CM Ng 伍超明
HKL Yuen 袁國禮
KL Choi 蔡建霖
MK Chan 陳文光
KT Yuen 袁錦堂
YW Ng 伍英偉
SC Tiu 張秀祥

Combined orbital irradiation and systemic steroids compared with systemic steroids alone in the management of moderate-to-severe Graves' ophthalmopathy: a preliminary study

在處理中度至嚴重葛瑞夫茲氏眼病時，單以口服類固醇和將其結合眼窩放射法的治療結果的初步比較研究

Objective. To assess the efficacy and safety of combined orbital irradiation and systemic steroids in the management of moderate-to-severe Graves' ophthalmopathy.

Design. Single-blind randomised prospective study.

Setting. Regional hospital, Hong Kong.

Patients. Sixteen patients with active moderate-to-severe Graves' ophthalmopathy who were randomly assigned to steroid therapy (ST group) or combination therapy of orbital irradiation and systemic steroids (SRT group) between June 2000 and June 2003.

Main outcome measures. NOSPECS scoring system, total eye score, subjective eye score, and extra-ocular muscle thickness as determined by either computed tomographic or magnetic resonance imaging scans.

Results. The study was completed by 15 of 16 patients. Both groups experienced improvement in total eye score, soft tissue swelling, ocular motility, visual acuity, and subjective eye score at 52-week follow-up. Total eye score improved earlier in the SRT group, achieving statistical significance ($P<0.05$) at as early as 4 weeks of follow-up. Improvement in ocular parameters was greater and led to a significantly greater reduction in total eye score than in the ST group at weeks 16, 24, and 52. Maximum extra-ocular muscle thickness was significantly reduced in the SRT group only. No change was observed in proptosis in either group. No serious adverse effect was observed with the addition of orbital irradiation to steroid therapy.

Conclusion. A combination of orbital irradiation and systemic steroids is well tolerated and more effective than steroids alone in the treatment of active moderate-to-severe Graves' ophthalmopathy. It achieves greater and more rapid improvement in soft tissue swelling, ocular motility, and visual acuity.

目的：評估在治療中度至嚴重葛瑞夫茲氏眼病時，結合眼窩放射法和口服類固醇的治療成效和安全程度。

設計：前瞻性隨機單盲對照研究。

安排：地區醫院，香港。

患者：16名患有中度至嚴重葛瑞夫茲氏眼病的病人。他們被隨機編入類固

Key words:
Eye diseases;
Graves' disease;
Orbit/radiation effects;
Steroids;
Treatment outcome

關鍵詞：
眼疾；
葛瑞夫茲氏眼病；
眼窩／放射效果；
類固醇；
治療結果

Hong Kong Med J 2005;11:322-30

Queen Elizabeth Hospital, 30 Gascoigne Road, Hong Kong:
Department of Medicine
CM Ng, MRCP, FHKAM (Medicine)
KL Choi, MRCP, FHKAM (Medicine)
YW Ng, MRCP, FHKAM (Medicine)
SC Tiu, FRCP, MD
Department of Radiology and Imaging
MK Chan, FRCR, FHKAM (Radiology)
Department of Clinical Oncology
KT Yuen, MB, BS, FHKAM (Radiology)
Hong Kong Eye Hospital, Hong Kong
HKL Yuen, MB, ChB, FHKAM (Ophthalmology)

Correspondence to: Dr CM Ng
(e-mail: jasoncmng@yahoo.com)

醇組（ST 組）或類固醇結合眼窩放射法的合併組（SRT 組）。

主要結果測量：NOSPECS評級系統、整體眼力評分、客觀眼力評分、及由電腦斷層或磁力共振掃描測定的眼外肌厚度。

結果：16名病人中有15人完成研究。兩組病人在隨後52週的整體眼力評分、軟組織腫脹、眼球活動度、視敏度和客觀眼力評分都有改善。SRT 組的整體眼力評分在第 4 星期時已有明顯改善（P<0.05）。眼球參數的改善較大，引致在第16週、24週和52週的整體眼力評分，SRT組比ST組跌幅明顯。眼外肌厚度明顯減低則只在SRT組出現。而兩組病人眼球突出的情況都沒有改變。而在類固醇治療外加上眼窩放射法治療，觀察不到有嚴重的負面影響。

結論：在治療中度至嚴重葛瑞夫茲氏眼病時，結合眼窩放射法和口服類固醇的治療比單用類固醇有效。在軟組織腫脹、眼球活動度和視敏度上，合併治療的療效更好更快。

Introduction

Graves' ophthalmopathy is an orbital inflammatory condition that occurs in association with autoimmune thyroid disease.[1] It is severe and disabling in 3% to 5% of cases.[2] The management strategy for moderate-to-severe Graves' ophthalmopathy is controversial. Systemic steroids are often effective,[3-6] but relapse is common when they are tapered or withdrawn.[7] A number of retrospective studies have reported the efficacy of orbital irradiation,[8,9] but prospective studies have shown conflicting results.[10-12] Some investigators have suggested that steroids provide excellent improvement in orbital inflammation in the short term, whereas the effects of orbital irradiation take longer time to appear.[13] Studies that have compared combination therapy of orbital irradiation and systemic steroids with steroids-alone therapy have produced conflicting results.[14-16] We conducted a 1-year randomised controlled trial to assess the efficacy and safety of the combination therapy versus steroids-alone therapy in the management of moderate-to-severe Graves' ophthalmopathy.

