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Pentoxifylline (PTX) - An alternative treatment in Graves' ophthalmopathy (inactive phase): Assessment by a disease specific quality of life questionnaire and by exophthalmometry in a prospective randomized trial

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PURPOSE. *To investigate the effect of pentoxifylline (PTX) in subjects with inactive Graves' ophthalmopathy (GO) through a specific quality of life (QOL) questionnaire and exophthalmometry readings.*

METHODS. *Eighteen females were randomly divided in two groups. Group A (n=9) was treated with PTX 1200 mg orally/day for 6 months. Group B (n=9) received placebo during the initial 6 months and then PTX for another 6 months. Proptosis measurements were carried out every 3 months and a questionnaire graded from 0 to 10 according to the severity of the symptoms was performed at baseline and after placebo and PTX administration.*

RESULTS. *At baseline, Group A questionnaire score values were 5.5 (median; range 3.5 to 8.0), and 5.0 after 6 months (3.0 to 6.0; p=0.01). In Group B, baseline values were not significantly different after 6 months of placebo: 6.0 (4.5 to 7.0) and 5.5 (4.5 to 7.0), respectively. However, a significant change was observed 6 months after PTX: 4.0 (2.0 to 5.0; p<0.001). Patients in Group A had a progressive improvement of proptosis during PTX: at baseline, 23 mm (median; range 20 to 32); after 3 months, 23 mm (18 to 30; p=0.02); and after 6 months, 23 mm (18 to 30; p=0.005). In Group B, proptosis remained stable during placebo: at baseline, 23 mm (21 to 25); after 3 months, 23 mm (20 to 25); and after 6 months, 23.5 mm (20 to 25). A significant change was observed after 3 and 6 months of PTX: 22 mm (19 to 24; p=0.0006) and 20.8 mm (17 to 25; p=0.0003), respectively.*

CONCLUSIONS. *Pentoxifylline seems to improve the QOL of patients in the inactive phase of GO. The objective findings of the proptosis readings corroborate to suggest that PTX may be an effective and promising drug in the inactive phase of GO. (Eur J Ophthalmol 2004; 14: 277-83)*

KEY WORDS. *Graves' ophthalmopathy, Pentoxifylline*

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INTRODUCTION

Graves' ophthalmopathy (GO) is an incapacitating eye disease, causing pain, redness, and grittiness of the eyes, disfiguring proptosis, eyelid disorders, and diplopia in its active and inactive phases (1-3). Its pathology is not well understood, and frequently it is hard to define the activity of the pathologic process and particularly the presence or absence of fibrosis upon clinical ocular examination.

Several studies have recognized the psychological burden of the progressive disfigurement resulting from GO. Also, visual problems, in general, can have a major impact on daily functioning and well-being (1, 4-10). Patients with inactive GO frequently experience substantial facial disfigurement, mainly as a consequence of their chronic eye condition: puffy eyes (proptosis and swelling of the periorbital area), eyelid retraction, and deviation of the position of the eyes (11, 12). This visible deformity often results in embarrassment for patients (13-16).

The concept of quality of life (QOL) is relatively recent. It was first introduced into medicine during the mid-1960s (17, 18), and since then, subjective well-being as well as the physical and mental ability to function in everyday life became the focus of attention in several studies (1, 17, 19, 20).

In 1992, a joint committee of thyroid associations stated that self-assessment of the eye condition by the patient should be included in evaluations of treatments for patients with GO (21). However, it was not until 1997 that the first report, using a general questionnaire, was published on health-related QOL (HRQL) in patients with GO (22). In 1998, Terwee et al developed a reliable and valid disease-specific QOL questionnaire for patients with GO (GO-QOL) that could be used to describe the HRQL and its changes over time as a consequence of disease and treatment (1).

Many studies have pointed out that cytokine antagonists may be effective and valuable for GO treatment (23-30). Pentoxifylline (PTX) is an analogue of the methylxanthine theobromine, which inhibits the proliferation and certain biosynthetic activities of fibroblasts in some fibrotic disorders (31-35). Indeed, PTX seems to modify the immune process in the orbits presumably as a cytokine modulator (23, 36).

