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Randomized trial of intravenous immunoglobulins *versus* prednisolone in Graves' ophthalmopathy

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SUMMARY

Glucocorticoids are usually given for management of Graves' ophthalmopathy (GO), but they may cause side effects. By comparison, intravenous administration of immunoglobulins resulted in clinical improvement and decreased antibody titres in a large number of autoimmune diseases. Therefore, a randomized trial was done, in which 19 patients with active GO were treated with a 20-week course of oral prednisolone (P, starting dose 100 mg/day), and 21 received 1 g immunoglobulin/kg body weight for 2 consecutive days every 3 weeks. The immunoglobulin course was repeated six times. Before and at the end (20 weeks) of immunomodulating therapy, ophthalmological investigation and quantitative magnetic resonance (MR) imaging were performed. A successful outcome was observed in 12 (63%) P- and in 13 (62%) immunoglobulin-treated patients. Overall, there were no marked differences in degree of improvement between the two groups. Responders to treatment in both groups showed improvements in proptosis (median from 24·5 to 21·5 mm; $P < 0{\cdot}005$), visual acuity (from 0·6 to 0·85; $P < 0{\cdot}001$), intraocular pressure (from 25 to 20 mmHg; $P < 0{\cdot}0001$), lid aperture (from 14 to 12 mm; $P < 0{\cdot}01$) and a decrease in eye muscle area (inferior, from 44 to 33 mm^2; medial, from 43 to 34 mm^2; both $P < 0{\cdot}0005$). Among the immunoglobulin-treated patients, there was a marked decrease of thyroid antibody titres. Side effects were more frequent and severe during P than during immunoglobulin therapy. Thus, with respect to the above mentioned objective parameters, P and immunoglobulin appeared to be equally effective in treatment of active GO.

Keywords immunoglobulin therapy Graves' ophthalmopathy

INTRODUCTION

Immunoglobulin preparations from human blood were first used in clinical medicine to treat patients having a deficiency of circulating antibodies [1]. Interest in the manipulative effects of immunoglobulin on the immune system first developed with the discovery that immunologic reactions can be modified, often dramatically, by the intravenous (i.v.) administration of large amounts of immunoglobulin (400–2000 mg/kg body weight over a period of 2–5 days [2]). Over the years, i.v. infusion of pooled normal polyspecific immunoglobulin for therapeutic use has resulted in clinical improvement and/or decrease in antibody titre in a number of human autoimmune diseases [3]. I.v. immunoglobulin contains anti-idiotypes against a variety of autoantibodies from patients with autoimmune diseases and against natural autoantibodies from normal individuals [4]. Much of the evidence regarding the manipulative effects of immunoglobulin on the immune system suggests that the idiotypic and Fc portions of the molecule are important.

Graves' ophthalmopathy (GO) is an organ-specific autoimmune disease, and orbital infiltration with mononuclear cells and local release of cytokines suggest that activated T cells are involved in its pathogenesis [5]. During the active inflammatory stage, the retrobulbar tissue shows marked lymphocytic infiltration and interstitial oedema [6]. Thus, immunosuppression is often used initially, and by suppressing inflammatory changes it can result in subjective and objective improvement of the disease [7,8]. Although glucocorticoids are the first-choice immunomodulating treatment, they often cause side-effects. By comparison, positive results with i.v. immunoglobulin as second-line treatment have been reported in patients with severe GO and related dermopathy [9–11], but controlled clinical trials have not been done, and the benefits of i.v. immunoglobulin therapy have been questioned. Therefore, in the following randomized prospective trial, we compared efficacy and tolerability of oral prednisolone (P) and i.v. immunoglobulin in patients with active GO.