Patients and methods

This was a prospective single-blind randomised controlled trial. Informed written consent was obtained from all patients and study approval granted by the Ethics Committee of the Queen Elizabeth Hospital.

Patients with previously untreated moderate-to-severe Graves' ophthalmopathy who had normal values of free thyroxine (FT_4) at presentation were recruited. Moderate-to-severe ophthalmopathy was defined by the NOSPECS categories[17]—class 2 grade a, b, c plus one or more of the following: class 3 grade b, c (significant proptosis); class 4 grade a, b, c (impairment of ocular motility); or class 6 grade a, b, c (impairment of visual acuity). Class 5 patients were not recruited because corneal injury is usually healed by local measures and does not necessarily reflect disease severity. Patients with compressive optic neuropathy were recruited only if they refused surgery or if surgery was contra-indicated. Exclusion criteria included a history of Graves' ophthalmopathy longer than 2 years; previous treatment for Graves' ophthalmopathy; pregnancy; active peptic ulcer; sepsis; aged younger than 20 or older than 80 years; history of other eye diseases such as glaucoma, diabetic retinopathy, or maculopathy; history of other diseases requiring steroid treatment or psychiatric disorders; and reluctance to participate in a study.

All patients were assessed by an independent ophthalmologist and an endocrinologist prior to randomisation. Information on age, past health, smoking habit, duration of Graves' disease and Graves' ophthalmopathy, and previous as well as current treatment histories were obtained. A thorough physical assessment was performed including measurement of blood pressure and body weight. Computed tomography or magnetic resonance imaging (MRI) of the orbits was performed before starting treatment, together with chest X-ray and the following baseline measurements: FT_4, thyroid-stimulating hormone (TSH), anti-thyroglobulin antibody titre, anti-microsomal antibody titre, renal and liver function tests, fasting cholesterol and triglyceride levels, complete blood picture, hepatitis B surface antigen, and stool for ova and cyst.

Patients were randomised to one of the two treatment groups—steroids-alone therapy (ST group) or combination therapy of orbital irradiation and systemic steroids (SRT group). The steroid regimen was the same for each group: intravenous methylprednisolone 500 mg in 100 mL normal saline over 1 hour for 3 consecutive days, followed by 0.7 mg/kg oral prednisolone daily for 4 weeks. From week 5, the dose of prednisolone was reduced by 5 mg per week until it reached 5 mg per day. It was then further reduced to