In this study we prospectively analyzed the potential benefit of long-term PTX administration in the objective and subjective well being of patients during the inactive chronic phase of GO, using a simplified specific disease questionnaire adapted from the original one developed by Terwee et al. Proptosis measurements were performed to clinically support the possible action of PTX in these patients.

PATIENTS AND METHODS

Subjects

We prospectively enrolled 20 consecutive female euthyroid patients with inactive GO, average age 40.1 ± 9.1 years (mean ± SD), who were selected for the protocol within a period of 6 months. The diagnosis of GO was based on typical features of the disease combined with enlarged extraocular eye muscles and retro-orbital tissues documented by previous ultrasounds and/or computed tomography scans. Duration of GO was 8 years (median, range: 3 to 17 years), and all patients were euthyroid for 2.5 years (median, range: 1 to 7 years). To assess the inflammatory activity of the ophthalmopathy we used the Clinical Activity Score proposed by Mourits and coworkers (37). Using a cut-off point of 4, all patients scored ≤3 and were classified as in the inactive chronic phase of GO. Diplopia was present in 66.7% of patients (six patients in Group A and six in Group B), low visual acuity in 33.3% (two patients in Group A and four in Group B), and a proptosis of at least 20 mm was present in all subjects.

Two patients, who presented peptic ulcer and other gastrointestinal contraindications to the use of PTX, were excluded from the protocol. Other exclusion criteria were the presence of severe optic neuropathy (no light perception) at baseline and the necessity of use of anti-thyroid drugs.

Patients were randomly divided in two groups (Tab. I). Group A (n=9) was treated with PTX 400 mg orally three times a day for 6 months. Group B (n=9) first received placebo orally three times a day during the initial 6 months and then PTX 400 mg orally three times a day orally for another 6 months. An observer, unaware of the trial, was responsible for the sorting process and for the distribution of the tablets, which were identical in all characteristics.

Fourteen patients had been previously treated with

radioiodine therapy (all patients in Group A and five in Group B) and two with subtotal thyroidectomy (both in Group B). No rehabilitative surgery (orbital decompression, strabismus surgery, or eyelid correction) had been performed in any subject. Five out of 18 patients (three patients in Group A and two in Group B) reported smoking for the last 5 years (Tab. I).

The only other treatment administered during this period consisted of eye drops and levothyroxine replacement (6/9 patients in Group A and 7/9 patients in Group B), adjusted to maintain serum thyroid-stimulating hormone (TSH) concentration between 0.6 and 4.0 mU/L. None of them had associated diseases or was taking any other medication. Patients in Group A were seen every 3 months for a period of 6 months and patients in Group B in the same intervals for a period of 12 months. All subjects were instructed to report any progression of eye disease during the study.

The treatment plan for inactive GO was extensively discussed with patients, who were informed about alternative treatments including different options of rehabilitative surgeries. During the study period, all patients were told about the most important side effects of PTX and that they could abandon the treatment at any time they judged appropriate. All patients gave their informed consent to this study, and the protocol was approved by the ethical committee of our institution.

No patient was lost to follow-up.

Methods

Questionnaire. The 10-item questionnaire was always performed by the same clinical observer who was unaware of treatment data. This information was taken at baseline and after 6 months of treatment with PTX in Group A, and at baseline, after placebo, and after PTX administration in Group B. The questionnaire could be graded from 0 to 10 according to the severity of the symptoms. On each item of evaluation, the degree of perceived impairment was scored on a three-point Likert scale (not impaired, a little impaired, severely impaired) (Tab. II).

The questionnaire evaluated the consequences of double vision and decreased acuity on visual functioning and the psychosocial consequences of a changed appearance. The patients were asked to report if these aspects of their health had become worse, were about the same, or better than before treatment.