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PATIENTS AND METHODS

Forty consecutive patients with active GO (aged 39–61 years) who had been euthyroid for at least 2 months were enrolled (Table 1). The diagnosis of GO was based on ophthalmological investigation [12], which encompassed ultrasonography of the orbit. Written informed consent was obtained from all patients and the study received local Ethical Committee approval. A randomization list was used to assign each patient to receive either oral P or i.v. immunoglobulin. Nineteen patients were treated with a 20-week course of P (starting dose 100 mg/day for 1 week, then tapering the dose by 5 mg/week), and 21 patients received 1 g immunoglobulin/kg body wt intravenously for 2 consecutive days every 3 weeks. The immunoglobulin course was repeated six times. The type of therapy was known neither to the ophthalmologist nor to the neuroradiologist who assessed treatment results. All patients were examined by the same ophthalmologist according to the new classification of eye changes of Graves' disease [12] on the day before and at 20 weeks (endpoint) after the start of treatment. Response to therapy was defined as a marked amelioration of at least three objective signs (decrease of eye muscle area $>5\,mm^2$, proptosis >2 mm, intraocular pressure in upgaze >3 mmHg, and/or abscence of diplopia in primary position). Thyroid medication was not changed during the study period (methimazole 5–20 mg/day). Thyroid hormones (Boehringer, Mannheim, Germany), thyroglobulin and microsomal (ELISA; Elias, Freiburg, Germany), as well as TSH receptor (radioreceptor assay; TRAK, Brahms, Germany) autoantibodies were measured using commercially available kits. Exclusively immunoglobulins prepared from anti-hepatitis C virus (HCV)-negative plasma donors according to manufacturer's information (Serapharm, Münster, Germany) were administered. Laboratory tests (liver and renal function) were assessed regularly. All patients were examined for hepatitis B surface antigen (HBsAg), anti-HCV, and anti-HIV (ELISA; Abbott Diagnostika, Wiesbaden, Germany).

Quantitative magnetic resonance (MR) imaging of the orbits with a 0·28-T magnet (BMT 1100; Brucker, Erlangen, Germany) was performed and the T2 relaxation time (T2) was measured in a coronal section with 5 mm thickness. Squares containing nine pixels were chosen for T2 determination within the rectus eye muscles. Calculations of T2 were performed with a Carr-Purcell-Meiboom-Gill sequence with eight consecutive echoes (800/34-272; repetition time second/echo time second). Normal range of T2 within the extraocular muscles was 92 ms (80–97 ms).

All values are expressed as the median (range) of values recorded for affected eyes. Comparison between groups was by two-sided, two-sample *t*-test or by Mann–Whitney *U*-test. To compare percentages, we used the χ^2 test. Correlations among various parameters were calculated using Spearman's test.

Table 1. Baseline clinical and laboratory variables in patients with Graves' ophthalmopathy according to randomization to treatment with intravenous immunoglobulins or oral prednisolone (P)

	Immunoglobulin	P
Number of patients	21	19
Female/male	16/5	15/4
Age (years), median	48	47
range	39–61	40–59
Pretreated (steroids/irradiation)	11	9
Duration of eye disease (months)	9	7
	5–19	3–18
Duration of thyroid disease (months)	16	13
	10–24	4–21
Thyroid volume (ml)	33	36
	24–42	23–44
Plasma TSH (mU/*l*)	1·1	1·0
	0·6–1·4	0·5–1·2
TSH-receptor antibodies (U/*l*)	104	87
	28–136	19–108
Proptosis (mm)	23·5	24
	21–26	21–27
Visual acuity	0·7	0·6
	0·5–0·9	0·5–0·8
Lid aperture (mm)	13	13
	12–15	11–16
Intraocular pressure	24·4	25
in upgaze (mmHg)	21–27	21–29
Rectus muscle surface area (mm^2)		
inferior	39	38
	36–46	35–44
medial	40	41
	36–45	36–47
T2 relaxation time of	119	123
rectus muscles (ms)	108–141	114–157