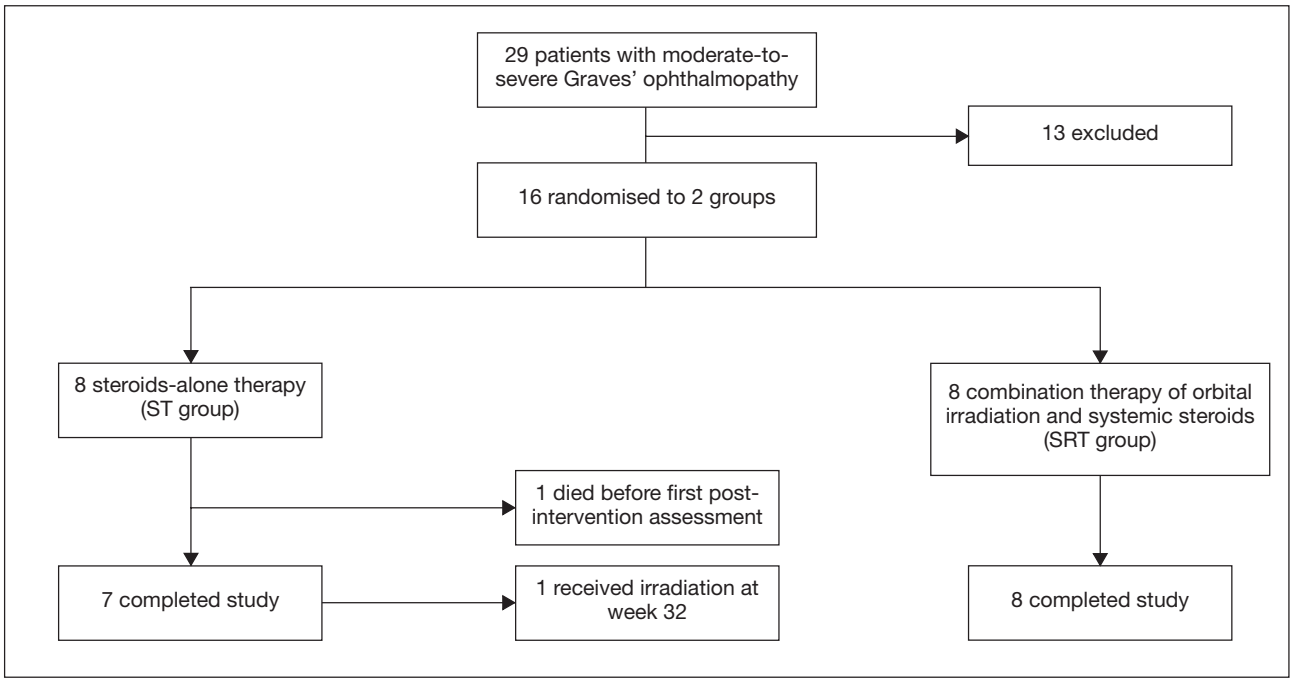


Fig 1. Trial profile

2.5 mg daily for 1 more week and then stopped. Total length of steroid therapy was approximately 3 months. If total eye score (TES) deteriorated by more than 4 during steroid reduction, the previous dose of steroid was reinstated and reduction slowed to 5 mg every 2 weeks. Patients in the SRT group underwent bilateral orbital irradiation within 2 weeks of pulse steroid therapy. A total of 20 Gy was delivered via two laterally opposed 6 mega volts photon beams in 10 fractions over 2 weeks. The 4 by 4 cm fields had the anterior border located just behind the lateral canthus and covered the entire orbit on both sides. The fields were angled 10 degrees posteriorly to avoid irradiating the contralateral lens and cornea.

Patients were re-assessed at weeks 4, 8, 12, 16, 24, and 52 by the same endocrinologist, ophthalmologist, and radiologist; the latter two blinded to treatment regimen. Ophthalmic parameters including soft tissue involvement, degree of diplopia (ocular motility), proptosis, intra-ocular pressure, and best-corrected visual acuity (BCVA) were recorded. Disease severity was classified according to the NOSPECS system.[17] Response in soft tissue swelling and diplopia was defined as follows: "Improved" if there was a decrease in the grade of NOSPECS scale from baseline, "static" if there was no change, and "worse" if there was an increase. To give a composite picture, the TES was calculated by multiplying each NOSPECS grade by its class (substituting 1, 2, 3 for grade a, b, c, respectively) and taking the sum of all products.[18] Computed tomography or MRI of the orbits was repeated at week 24 to assess the maximum extra-ocular muscle thickness. The thickness of superior rectus and inferior rectus was determined in the coronal section, whereas the thickness of medial rectus and lateral rectus was measured in the transverse section. In addition, subjects were asked to rate their eye symptoms on a scale from 1 to 5 (with 1 being worst and 5 best) to produce a subjective eye score (SES).

Blood pressure, body weight, FT_4, renal and liver function tests, and complete blood picture were monitored at every follow-up visit. Fasting lipids were checked again at week 12. Drug compliance was assessed by pill counting.

Statistical analysis

Statistical analysis was performed on an intention-to-treat basis, provided that the patients had at least one set of post-baseline efficacy data at week 4. The last-value carried forward principle was applied to subjects who did not complete the study. Baseline data of the two treatment groups were compared using Chi squared test, Fisher's exact test, or student's *t* test, as appropriate. Outcome parameters at different time points were compared with baseline within the same group by Wilcoxon signed rank test. Parameters between the two treatment groups were compared using the Mann Whitney *U* test for continuous data. To avoid the pitfall of finding a difference by chance due to multiple testing, results were confirmed by

Table 1. Baseline characteristics of study subjects

Characteristic	Group receiving systemic steroids only, n=8*	Group receiving a combination of orbital irradiation and systemic steroids, n=8*
Sex ratio (F:M)	1:7	5:3
Mean age (SD) [years]	48.3 (16.0)†	64.1 (9.7)†
Duration (months) before intervention of		
hyperthyroidism	10.0 (4.0-76.0)	12.0 (4.0-60.0)
Graves' ophthalmopathy	3.0 (1.0-10.0)	2.5 (0.5-10.0)
No. of subjects with a history of		
anti-thyroid drugs	8	8
radioactive iodine	2	3
thyroidectomy	0	0
No. of current smokers	3	2
Mean free thyroxine (SD) [pmol/L]	17.3 (4.1)	20.2 (8.2)
Soft tissue involvement		
None	0	0
Mild	1	2
Moderate	6	5
Marked	1	1
Proptosis by Hertel exophthalmometer (mm)	21.5 (19.0-26.0)	21.0 (18.0-25.0)
No. of subjects with diplopia		
None	0	0
Limitation of motion in extreme gaze	4	5
Evident restriction of motion	4	3
Fixation of globe	0	0
logMAR best-corrected visual acuity	0.15 (0.00-1.30)	0.19 (0.10-2.00)
Total eye score (range, 0-45)	16.5 (9.0-37.0)	18.0 (11.0-34.0)
Intra-ocular pressure (mm Hg)	15.0 (9.0-23.0)	18.0 (15.0-28.0)
No. of patients with optic neuropathy	2	3
Subjective eye score (reference range, 1-5)	2.0 (1.0-3.0)	2.0 (1.0-3.0)
Maximum thickness of extra-ocular muscle on imaging (cm)	0.80 (0.60-0.90)	0.86 (0.66-1.00)

* Data are shown in median (range), unless otherwise stated
† P=0.01

Table 2. Changes in the grades of soft tissue involvement and ocular motility versus baseline in the NOSPECS system at week 52 in the two treatment groups

