteroids (14,18). One recent prospective, double-masked, sham-controlled clinical trial produced more debate than consensus regarding the efficacy of XRT therapy for TED (19,20).

There is no agreement on the management of TED (18,21,22). As an alternative to corticosteroids and XRT, other immunomodulatory agents such as azathioprine, cyclosporine, intravenous immunoglobulin (IVIg), and plasmapheresis have been used, but they play a more limited role (23–28). Efficacy studies have not been well modeled, and are mainly small, retrospective, or uncontrolled (18,21,22,29,30). Interpretation of the data from the existing studies is limited by the lack of good natural history data and the highly variable nature of the disease. We have evaluated the relevant publications in the English language to compare the outcomes of TED patients treated with corticosteroids and/or XRT.

METHODS

We performed a review of published studies identified in a PubMed on-line review from January 1966 to July 2006 using the following key words: Graves ophthalmopathy, thyroid eye disease, Graves disease, and thyroid orbitopathy. Inclusion criteria required at least eight enrolled subjects within a retrospective or prospective study published in the English language. Our review compared the outcomes of using corticosteroids with or without XRT. We included only those studies that compared the outcomes through definable measurements, orbital imaging studies (CT or MRI), self-assessment surveys, or clinical examinations.

RESULTS

Study Profiles

We identified nineteen studies for our review. Seven had enrolled patients in randomized prospective studies (12,14,28,30–33); the remainder were either prospective or retrospective case series.

General Patient Treatment Profile

A total of 834 patients from nineteen studies were reviewed. Study patient populations were dissimilar, and inclusion and exclusion criteria varied. In particular, some studies excluded patients who had had prior treatment for TED (12,14,31–34). Others included patients that had already been treated with XRT, immunomodulatory agents, or decompressive surgery (21,28,30,35–40). Still others failed to detail prior treatment (41–44). The study of Marcocci et al (30) was the only one that detailed the thyroid metabolic status of the patients such that 81 (99.8%) of 82 patients presented with hyperthyroidism and TED; one patient had euthyroid TED.

Of the 834 patients, 597 (71.6%) from 13 studies were treated with oral corticosteroids with or without XRT. Of the 597 patients, 265 had received only oral prednisone (average of 76 +/− 26 mg/day). The length of oral corticosteroid treatment (including taper) averaged 17.5 +/− 5.4 weeks. In 10 studies, 237 patients (28.4%) were treated predominantly with IV corticosteroids (methylprednisolone) with or without XRT. Seven of these studies mainly used 1000 mg/pulse and the remaining three studies used a 500 mg/pulse. The average number of pulses received was 5.8 +/− 3.8 over an average length of 13 +/−1.5 weeks of treatment. Most of the patients who had received IV corticosteroids (n = 177) without XRT had also received oral corticosteroids between pulses of IV corticosteroids and were given a tapered course of oral corticosteroids that averaged 37.9 +/− 4.9 mg/day over 14 +/− 17 weeks. The follow-up interval for all studies averaged 59 weeks (range 12 weeks to 3 years) (Table 1).

Clinical Measurement of Disease Severity and Treatment Response

TED severity and activity were assessed using different scoring systems, including the NOSPECS classification system (No signs or symptoms [grade 0]; Only signs [grade 1]; Soft tissue involvement with symptoms and signs [grade 2]; Proptosis [grade 3]; Extraocular muscle involvement [grade 4]; Corneal involvement [grade 5]; Sight involvement [grade 6]), American Thyroid Association classification, Stanford Score, International Index, clinical activity score (CAS), and self-assessment surveys. Other data came from the clinical examination findings, including proptosis, gaze-evoked changes in intraocular pressure (IOP), and from neuroimaging abnormalities.

The NOSPECS classification system was most commonly used (12 of 19 studies). It documents the presence of specific symptoms and signs of which only some are characteristic of active disease. The CAS was used in 6 of 19 studies. It takes into account seven clinical measurements and assigns a point to each symptom or sign (retrobulbar pain, pain on eye movements, eyelid erythema, conjunctival injection, chemosis, swelling of the caruncle, eyelid edema or fullness). Many studies included self-assessment patient surveys (Table 1).