RESULTS

As predefined, therapeutic outcome after 20 weeks was similar in each treatment group, with 13 (62%) patients responding successfully to immunoglobulin and 12 (63%) responding to P. Of the eight (38%) in the immunoglobulin group and seven (37%) in the P group in whom treatment was unsuccessful, six (29%) and five (26%), respectively, showed no change, and two (9% and 11%) in each group were classified as treatment failures. A significant improvement of proptosis under both treatments was observed (Fig. 1a), whereas responders to both regimens showed a similar marked decrease of exopthalmos (Fig. 1b). Visual acuity slightly increased during immunoglobulin and P therapy, respectively (Fig. 2a), but only four patients had a vision below 0·5. Intraocular pressure in upgaze was strongly lowered by immunoglobulin treatment (Fig. 2b), in contrast to P therapy where no significant changes were demonstrated. Response to either treatment was also due to changes in soft-tissue involvement (Fig. 3a), as well as in eye muscle motility (Fig. 3b). Corneal involvement was noted in four P *versus* five immunoglobulin patients before and in none after therapy. Eye muscle area decreased significantly under both therapy regimens (Fig. 4a), whereas in responders to immunoglobulin and P treatment, a sharp decrease of muscle area (Fig. 4b) was noted. Overall, there were no marked differences in degree of improvement between the two groups, but inflammatory signs resolved more rapidly in P patients. Side-effects were more common during P than during immunoglobulin therapy (Table 2).

Responders to treatment in both groups showed improvements in proptosis (median from 24·5 to 21·5 mm; $P < 0·005$), visual acuity (from 0·6 to 0·85; $P < 0·001$), intraocular pressure (from 25 to 20 mmHg; $P < 0·0001$), lid aperture (from 14 to 12 mm; $P < 0·01$) and a decrease in muscle area (inferior, from 44 to 33 mm^2; medial, from 43 to 34 mm^2, both $P < 0·0005$). Before therapy, T2 of the eye muscles was significantly higher in the responder group and decreased markedly after 20 weeks, in contrast to the non-responder group (45 *versus* 7 ms;

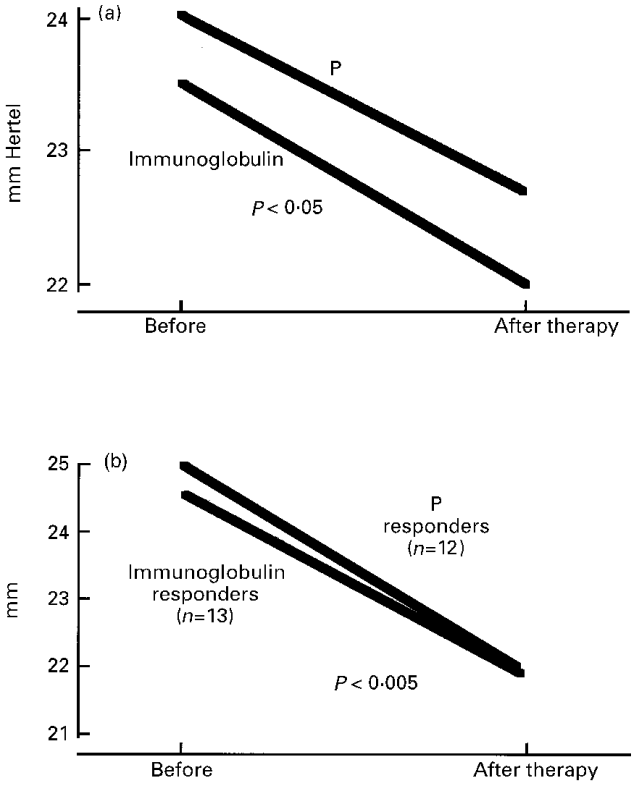

Fig. 1. (a) In patients with Graves' ophthalmopathy (GO), the course of proptosis (Hertel exophthalmometer, median value in mm) is shown before and after i.v. immunoglobulin (before, range 21–26 mm; after, 19–26 mm) and oral prednisolone (P; before, 21–27 mm; after, 20–28 mm) treatment, respectively. (b) In patients with GO who responded to immunomodulating therapy ($n = 13$ out of 21 for immunoglobulin and 12 out of 19 for P), the course of proptosis (Hertel exophthalmometer, median value in mm) is shown before and after i.v. immunoglobulin (before, 22–26 mm; after, 19–22 mm) and oral prednisolone (P; before, 21–27 mm; after, 19–23 mm) treatment, respectively.