TABLE I - CLINICAL AND BIOCHEMICAL FEATURES OF THE PATIENTS

Characteristics	Group A	Group B
Subjects	9	9
Mean age (yr), mean ± SD	41.5 ± 8.0	40.0 ± 10.5
Smokers, n	3	2
Duration of GO (yr), mean ± SD	7.4 ± 3.5	10.2 ± 5.3
TSH at randomization, mean ± SD*	2.2 ± 1.6	1.9 ± 0.9
FT4 at randomization, mean ± SD*	14.0 ± 5.7	11.0 ± 6.5
Previous ^{131}I dose	9	5
Previous thyroidectomy	—	2

Thyroid-stimulating hormone (TSH) receptor antibody was negative in all subjects (negative values: < 10 U/L). No differences were significant.
*Normal values: FT4: 6.0 to 15.0 pmol/L; TSH: 0.5 to 4.0 mU/L
GO = Graves' ophthalmopathy

TABLE II - DISEASE-SPECIFIC QUALITY OF LIFE QUESTIONNAIRE

Questionnaire	
1. Limited in walking indoors	Not impaired: 0 points A little impaired: 0.5 points Seriously impaired: 1 point
2. Limited in walking outside	
3. Limited in reading	
4. Limited in watching TV	
5. Feeling of social isolation	
6. Using camouflage	
7. Change in appearance	
8. Unpleasant reactions (by others)	
9. Influence on self confidence	
10. Influence on friendship	

Proptosis measurements. Proptosis was measured every 3 months with a Hertel's exophthalmometer (Handaya Co. Ltd., Tokyo, Japan) by the same ophthalmologist who was blind to the treatment given to the patient. The mean (± SD) Hertel reading in the Brazilian population is 15.1 ± 1.1 mm (38), and readings ≥ 18 were considered abnormal.

Statistical analysis. Friedman's analysis of variance was performed to compare changes in the proptosis measurements and the Wilcoxon test to compare changes in the questionnaire punctuation in Groups A and B. The Mann-Whitney test was performed to verify uniformity at baseline in both groups. The results were

expressed as median and ranging values; p<0.05 was considered statistically significant. The proptosis results, in the Figures, are expressed as mean ± SE only for illustration.

RESULTS

Questionnaire

Before treatment, there was no difference in the score values between the two groups.

At baseline, median Group A score value was 5.5 (range: 3.5 to 8.0, 95% CI: 4.7 to 6.5) and after 6 months, 5.0 (range: 3.0 to 6.0) (95% CI: 3.7 to 5.3; p=0.02) (Fig. 1).

In Group B, baseline score values were not significantly different after 6 months of treatment with placebo: median 6.0, range: 4.5 to 7.0 (95% CI: 4.9 to 6.4) and 5.5, range: 4.5 to 7.0 (95% CI: 4.8 to 6.3; p=0.50), respectively. However, in this group, a significant change was observed 6 months after PTX administration: 4.0, range 2.0 to 5.0 (95% CI: 3.2 to 4.6; p<0.001) (Fig. 1).

Proptosis measurements

Before treatment, all patients had their baseline values of proptosis ≥ 20 and there was no difference in proptosis between the groups (p=0.55).

At baseline, Group A proptosis measurements were 23 mm, range: 20 to 32 (95% CI: 22.4 to 25.6); after 3 months: 23 mm, range: 18 to 30 (95% CI: 21.7 to 24.9; p=0.02); and after 6 months of PTX: 23 mm, range 18 to 30 (95% CI: 21.7 to 24.4; p=0.005) (Fig. 2).

In Group B, baseline values were not significantly different after 3 and 6 months of placebo: 23 mm, range: 21 to 25 (95% CI: 22.3 to 23.7); 23 mm, range: 20 to 25 (95% CI: 22.3 to 23.8; p=0.84) and 23.5 mm, range: 20 to 25 (95% CI: 22.5 to 23.9; p=0.38), respectively (Fig. 2). However, in this group, a significant change in proptosis was observed after 3 months: 22 mm, range: 19 to 24 (95% CI: 21.1 to 22.5; p=0.0006) and after 6 months of PTX: 20.8 mm, range: 17 to 25 (95% CI: 20.0 to 22.2; p=0.0003) (Fig. 3).