Neuroimaging

Ten studies employed neuroimaging to measure the outcome of TED treatment (12,28,33,34,36–38,40,42,44). CT, MRI, and B-ultrasound were used to evaluate EOM size. There was no standardized grading protocol (Table 1). All studies showed an overall improvement in EOM thickness or proptosis after oral or IV corticosteroid treatment with and without the use of external beam radiation (x-irradiation, XRT). The degree of improvement correlated well with the overall favorable response reported by clinical measures. Matejka et al (37) measured the amount of proptosis on CT and found an overall improvement in all eight patients who had received predominantly IV corticosteroids. The study of Hiromatsu et al (44) was unique in using MRI to judge response in patients treated predominantly with IV corticosteroids. The activity of TED was measured by MRI signal intensity of the EOMs as well as their thickness. Baschieri et al (34) found reduction in EOM thickness on CT after oral prednisone 80 mg/day for a total two weeks with a five month taper. One of the studies employed B-ultrasound to note significant greater reduction in EOM thickness in patients who had received IV corticosteroids than in those who had received oral corticosteroids (33).

Intravenous vs. Oral Corticosteroids

Because of dissimilar assessment measures within and among studies, treatment outcomes are reported in relation to each study's outcome measures. We judged the results as favorable if the author reported the results as either good or excellent.

Corticosteroids were the primary medical therapy used to treat active TED. There was an overall 66.9% favorable response to corticosteroid treatment among all 834 patients, which included those that may also have been treated with XRT. A total of 442 patients were treated with oral or predominantly IV corticosteroids alone. A total of 151 (55.5%) of 265 patients treated with oral corticosteroids alone had a favorable response, and 132 (74.6%) of 177 patients treated with IV corticosteroids alone had a favorable response.

Patients who had received predominantly IV corticosteroids seemed to have greater improvement in diplopia, ocular motility, and proptosis than those who had received only oral corticosteroids. But patients who received only oral corticosteroids showed a greater improvement in EOM thickness than patients who received predominantly IV corticosteroids (Table 2).

Two prospective randomized studies compared IV to oral corticosteroid treatment (30,32,33). Neither of these studies used a tapered regimen of oral corticosteroids followed a regimen of IV corticosteroids. Kahaly et al (33) showed an improvement in the CAS in 27 (77%) of 35 patients treated with IV corticosteroids as compared to 18 (51%) of 35 patients treated with oral corticosteroids. Based on a self-assessment survey, 80% of patients receiving IV corticosteroids as compared to 54% receiving oral corticosteroids were satisfied with the treatment results and had an improved quality of life. Macchia et al (32) reported similar results, such that 21 (84%) of 25 patients treated with IV corticosteroids had a favorable response as compared to 15 (57%) of 26 treated with oral corticosteroids. However, proptosis improved equally among both groups.

Combined Corticosteroid and XRT Treatment

The cumulative radiation dose and the radiation field were similar in nearly all studies (Table 1). A total of 20 Gy

TABLE 2. ***Outcomes following treatment of patients with active thyroid eye disease***

	Cort PO only	Cort IV only	Cort PO and XRT	Cort IV and XRT	Cort PO (+/− XRT)	Cort IV (+/− XRT)
Total patients	265	177	332	60	597	237
Overall favorable response	151/265 (57.0%)	132/177 (74.6%)	223/332 (67.2%)	52/60 (86.7%)	374/597 (62.6%)	184/237 (77.6%)
Improvement in diplopia	50/135 (37.0%)	61/122 (50.0%)	133/169 (78.7%)	14/19 (73.7%)	40/105 (38.1%)	75/141 (53.2%)
Improvement in motility	20/53 (37.7%)	32/54 (59.3%)			20/53 (37.7%)	32/64 (50.0%)
Improvement in proptosis	40/94 (42.6%)	100/163 (61.3%)	170/273 (62.3%)		31/48 (64.6%)	79/117 (67.5%)
Improvement in extraocular muscle thickness	35/42 (83.3%)	27/38 (71.1%)	20/30 (66.6%)	6/8 (75%)	50/60 (83.3%)	33/46 (71.2%)

Cort, corticosteroid; XRT, external beam x-irradiation; IV, intravenous administration; PO, oral administration.

was delivered to each orbit over a period of two weeks. There was an overall 70.2% favorable response in the 392 patients who underwent both XRT and IV or oral corticosteroid treatment. Compare this to an overall 64.0% favorable response in the 442 patients who received IV or oral corticosteroids without XRT. More specifically, 223 (67.2%) of 332 patients who received oral corticosteroids and XRT (14,21,30,35,39) responded favorably as compared to 52 (86.7%) of 60 patients who received predominantly IV corticosteroids and XRT (30,36,40) (Table 2).