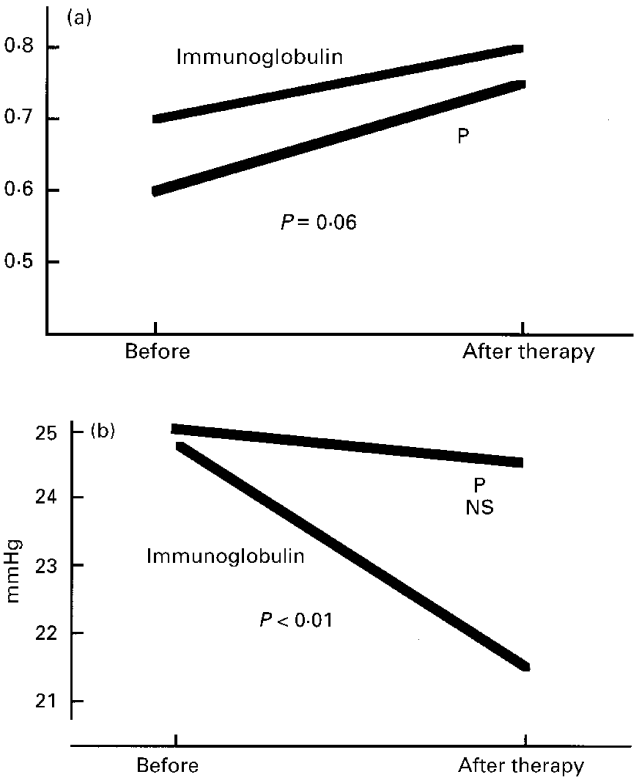

Fig. 2. (a) In patients with Graves' ophthalmopathy (GO), the course of visual acuity (median value) is shown before and after i.v. immunoglobulin (before, range 0·5–0·9; after, 0·7–1·0) and oral prednisolone (P; before, 0·5–0·8; after, 0·6–1·0) treatment, respectively. (b) In patients with GO, the course of intraocular pressure in upgaze (median value in mmHg) is shown before and after i.v. immunoglobulin (before, 21–27 mmHg; after, 17–26 mmHg) and oral prednisolone (P; before, 21–29 mmHg; after, 18–28 mmHg) treatment, respectively.

$P < 0{\cdot}0001$). When responders were compared with non-responders for both treatment groups, there were no differences in baseline characteristics (e.g. age, sex distribution, duration of eye/thyroid disease, pretreatment of ophthalmopathy, thyroid volume, plasma TSH, and levels of TSH-receptor antibodies).

In 18 immunoglobulin patients positive for thyroid microsomal antibodies, the median value dropped from 2850 to 490 U/ml (normal <350 U/ml; $P < 0{\cdot}0001$). Similar results were observed in 15 cases, where the thyroglobulin antibody level dropped from 1980 to 500 U/ml; $P < 0{\cdot}001$. In 18 TSH-receptor antibody-positive patients, the titre was 104 before and 10 U/*l* (normal <9 U/*l*; $P < 0{\cdot}0001$) after immunoglobulin therapy. In comparison, the level in 15 TSH-receptor antibody-positive P patients dropped from 87 to 50 U/*l* ($P < 0{\cdot}01$).

After completion of the study, 10 (five P-treated) out of 15 non-responders had active eye disease, and received a combination of immunoglobulin (1 g/kg body wt per day) and i.v. methylprednisolone (250 mg/day) for 2 consecutive days every 3 weeks. After repeating this course four times, seven patients responded to this combined regimen (Table 3). The remaining five (three immunoglobulin) non-responders to monotherapy were submitted to decompressive surgery. No liver chemistry abnormalities were detected after immunoglobulin administration, and all immunoglobulin-treated patients were negative for HBsAg, anti-HCV and HIV antibodies 40 weeks after start of treatment.