	Group receiving systemic steroids only, n=7 (ST group)			Group receiving a combination of orbital irradiation and systemic steroids, n=8 (SRT group)			P value (ST vs SRT groups)
	Improved	Static	Worse	Improved	Static	Worse	
Soft tissue involvement at week 52	2	5	0	7	1	0	0.04
Ocular motility at week 52	2	4	1	7	1	0	0.04

using repeated analysis of variance (ANOVA) measures after logarithmic transformation of the data to obtain parametric distributions. Since visual acuity as measured by the Snellen chart was not linear, it was transformed into logMAR units (decimal logarithm of the minimum angle of resolution) before statistical analysis. Analysis was performed using Statistical Package for the Social Sciences (Windows version 11.0; SPSS Inc, Chicago [IL], United States). All statistical tests were two-sided, with an α level of 0.05.

Results

A total of 29 patients with moderate-to-severe Graves' ophthalmopathy who presented to the thyroid clinic of the Queen Elizabeth Hospital or the Hong Kong Eye Hospital between June 2000 and June 2003 were assessed. Thirteen patients were excluded for the following reasons: aged younger than 20 years (n=1), compressive optic neuropathy requiring urgent decompression (n=2), previous treatment for Graves' ophthalmopathy (n=6), reluctance for immunosuppres-

Table 3. Degree of proptosis, logMAR best-corrected visual acuity (BCVA), total eye score (TES), and intra-ocular pressure of subjects in the two treatment groups at week 0, 4, 8, 12, 16, 24, and 52*

Week	Proptosis (mm)		logMAR BCVA (absolute value)		TES		Intra-ocular pressure (mm Hg)	
	ST†	SRT‡	ST	SRT	ST	SRT	ST	SRT
0	22.3 (2.5)	21.1 (2.6)	0.31 (0.43)	0.60 (0.74)	18.1 (8.7)	20.6 (8.5)	16.1 (5.0)	19.4 (4.3)
4	22.1 (2.5)	20.6 (1.8)	0.19 (0.05)	0.45 (0.65)	14.3 (3.7)	16.8 (7.5)§	17.0 (4.7)	20.6 (2.2)
8	22.1 (2.4)§	20.4 (1.8)	0.19 (0.06)	0.45 (0.65)	13.7 (3.4)	15.1 (7.4)§	19.7 (1.2)	18.3 (2.3)
12	22.7 (2.9)	20.8 (2.1)	0.19 (0.06)	0.47 (0.64)	13.4 (3.9)	13.9 (8.4)§	20.3 (0.6)	19.4 (3.0)
16	22.4 (2.2)	20.9 (1.6)	0.16 (0.10)	0.45 (0.54)	13.4 (3.9)	11.8 (5.1)§	16.3 (5.5)	18.3 (2.4)
24	23.0 (2.9)	20.0 (2.0)	0.09 (0.07)	0.39 (0.55)§	12.0 (4.2)§	9.5 (5.5)§	15.0 (4.7)	16.0 (2.3)§
52	22.6 (2.8)	20.8 (2.0)	0.12 (0.06)	0.22 (0.38)§	10.4 (4.8)§	8.9 (5.1)§	14.9 (4.0)	14.9 (3.5)§

* Data are shown in mean (SD)
† Group receiving systemic steroids only
‡ Group receiving a combination of orbital irradiation and systemic steroids
§ P<0.05 compared with values at week 0

Table 4. Mean changes between baseline and week 52 in ophthalmic parameters in the two treatment groups*

Ophthalmic parameter	Group receiving systemic steroids only, n=7 (ST group)	Group receiving a combination of orbital irradiation and systemic steroids, n=8 (SRT group)	P value (ST vs SRT groups)
Proptosis (mm)	-0.14 (-1.27 to 0.98)	-0.31 (-1.51 to 0.89)	0.955
logMAR best-corrected visual acuity	-0.05 (-0.21 to 0.11)	-0.38 (-0.77 to 0.02)	0.054
Total eye score	-5.00 (-7.72 to -2.28)	-11.75 (-18.13 to -5.37)	0.029
Intra-ocular pressure (mm Hg)	-1.29 (-5.34 to 2.77)	-4.44 (-8.52 to -0.36)	0.054
Subjective eye score	+1.14 (0.31 to 1.98)	+1.13 (0.83 to 1.42)	0.779
Maximum thickness of extra-ocular muscle† (cm)	-0.12 (-0.34 to 0.10)	-0.21 (-0.38 to -0.05)	0.491