One prospective randomized study compared the outcome following IV corticosteroids and XRT to the outcome following oral corticosteroids and XRT. Marcocci et al (30) found a significantly greater short-term improvement of periocular edema, erythema, orbital ache, and ocular motility in patients who had received IV corticosteroids and XRT (88%) when compared to oral corticosteroids and XRT (63%). Proptosis improved in 19 (47.5%) of 40 patients receiving IV corticosteroids and XRT and in 16 (40%) of 40 patients receiving oral corticosteroids and XRT. Optic neuropathy improved in 13 (92%) of 14 patients after treatment with IV corticosteroids and XRT, but only in 3 (33%) of 9 patients who received oral corticosteroids and XRT. This difference, however, was not statistically significant (30).

Intravenous vs. Oral Corticosteroid Treatment With or Without Adjunctive XRT

Overall, treatment with pulsed IV corticosteroids was more effective and better tolerated than chronic treatment with oral corticosteroids alone. Oral corticosteroids produced a favorable response in 62.6% of patients with or without the use of XRT (n = 597). This compares to a favorable response in 77.6% of patients treated with IV corticosteroids with or without XRT (n = 237). In the studies reporting results, the patients who received predominantly IV corticosteroids showed greater improvement in diplopia, ocular motility, and proptosis in comparison to those who received oral corticosteroids with or without adjunctive XRT. In contrast, the patients who received oral corticosteroids showed a greater improvement in EOM thickness in comparison to the patients who received predominantly IV corticosteroids with or without adjunctive XRT (Table 2).

Corticosteroid Side Effects

There was a higher rate of side effects to corticosteroids administered via the oral route than to corticosteroids administered via the IV route. Chronic oral corticosteroid treatment was associated with Cushingoid facies, weight gain, osteoporosis, gastric irritation, labile hypertension, elevated intraocular pressure, elevation in blood sugar, and mood alteration. Marcocci et al (30) documented that 35 (85.4%) of 41 patients treated with an approximately six-month oral corticosteroid taper (starting at 100 mg prednisolone by mouth daily for a cumulative dose of 6 grams) demonstrated side effects including weight gain, urinary tract infections, transient hyperglycemia, and decreased bone mineral density. Three patients who had received oral steroids in the randomized study of Macchia et al (32) had to withdraw from their treatment due to "severe signs or symptoms of hypercortisolism." Prummel et al (12) found that 25 of 28 patients who received a 20-week oral corticosteroid taper (starting at 60 mg prednisolone by mouth daily for four weeks followed by a taper) experienced only minor side effects. One patient developed depression and a second patient manifested a recurrent herpetic zoster eruption. Baschieri et al (34) reported two cases of hemorrhagic gastritis in patients receiving 80 mg prednisone by mouth daily with a 5-month taper. One patient developed bipolar disorder. More frequent side effects included Cushingoid facies (5 out of 30 patients) and abnormal glucose tolerance (5 out of 30 patients).

Intravenous corticosteroid treatment was associated with a lower rate of adverse side effects. Kahaly et al (33) reported adverse events in only 6 (17%) of 35 patients, including weight gain, insomnia, palpitations, and gastrointestinal discomfort. However, Marcocci et al (30) reported adverse effects in 23 (56.1%) of 41 patients, including urinary tract infections and impaired glucose tolerance. Nine patients inexplicably had a mean percentage increase in bone mineral density after IV corticosteroid treatment. One patient had transient elevation of serum aminotransferase levels (34).

Radiation Side Effects

Radiation was well tolerated and produced few short-term side effects. Koshiyama et al (36), Marcocci et al (30), Staar et al (39), and Prummel et al (12) reported no side effects from radiation. In the study of Bartalena et al (21), with a follow-up over 26 months, there were no new cataracts. However, Prummel et al (12) found that 15 (54%) of 28 patients surveyed had side effects, usually minor, including transient hair loss at temples, tiredness, myalgias, headaches, insomnia, and nausea.