Ten orbits in Group A (55.6%) had a decrease in proptosis of 2 mm or more at the end of the treatment with PTX. In Group B, during placebo, significant decrease was not observed; however, during PTX ad-

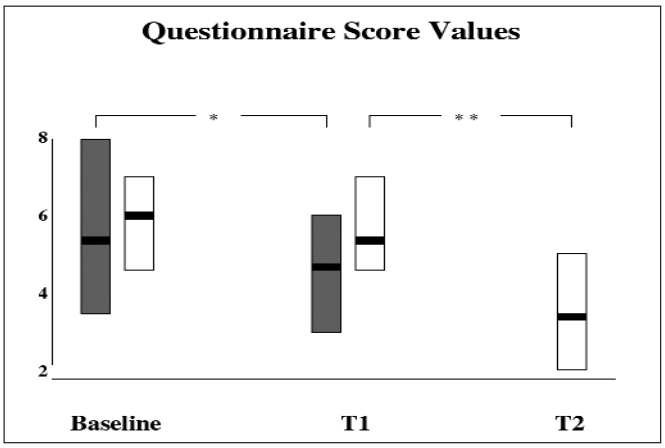

Fig. 1 - *Median (–) and range values of health-related quality of life (HRQL) questionnaire in Group A patients during pentoxifylline (PTX) treatment (■) and in Group B patients during placebo and PTX administration (□). *p=0.01; **p<0.001 (Wilcoxon test). T1: 6 months after PTX treatment (Group A) and 6 months after placebo administration (Group B); T2: 6 months after PTX treatment (Group B).*

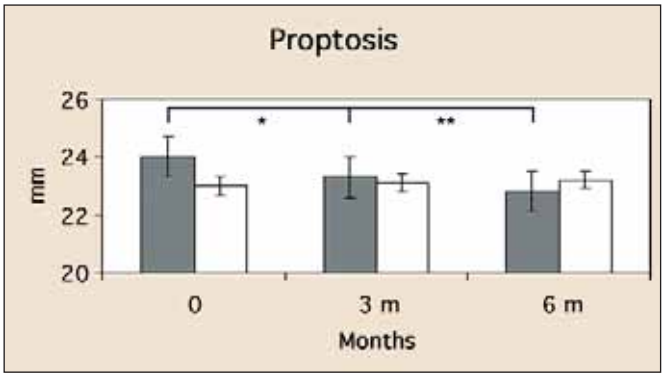

Fig. 2 - *Mean ± SE values of proptosis in Group A patients during pentoxifylline (PTX) treatment (■) and in Group B patients during placebo administration (□). *p=0.02, **p=0.005 (Friedman's analysis of variance).*

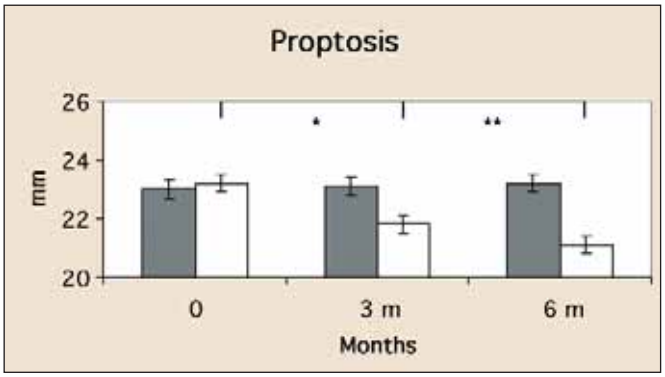

Fig. 3 - *Mean ± SE values of proptosis in Group B patients during placebo administration (■) and during pentoxifylline (PTX) treatment (□). *p=0.0006, **p=0.0003 (Friedman's analysis of variance).*

ministration, 11 orbits (61%) had their values decreased above 2 mm.

Thyroid status

During PTX or placebo administration all patients remained euthyroid. Levothyroxine adjustments were performed whenever necessary to maintain TSH levels in the normal range.

Side effects

Minor gastrointestinal side effects, such as nausea and abdominal pain, were mentioned only by 3 patients (16.7%) in the beginning of PTX administration, but they rapidly improved after symptomatic therapy.