DISCUSSION

This randomized study showed that i.v. immunoglobulin therapy was equally effective and better tolerated than the standard regimen oral P in patients with active GO. Response to therapy was independent of duration of eye and/or thyroid disease, pretreatment of GO and level of thyroid antibodies. Combination of both immunomodulating drugs was successful in 70% of the non-responders to monotherapy and may present an alternative second-line treatment for patients with severe and active GO, not responding to steroids and retrobulbar irradiation.

Graves' hyperthyroidism and GO are characterized by a lymphocyte infiltration of the target organ, and evidence of immune system activation, particulary during the active phase of the disease when autoantibodies to the TSH receptor and activated T cells are present in the circulation [7]. In a preliminary study, eight women with GO were treated with 3 monthly i.v. infusions of 2 g/kg of pooled IgG [9]. All patients experienced subjective and objective clinical improvement following therapy. A significant fall in the level of thyroid-stimulating antibodies was also

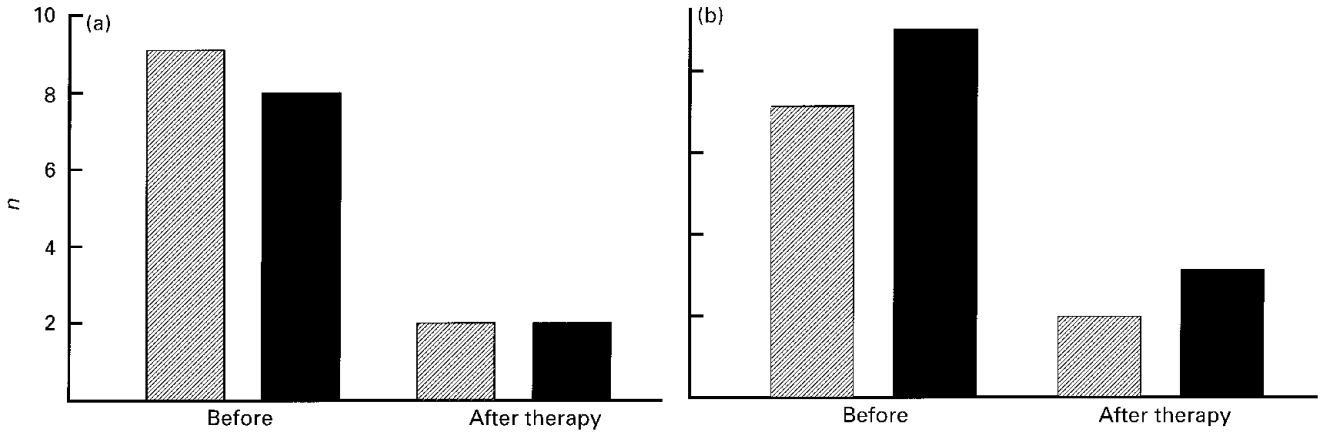

Fig. 3. (a) Changes in soft-tissue involvement are shown before and after i.v. immunoglobulin (■) and oral prednisolone (▨) treatment, respectively. Chemosis was present in nine (P) *versus* eight (immunoglobulin) patients before and in two (P) *versus* two (immunoglobulin) after immunomodulating therapy. (b) Changes in eye muscle motility are shown before and after i.v. immunoglobulin and oral prednisolone (P) treatment, respectively. Diplopia in primary position was present in nine (P) and 11 (immunoglobulin) patients before but in only four (P) and five (immunoglobulin) cases, respectively, after immunomodulating therapy.