Reactivation of TED After Treatment

Seven of the reviewed studies addressed the incidence and timing of disease recurrence after successful initial treatment (21,32,35,36,39,42,43). The study of Koshimaya et al (36) found no recurrence of TED among all eight patients who had received predominantly IV corticosteroids and combined XRT after a three-year follow-up. The study of Macchia et al (32) found no

recurrence of TED among 51 patients who had received either oral (n = 26) or IV corticosteroids (n = 25). However, four other studies reported substantial recurrence in treated patients. Chang et al (42) reported that 4 of 10 patients worsened when the oral corticosteroids were discontinued or quickly tapered to 20 mg/day over a course of five months. Noth et al (35) documented that 12 (63.2%) of 19 patients followed for three years required further immunosuppressive therapy and XRT due to disease recurrence or progression. Staar et al (39) also reported that because of disease progression or recurrence, 72 (32%) of 225 patients eventually proceeded to orbital decompressive surgery after a year's treatment with a combination of oral corticosteroids and XRT.

Summary of Outcomes

A review of the published literature in English has suggested that corticosteroid-mediated treatment produces benefit in 66.9% in TED patients who have moderate to severe disease. IV corticosteroids used in repeated daily or weekly pulses (average of 5.8 pulses/treatment epoch) were more effective than daily oral corticosteroids. Intravenous administration of corticosteroids appeared to be more effective than oral administration alone. A combination of corticosteroids and XRT was more effective than corticosteroids alone. In combination with XRT, IV administration of corticosteroids was more effective than oral administration.

Intravenous corticosteroids were associated with fewer side effects than oral corticosteroids. However, single case reports not included in this series have reported fatal cardiac and fatal hepatic necrosis with the use of IV corticosteroids for TED (45,46).

XRT appeared to be well tolerated with few if any side effects. However, a report by Gorman et al (20), not included in this review, discovered newly dilated capillaries or microaneurysms on fluorescein angiograms or fundus photographs in five eyes among 3 of 37 treated patients three years after receiving XRT.

Among the three prospective randomized studies, IV corticosteroids had a clear benefit in treatment outcome over oral corticosteroids (30,32,33). Patients treated with IV or oral corticosteroids showed improvement in proptosis, diplopia, ocular motility, and in self assessment of benefit, but the treatment outcomes were more substantial in those treated with IV corticosteroids (over 77% favorable outcome) than with oral corticosteroids (up to 62% favorable outcome). The only study (12) that compared oral corticosteroid administration to XRT in a prospective, double-blind randomized trial showed similar treatment outcomes (self assessment, EOM size on CT), but XRT seemed to improve ocular motility more than did oral corticosteroids, while oral corticosteroids seemed to improve soft tissue swelling more effectively.

Cautions

Caution is warranted regarding the interpretation of outcomes in the studies we have reviewed. The studies differed in design, treatment protocol, and outcome measures. The potential clinical impact of corticosteroids and XRT in the treatment of TED was difficult to assess reliably. These studies provide little insight regarding pathophysiology or effect of treatment on quality of life.

It was particularly difficult to interpret the results of TED severity and activity among different scoring systems. NOSPECS was the most commonly used scoring system yet it documents manifestations not always characteristic of active disease. Clinical worsening may not represent increased inflammatory activity but rather progressive fibrosis associated with resolving inflammation. CAS, another scoring system used in several of the studies reviewed, does not provide information regarding overall progression or severity of TED. Self-assessment surveys used to document improvements in quality of life are non-standardized and difficult to interpret across studies. The identification of active TED remains an imperfect combination of the patient's impression and the clinician's interpretation of the physical signs.

We conclude that there is inadequate case-based evidence to ascertain reliably whether medical therapy with corticosteroids or XRT shortens the active phase of disease or improves long-term disfigurement and disability in patients with moderate to severe TED. To answer this question more rigorously, the North American Neuro-Ophthalmology Society (NANOS), American Society of Ophthalmic Plastic and Reconstructive Surgery (ASOPRS), and the Orbital Society, working in conjunction with Neuro-Ophthalmology Research and Development Consortium (NORDIC), have established a committee to pursue the design and funding of a large, multi-center, double-masked, placebo controlled study.

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