No side effects were reported during placebo administration.

DISCUSSION

The inactive phase of GO frequently imposes a severe psychological, social, and economic burden on the patient. Most authors agree that medical treatments for GO are only likely to be effective during the active phase of the disease, and that surgery represents the only treatment available in inactive stages of GO. However, rehabilitative and extraocular muscle final results frequently are poor and a considerable number of patients remain unhappy with their ultimate appearance. Also, the goal of medical care for most patients today is to obtain a more effective life and to preserve functioning and well being (17).

Scoring standardized responses to standardized questions is an efficient way to measure health status and individual HRQL (17), although these data concerning a patient's experience of disease and treatment are not routinely collected. In our study, both groups showed, at baseline, seriously impaired scores in HRQL. This finding is in agreement with a study in which Gerding et al have demonstrated that patients with GO had a markedly decreased HRQL compared with a general population and with patients with other chronic diseases (22). In addition, the high scores (impaired function) observed in our study did not correlate with the activity of the ophthalmopathy, since all patients were in the chronic and inactive stage of GO, suggesting that the negative impact of this disfiguring disease is not necessarily related to its clinical inflammatory activity.

In this trial, we observed through the questionnaire evaluation that PTX administration resulted in a significant improvement in esthetic appearance, visual acuity, visual functioning, and psychosocial consequences of a changed appearance in both groups studied. However, we were not able to highlight any one of the 10 items of the questionnaire as all of them improved similarly.

Spontaneous improvement in HRQL seems to be unlikely since, during placebo therapy, patients in Group B remained stable in their vision functioning, without any significant clinical or psychological improvement.

Terwee et al have demonstrated in a cross-sectional follow-up study that GO should be considered a chronic disease (39). Through analyses of the GO-HRQL questionnaire they have observed that more than half of the patients in the inactive phase of GO had diplopia, 28% had a low visual acuity, and 60% had a proptosis of at least 20 mm. Their HRQL scores were better than those of newly diagnosed GO patients (active phase), but worse than those of "healthy" persons. These findings support the idea that continuous aftercare is needed for these patients after their initial approach in the active phase of GO (39).

We also observed that a 6-month period of PTX administration resulted in significant improvement in proptosis measurements (Figs. 2 and 3). This amelioration was noticed in both groups during a short period of 3-month PTX treatment. This finding is important to encourage the use of PTX in inactive GO since spontaneous improvement of proptosis was not observed during placebo administration. Also, through this clinical ophthalmologic assessment, we were able to show that PTX administration in inactive GO resulted in an objective beneficial effect. Therefore, the interesting findings observed in the HRQL questionnaire are supported and linked to a specific ocular finding, suggesting more clearly that PTX may play a role in the treatment of GO during the chronic inactive stage.

PTX is a drug that acts by downregulating cytokines production and inhibiting fibroblast proliferation and the consequent fibrosis in the pathogenesis of GO. These immune and pathogenic events are the major points to justify the observed results. Recent studies have supported the idea that PTX may play a role as

a cytokine antagonist in the immune process of GO (23, 28, 29, 36, 40). Balazs et al have demonstrated that this agent has a significant anti-cytokine activity, inhibiting IL-1-, TNF-alpha-, and IFN-gamma-induced HLA-DR expression, and GAG synthesis in cultural orbital fibroblasts (40). Also, they have reported that patients with moderately inflammatory GO showed some improvement of soft tissue swelling and, to a lesser degree, of proptosis and extraocular muscle involvement (23). However, that was a short-term study, and the authors have not established any kind of self-assessment of the GO condition by the patient.

This is the first study to describe the effects of long-term treatment with an immune modulator drug in the subjective well being of patients in the inactive phase of GO. PTX seems to be an alternative treatment for these patients with consequences of the fibrosis and the immune process in the final stage of GO.

Our results show that PTX may be effective, improving considerably the HRQL in patients in the inactive phase of GO. The modified GO-QOL questionnaire is a useful tool to measure specific aspects of QOL in patients with GO; also, it is simpler to apply and easier to interpret than the original one proposed by Terwee et al. This cytokine antagonist and inhibitor of fibrosis deserves further evaluation in the treatment of inactive GO.