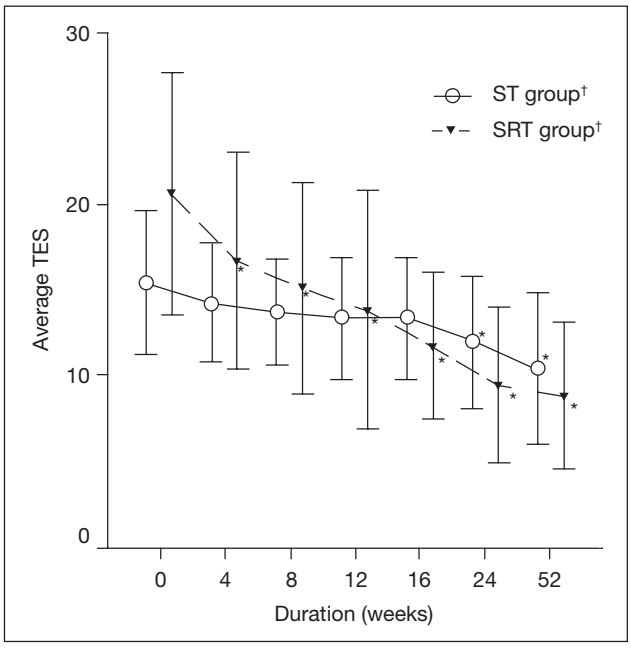
* Data are shown in mean (95% CI)
† Orbital imaging was done at weeks 0 and 24

sive therapy (n=2), or a history of ophthalmopathy for more than 2 years (n=2) [Fig 1]. Sixteen subjects were recruited: eight were randomised to receive steroids alone and another eight a combined orbital irradiation and systemic steroids. One patient in the ST group died of community-acquired pneumonia 3 weeks after initiation of treatment. As he died before the first post-intervention assessment (week 4), his results were excluded in the efficacy analysis. The remaining seven subjects were followed up until week 52. All eight subjects in the SRT group were followed up until week 52. A history of radioiodine therapy was present in five patients: the mean time between therapy and onset of ophthalmopathy was 16.0 months (standard deviation [SD], 18.1; median, 9; range, 5-48 months). During the study period, all patients fell within the normal ranges for FT_4 (12-22 pmol/L) and TSH (0.27-4.2 mIU/L). Steroids were withdrawn prematurely in one of the ST group patients because of recurrent Ramsay Hunt syndrome, and one in the SRT group because of gastro-intestinal upset.

Reintroduction of or stepping up to a previous steroid dose was required by three subjects in the ST group and four in the SRT group because of a recurrence or flare-up of soft tissue inflammation. The total duration of steroid treatment was less than 6 months in all subjects. The cumulative dose of steroids was similar in both treatment groups (4460 mg [SD, 2613 mg] and 4243 mg [SD, 1454 mg] for ST and SRT groups, respectively; P=0.78). One patient in the ST group had markedly congested eyes and requested adjuvant irradiation at week 32.

Both eyes were often not affected to the same degree in Graves' ophthalmopathy. Data for the worse eye were reported and used for analysis. Baseline characteristics of the study subjects are presented in Table 1. There was no statistically significant difference between the two groups in baseline characteristics, except for the greater age of subjects in the SRT group.

Changes in soft tissue and ocular motility are shown in Table 2. At 52-week follow-up, seven (87.5%) of eight subjects in the SRT group versus only two (28.6%) subjects in the ST group showed improvement in both parameters (P=0.04). None of the subjects in the ST group achieved normal eye motion by week 52, in contrast to five (62.5%) subjects in the SRT group (Fisher's exact test;



* P<0.05 compared with value at week 0
† Error bars indicate 95% CIs

Fig 2. Changes in the total eye score (TES) in the group receiving systemic steroids only (ST group) and the group receiving a combination of orbital irradiation and systemic steroids (SRT group), illustrating improvement in both groups
Improvement was observed earlier in SRT group

P=0.026). No significant improvement was observed in the degree of proptosis in either group up to 52 weeks of follow-up. In the ST group, a transient improvement was seen at week 8, but did not persist and was clinically insignificant.

For visual acuity, pretreatment Snellen BCVA ranged from 20/400 to 20/20 in the ST group, with a median of 20/30 (logMAR, 0.15) and a mean of 20/31, corresponding to a mean logMAR BCVA of 0.31 (SD, 0.43). At 52 weeks, the Snellen BCVA ranged from 20/30 to 20/20, with a median of 20/29 and a mean of 20/26, corresponding to a mean logMAR BCVA of 0.12 (SD, 0.06). The change in logMAR BCVA at 52 weeks was not statistically significant (P=0.40 by Wilcoxon signed rank test, P=0.09 by repeated measures ANOVA). In the SRT group, pretreatment Snellen BCVA ranged from 20/2000 to 20/25, with a median of 20/36 and a mean of 20/42, corresponding to a mean logMAR BCVA of 0.60 (SD, 0.74). At 52 weeks, the Snellen BCVA ranged from 20/285 to 20/20, with a median of 20/29 and a mean of 20/26, corresponding to a mean logMAR BCVA of 0.22 (SD, 0.38). The change in logMAR BCVA was statistically significant at 24 (P=0.022) and 52 (P=0.009) weeks (repeated measures ANOVA, P=0.01) [Table 3]. Comparison between the two groups showed that the SRT group had a marginally greater improvement in logMAR BCVA at week 52, with borderline statistical significance (P=0.054) [Table 4]. Nonetheless this was not confirmed by repeated measures ANOVA (P=0.135).

In the ST group, there was no significant reduction in intra-ocular pressure after treatment. In the SRT group, mean intra-ocular pressure decreased from 19.4 mm Hg (SD, 4.3 mm Hg) to 14.9 mm Hg (SD, 3.5 mm Hg) at week 52 (P=0.01) [repeated measures ANOVA, P<0.01; Table 3]. One subject in the ST group and two in the SRT group were given topical glaucoma medication transiently for elevated intra-ocular pressure. Comparison between the two groups showed a marginally greater reduction in intra-ocular pressure for the SRT group by week 52 (P=0.054) [Table 4], but significance was not confirmed by repeated measures ANOVA (P=0.13).

Total eye score declined more quickly in the SRT group than in the ST group (Fig 2). In the ST group, TES at week 24 and 52 were significantly lower than baseline (P=0.027 and P=0.017, respectively) [repeated measures ANOVA, P<0.01]. In the SRT group, TES at week 4, 8, 12, 16, 24, and 52 were all significantly lower than baseline (P=0.024, 0.017, 0.027, 0.018, 0.012, and 0.012, respectively) [repeated measures ANOVA, P<0.01; Table 3]. The differences between the two groups were statistically significant at weeks 16, 24, and 52 (P=0.029, 0.006, and 0.029, respectively). These differences were confirmed by repeated measures ANOVA (P<0.01). No association was found between the improvement in TES and age using the linear regression model (P=0.09).

The mean SES of the ST group increased from 2.0 (SD, 0.9) at week 0 to 3.3 (SD, 0.8) at week 52 (P=0.02), whereas that of the SRT group increased from 2.1 (SD, 0.8) to 3.3 (SD, 0.7) [P<0.01]. There was no statistically significant difference in the change in SES between two groups (P=0.779) [Table 4].

The mean maximum thickness of extra-ocular muscles was 0.82 cm (SD, 0.12 cm) before therapy and 0.61 cm (SD, 0.12 cm) 6 months after therapy in the SRT group, with a significant mean reduction of 0.21 cm (95% confidence interval, -0.38 to -0.05; P=0.035). In the ST group, it measured 0.79 (SD, 0.11) cm before therapy and 0.64 (SD, 0.13) cm at 6 months (mean reduction, 0.12 cm; 95% confidence interval, -0.34 to 0.10; P=0.194). Comparison between the two groups showed no significant difference in the reduction in maximum extra-ocular muscle

thickness over a follow-up period of 24 weeks (P=0.491) [Table 4].

Most adverse effects could be attributed to steroid treatment, including moon face, weight gain, transient leukocytosis, and hyperlipidaemia. Each of these developed in three to four subjects in each group. In addition, hot flushes during pulse steroid therapy, gastro-intestinal upset, hypertension, insomnia, and eye or nose infections were each observed in two to three subjects. One patient had acne and another had recurrent Ramsay Hunt syndrome. Orbital irradiation was well tolerated. Three subjects experienced a mild exacerbation of peri-orbital swelling and transient redness of the eyes that lasted for a few days in the first week of irradiation, and three had temporal hair loss.

Discussion

Two phases are recognised in the natural history of Graves' ophthalmopathy: an initial active inflammatory phase and a late chronic fibrotic phase. During the active phase, various modalities of immunomodulatory therapy such as systemic steroids,[3-5,19] cyclosporine,[18] azathioprine, cyclophosphamide,[20] plasmapheresis,[21] intravenous immunoglobulin,[22] somatostatin[23] as well as orbital irradiation[9-11,13,24] have been employed. Nonetheless, studies of their efficacy, alone or in combination, are few and yield conflicting results.[10-12,14,16] This may be due to different study designs, recruitment of patients at different stages of Graves' ophthalmopathy, and the subjective nature of most ophthalmic parameters.

Experience is most extensive with systemic steroids that constitute the cornerstone of medical treatment for Graves' ophthalmopathy. Unfortunately up to 35% of patients with Graves' ophthalmopathy treated with systemic steroids show no significant improvement.[25] Whether a combination of orbital irradiation with systemic steroids can achieve better results is controversial. Steroids suppress the inflammatory process by reducing orbital infiltration by lymphocytes and synthesis of glycosaminoglycan by orbital fibroblast,[19] while orbital irradiation probably acts by killing off culprit lymphocytes and orbital fibroblasts. Since the actions of steroids and local irradiation are different, they may theoretically have synergistic effects in suppressing the inflammatory process. A greater improvement in soft tissue involvement, newly developed ophthalmoplegia and optic neuropathy with combined orbital irradiation and systemic steroids has been observed,[14] although a more recent study failed to demonstrate any treatment effect on rectus muscle hypertrophy or proptosis.[16]

Patients in this study were recruited early on in the course of disease, after a median duration of only 2.5 to 3 months of eye symptoms. This aimed to eliminate the confounding effect of spontaneous remission of Graves' ophthalmopathy. The changes in both individual ophthalmic parameters and the TES in the two treatment groups were measured. The TES was devised to facilitate a quantitative comparison between different treatment regimens.[18] A greater improvement in TES in the SRT group was observed by as early as week 16 and was associated with improvement in soft tissue swelling, ocular motility, and visual acuity. The improvement in soft tissue inflammation and ocular motility concurred with the previously reported effects of irradiation in Graves' ophthalmopathy.[10,11,24] Since the assessment of soft tissue swelling and extra-ocular muscle involvement using the NOSPECS grading is only semi-quantitative, we attempted to quantify the effects by measuring the maximum extra-ocular muscle thickness with imaging studies. While a greater improvement in this parameter was observed with the SRT group than with the ST group, the difference between the two groups did not achieve statistical significance, possibly because of the small sample size.