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REFERENCES

1. Terwee CB, Dekker FW, Wiersinga WM. Development of a disease-specific quality of life questionnaire for patients with Graves' ophthalmopathy: the GO-QOL. Br J Ophthalmol 1998; 82: 773-9.
2. Bartalena L, Pinchera A, Marcocci C. Management of Graves' ophthalmopathy: reality and perspectives. Endocr Rev 2000; 21: 168-99.
3. Weetman AP. Thyroid-associated eye disease: pathophysiology. Lancet 1991; 338: 25-8.
4. Salive ME, Guralnik J, Glynn RJ, et al. Association of visual impairment with mobility and physical function. J Am Geriatr Soc 1994; 42: 287-92.
5. Scott IU, Schein OD, West S, et al. Functional status and quality of life measurement among ophthalmic patients. Arch Ophthalmol 1994; 112: 329-35.
6. Mangione CM, Lee PP, Hays RD. Measurement of visual functioning and health-related quality of life in eye disease and cataract surgery. In: Spilker B, ed. Quality of Life and Pharmacoeconomics in Clinical Trials. 2nd ed. Philadelphia: Lippincott-Raven 1996; 1045-51.
7. Lee PP, Spritzer K, Hays RD. The impact of blurred vision on functioning and well-being. Ophthalmology 1997; 104: 390-6.
8. Dallow RL, Netland PA. Management of thyroid ophthalmopathy (Graves' disease). In: Albert DM, Jacobiec FA, eds. Principles and Practice of Ophthalmology: Clinical Practice. Philadelphia: WB Saunders 1994; 1905-22.
9. Lyons CJ, Rootman J. Orbital decompression for disfiguring exophthalmos in thyroid orbitopathy. Ophthalmology 1994; 101: 223-30.
10. Bartley GB, Fatourechi V, Kadrmass EF, et al. Long-term follow-up of Graves' ophthalmopathy in an incidence cohort. Ophthalmology 1996; 103: 958-62.
11. Terwee CB, Dekker FW, Wiersinga WM, et al. Facial disfigurement: is it in the eye of the beholder? A study in patients with Graves' ophthalmopathy. Clin Endocrinol 2003; 58: 192-8.
12. Burch HB, Wartofsky L. Graves' ophthalmopathy: current concepts regarding the pathogenesis and management. Endocr Rev 1993; 14: 747-93.
13. Clarke A. Psychosocial aspects of facial disfigurement:

problems, management and the role of a lay-led organization. Psychol Health Med 1999; 4: 127-42.
14. Dropkin MJO, Malgady RG, Strong EW, et al. Scaling disfigurement and dysfunction in postoperative head and neck patients. Head Neck Surg 1983; 6: 559-70.
15. Newell R. Living with disfigurement. Nurs Times 2002; 98: 34-5.
16. Thompson A, Kent G. Adjusting to disfigurement: process involved in dealing with being visibly different. Clin Psychol Rev 2001; 21: 663-82.
17. Kahaly GJ, Hardt J, Egle UT, et al. Psychosocial factors in subjects with thyroid-associated ophthalmopathy. Thyroid 2002; 12: 237-9.
18. Elkinton JR. Medicine and the quality of life. Ann Intern Med 1996; 64: 710-4.
19. Spilker B. Introduction to the field of quality of life trials. In: Spilker B, ed. Quality of Life and Pharmacoeconomics in Clinical Trials. Philadelphia: Lippincott-Raven 1996; 1-10.
20. Terwee CB, Gerding MN, Wiersinga WM, et al. Test-retest reliability of the GO-QOL: a disease-specific quality of life questionnaire for patients with Graves' ophthalmopathy. J Clin Epidemiol 1999; 52: 875-84.
21. Pinchera A, Wiersinga WM, Glinoer D, et al. Classification of eye changes of Graves' disease. Thyroid 1992; 2: 235-6.
22. Gerding MN, Terwee CB, Wiersinga WM, et al. Quality of life in patients with Graves' ophthalmopathy is markedly decreased: measurement by the Medical Outcome Study instrument. Thyroid 1997; 7: 885-9.
23. Balazs CS, Kiss E, Farid NR, et al. Beneficial effect of pentoxifylline on thyroid associated ophthalmopathy (TAO): a pilot study. J Clin Endocrinol Metab 1997; 82: 1999-2002.
24. Wall J, Kennerdell JS. Progress in thyroid-associated ophthalmopathy. Autoimmunity 1995; 22: 191-5.
25. Weetman AP. The role of T lymphocytes in thyroid-associated ophthalmopathy. Autoimmunity 1994; 13: 69-77.
26. Metcalfe RA, Weetman AP. Stimulation of extraocular muscle fibroblasts by cytokines and hypoxia: possible role in thyroid-associated ophthalmopathy. Clin Endocrinol 1994; 40: 67-78.
27. Kahaly G, Hansen C, Winand R, et al. Plasma glucosaminoglycan in endocrine ophthalmopathy. J Endocrinol Invest 1994; 17: 45-55.
28. Kahaly G, Stover C, Schuler M, et al. Glycosaminoglycans in thyroid associated ophthalmopathy. Autoimmunity 1992; 13: 81-9.
29. Balazs CS, Kiss E. Immunological aspects of the effect of pentoxifylline (Trental). Acta Microbiol Immunol Hung 1994; 41: 121-33.
30. Wiersinga WM, Prummel MF. Editorial: Pathogenesis of Graves' ophthalmopathy-current understanding. J Clin Endocrinol Metab 2001; 86: 501-3.
31. Mohler W, Bletz I, Reiser M. Die struktur von ausscheidungsprodukten des 1-Hexyl-3,7-dimethylxanthins. 1. Uber den Metabolimus des 1-Hexyl-3,7-dimethylxanthins. Arch Pharm 1966; 299: 448-56.
32. Desmoulière A, Guoxiong X, Tuchweber B. Effect of pentoxifylline on early proliferation and phenotypic modulation of fibrogenic cells in two tat models of liver fibrosis and on cultured hepatic stellate cells. J Hepatol 1999; 30: 621-31.
33. Ramadori G. The stellate cell of the liver. New insights into pathophysiology of an intriguing cell. Virchows Arch B Cell Pathol 1991; 61: 147-58.
34. Pinzani M, Marra F, Failli P, et al. Inhibition by pentoxifylline of extracellular signal-regulated kinase activation by platelet-derived growth factor in hepatic stellate cells. Br J Pharmacol 1996; 119: 1117-24.
35. Isbrucker RA, Peterson TC. Platelet-derived growth factor and pentoxifylline modulation of collagen synthesis in myofibroblasts. Toxicol Appl Pharmacol 1998; 149: 120-6.
36. Chang CC, Chang TC, Chien LF, et al. Pentoxifylline inhibits the proliferation and glycosaminoglycan synthesis of cultured fibroblasts derived from patients with Graves' ophthalmopathy and pretibial myxoedema. Acta Endocrinol 1993; 129: 322-7.
37. Mourits MP, Prummel MF, Wiersinga WM, Koornneef L. Clinical activity score as a guide in the management of patients with Graves' ophthalmopathy. Clin Endocrinol 1997; 47: 9-14.
38. Albuquerque AK, Santos LP. Avanços no Tratamento da Oftalmopatia de Graves. Programa de Atualização Continuada 1999. São Paulo, SP: Departmento de Oftalmologia, UNIFESP/EPM, 1999.
39. Terwee C, Dekker F, Wiersinga WM, et al. Long-term effects of Graves' ophthalmopathy on health-related quality of life. Eur J Endocrinol 2002; 146: 751-7.
40. Balazs CS, Kiss E, Farid NR. Inhibitory effect of pentoxifylline on HLA-DR and glycosaminoglycan synthesis of retrobulbar fibroblasts induced by interferon gamma. Acta Microbiol Immunol Hung 1997; 44: 173-9.