Combination therapy led to a marginally greater improvement in visual acuity at 1 year than the ST group. Improvement in intra-ocular pressure was also observed in the SRT group, in parallel with the improvement in visual acuity, though local medication might have contributed to the effect. Albeit not to a statistically significant level, subjects receiving the combined therapy had poorer vision and higher intra-ocular pressure at baseline, and the possibility of a greater improvement due to the 'regression towards the mean' phenomenon cannot be excluded.

The degree of proptosis was unaffected by the therapy in this study, in concordance with findings of others.[10,16] Proptosis develops as a result of increased volume of both extra-ocular muscles and orbital adipose tissue.[26] The latter has not been shown to respond to immunosuppression.[27] Although the maximum thickness of the extra-ocular muscles as measured from imaging studies was reduced by a mean of 0.21 cm, the magnitude of improvement may be too small to be detected clinically using the Hertel exophthalmometer. There was also no difference in the SES between the two groups; this

may have been due to the small sample size or the failure to use a validated disease-specific Graves' ophthalmopathy quality-of-life questionnaire.[28]

One patient in the ST group had to be excluded from analysis because he died from pneumonia at 3 weeks, before the first post-treatment assessment. High-dose systemic steroids induce potent, potentially fatal, immunosuppression, especially in the elderly and in subjects with other co-morbidities. In contrast, orbital irradiation is well tolerated and no patients reported any serious adverse effects. Nonetheless, the study was not long enough to detect late-onset side-effects such as secondary tumour development. Patients had only mild temporal hair loss and transient exacerbation of orbital congestion. Other complications such as cataracts, optic atrophy, and retinopathy have been infrequently reported in other studies.[27,29,30]

Performing good clinical trials in the treatment of Graves' ophthalmopathy is fraught with procedural and interpretive difficulties.[31] One patient in the ST group had rebound soft tissue inflammation and requested adjuvant irradiation at week 32. One may question whether his outcome data after the administration of orbital irradiation should be excluded from analysis. Based on the intention-to-treat principle, it was decided to include his outcome data at all time points in the analysis, with a note of caution that this might thereby overestimate the efficacy of the steroids-alone therapy. The strength of this study lies in the recruitment of patients early in the course of Graves' ophthalmopathy, while they were still in the inflammatory phase of the disease; and in the recruitment of patients who did not receive any prior treatment. However, the stringent recruitment criteria significantly limited the number of eligible subjects. The resultant sample size was small, making it difficult to ensure equivalence in baseline characteristics and introducing the possibility of inadequate statistical power. The patients receiving combination therapy were older by chance. Age did not correlate with the clinical response but the significance of age on the natural history of Graves' ophthalmopathy is unknown. Patients in this study were not free from bias, as they were not blinded to the allocation of treatment. A better study design would be the use of sham irradiation to the ST group. The detection of a significant difference between the two groups in TES despite the small sample size and wide confidence interval was nevertheless encouraging. It suggests that orbital irradiation considerably augments the treatment effects of systemic steroids. Larger-scale and longer-term studies will provide more definitive answers.

The preliminary results of this study suggest that a combination of orbital irradiation and systemic steroids is well-tolerated and more effective than steroids alone in the management of active moderate-to-severe Graves' ophthalmopathy. There is a greater improvement in soft tissue swelling, ocular motility, and visual acuity up to 52 weeks after treatment.

Acknowledgements

We thank Mr Peter D Christenson, Mr Savio Leung, and Dr Dexter Leung for their statistical assistance and our collaborators, Dr CC Liang and Dr YH Chong, for referring cases.

References

1. Burch HB, Wartofsky L. Graves' ophthalmopathy: current concepts regarding pathogenesis and management. Endocr Rev 1993;14:747-93.
2. Wiersinga WM, Smit T, van der Gaag R, Mouritis M, Koornneef L. Clinical presentation of Graves' ophthalmopathy. Ophthalmic Res 1989;21:73-82.
3. Brown J, Coburn JW, Wigod RA, Hiss JM Jr, Dowling JT. Adrenal steroid therapy of severe infiltrative ophthalmopathy of Graves' disease. Am J Med 1963;34:786-95.
4. Cortisone in exophthalmos: report on a therapeutic trial of cortisone and corticotrophin (ACTH) in exophthalmos and exophthalmic ophthalmoplegia by a panel appointed by the Medical Research Council. Lancet 1955;268:6-9.
5. Bartalena L, Marcocci C, Bogazzi F, Panicucci M, Lepri A, Pinchera A. Use of corticosteroids to prevent progression of Graves' ophthalmopathy after radioiodine therapy for hyperthyroidism. N Engl J Med 1989;321:1349-52.
6. Bartalena L, Marcocci C, Bogazzi F, et al. Relation between therapy for hyperthyroidism and the course of Graves' ophthalmopathy. N Engl J Med 1998;338:73-8.
7. Trobe JD, Glaser JS, Laflamme P. Dysthyroid optic neuropathy. Clinical profile and rationale for management. Arch Ophthalmol 1978;96:1199-209.
8. Marquez SD, Lum BL, McDougall IR, et al. Long-term results of irradiation for patients with progressive Graves' ophthalmopathy. Int J Radiat Oncol Biol Phys 2001;51: 766-74.
9. Wakelkamp IM, Tan H, Saeed P, et al. Orbital irradiation for Graves' ophthalmopathy: Is it safe? A long-term follow-up study. Ophthalmology 2004;111:1557-62.
10. Prummel MF, Mourits MP, Blank L, Berghout A, Koornneef L, Wiersinga WM. Randomized double-blind trial of prednisone versus radiotherapy in Graves' ophthalmopathy. Lancet 1993;342:949-54.
11. Mourits MP, van Kempen-Harteveld ML, Garcia MB, Koppeschaar HP, Tick L, Terwee CB. Radiotherapy for Graves' orbitopathy: randomised placebo-controlled study. Lancet 2000;355:1505-9.
12. Gorman CA, Garrity JA, Fatourechi V, et al. A prospective, randomized, double-blind, placebo-controlled study of orbital radiotherapy for Graves' ophthalmopathy. Ophthalmology 2001;108:1523-34.
13. Donaldson SS, Bagshaw MA, Kriss JP. Supervoltage

orbital radiotherapy for Graves' ophthalmopathy. J Clin Endocrinol Metab 1973;37:276-85.
14. Bartalena L, Marcocci C, Chiovato L, et al. Orbital cobalt irradiation combined with systemic corticosteroid for Graves' ophthalmopathy: comparison with systemic corticosteroids alone. J Clin Endocrinol Metab 1983;56:1139-44.
15. Marcocci C, Bartalena L, Bogazzi F, Bruno-Bossio G, Lepri A, Pinchera A. Orbital radiotherapy combined with high dose systemic glucocorticoids for Graves' ophthalmopathy is more effective than radiotherapy alone: results of a prospective randomized study. J Endocrinol Invest 1991;14: 853-60.
16. Ohtsuka K, Sato A, Kawaguchi S, Hashimoto M, Suzuki Y. Effect of steroid pulse therapy with and without radiotherapy on Graves' ophthalmopathy. Am J Ophthalmol 2003; 135:285-90.
17. Werner SC. Modification of the classification of the eye changes of Graves' disease: recommendations of the Ad Hoc Committee of the American Thyroid Association. J Clin Endocrinol Metab 1977;44:203-4.
18. Prummel MF, Mourits MP, Berghout A, et al. Prednisone and cyclosporine in the treatment of severe Graves' ophthalmopathy. N Engl J Med 1989;321:1353-9.
19. Sergott RC, Felberg NT, Savino PJ, Blizzard JJ, Schatz NJ. Graves' ophthalmopathy—immunologic parameters related to corticosteroid therapy. Invest Ophthalmol Vis Sci 1981;20: 173-82.
20. Kahaly G, Beyer J. Immunosuppressant therapy of thyroid eye disease. Klin Wochenschr 1988;66:1049-59.
21. De Rosa G, Menichella G, Della S, et al. Plasma exchange in Graves' ophthalmopathy. Prog Clin Biol Res 1990;337:321-5.
22. Antonelli A, Saracino A, Alberti B, et al. High-dose intravenous immunoglobulin treatment in Graves' ophthalmopathy. Acta Endocrinol (Copenh) 1992;126:13-23.
23. Kung AW, Michon J, Tai KS, Chan FL. The effect of somatostatin versus corticosteroid in the treatment of Graves' ophthalmopathy. Thyroid 1996;6:381-4.
24. Prummel MF, Terwee CB, Gerding MN, et al. A randomized controlled trial of orbital radiotherapy versus sham irradiation in patients with mild Graves' ophthalmopathy. J Clin Endocrinol Metab 2004;89:15-20.
25. Prummel MF, Wiersinga WM. Medical management of Graves' ophthalmopathy. Thyroid 1995;5:231-4.
26. Bahn RS, Heufelder AE. Pathogenesis of Graves' ophthalmopathy. N Engl J Med 1993;329:1468-75.
27. Gorman CA, Garrity JA, Fatourechi V, et al. The aftermath of orbital radiotherapy for graves' ophthalmopathy. Ophthalmology 2002;109:2100-7.
28. Gerding MN, Terwee CB, Dekker FW, Koornneef L, Prummel MF, Wiersinga WM. Quality of life in patients with Graves' ophthalmopathy is markedly decreased: measurement by the medical outcomes study instrument. Thyroid 1997;7: 885-9.
29. Kinyoun JL, Kalina RE, Brower SA, Mills RP, Johnson RH. Radiation retinopathy after orbital irradiation for Graves' ophthalmopathy. Arch Ophthalmol 1984;102:1473-6.
30. Marcocci C, Bartalena L, Rocchi R, et al. Long-term safety of orbital radiotherapy for Graves' ophthalmopathy. J Clin Endocrinol Metab 2003;88:3561-6.
31. Wiersinga WM, Prummel MF. An evidence-based approach to the treatment of Graves' ophthalmopathy. Endocrinol Metab Clin North Am 2000;29:297-319,vi-vii.