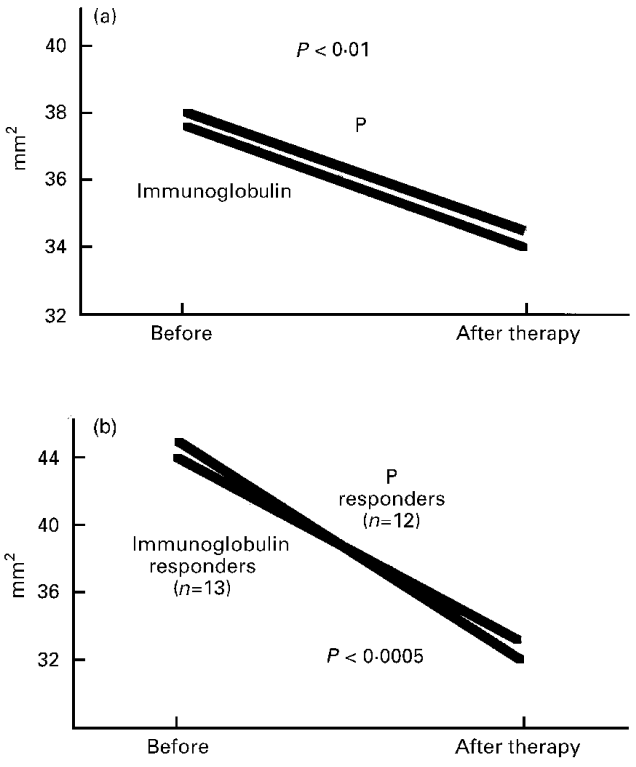

Fig. 4. (a) In patients with Graves' ophthalmopathy (GO), the course of the surface area of the inferior rectus muscle (quantitative magnetic resonance (MR) imaging, median value in mm^2) is shown before and after i.v. immunoglobulin (before, range 36–46 mm^2; after, 32–44 mm^2) and oral prednisolone (P; before, 35–44 mm^2; after, 32–45 mm^2) treatment, respectively. (b) In patients with GO who responded to immunomodulating therapy ($n = 13$ out of 21 for immunoglobulin and 12 out of 19 for P), the course of the surface area of the inferior rectus muscle (quantitative MR imaging, median value in mm^2) is shown before and after i.v. immunoglobulin (before, 37–46 mm^2; after, 32–35 mm^2) and oral prednisolone (P; before, 35–44 mm^2; after, 32–36 mm^2) treatment, respectively.

Table 2. Side-effects during treatment with intravenous immunoglobulins or prednisolone (P) in patients with Graves' ophthalmopathy

Side effects	Immunoglobulin	P	*P* value
Number of events	2	19	0·001
Moderate			
Weight gain	0	3	
Hirsutism	0	2	
Cushingoid face	0	2	
Myalgias	0	2	
Nausea/pyrosis	0	2	
Sleeplessness	0	2	
Tiredness	0	1	
Dysmenorrhoea	0	1	
Headache	1	1	
Fever	1	0	
Major			
Diabetes mellitus	0	1	
Hypertension	0	1	
Behavioural changes	0	1	
Number (%) of patients			
With side-effects	2/21 (10)	16/19 (84)	0·0002
With major side-effects	0	2/19 (11)	

observed. The efficacy and safety of immunoglobulin treatment in GO and related myxedema has also been demonstrated [10,11]. Clinical improvement of GO and dermopathy with disappearance of lymphocytic skin infiltration and immunoglobulin deposition was noted. A parallel reduction of the titre of circulating thyroglobulin, microsomal and TSH receptor antibodies was registered. In Graves patients treated with a combination of thyrostatics and immunoglobulin, relapse rate of hyperthyroidism 1 year after stopping methimazole was 29% *versus* 44% in cases receiving methimazole alone ($P < 0·01$). As in our study, the marked decrease of antibody levels may be explained in terms of a direct and local immunomodulating effect of immunoglobulin on the

Table 3. Ophthalmological parameters of 10 patients with active Graves' ophthalmopathy before and after receiving four times a combination of i.v. immunoglobulin (1 g/kg body wt per day) and i.v. methylprednisolone (250 mg/day) for 2 consecutive days every 3 weeks

	Before	After immunoglobulin + P therapy	*P* value
Proptosis (mm),			
median	24	21	0·001
range	22–28	19–26	
Intraocular pressure in upgaze (mmHg),			
median	24	20	0·001
range	21–28	18–23	
Visual acuity,			
median	0·7	0·8	0·01
range	0·6–0·8	0·7–0·9	
Lid aperture (mm),			
median	14	12	0·005
range	12–16	11–14	
Chemosis	$n = 4$	$n = 1$	
Conjunctivitis	$n = 7$	$n = 3$	
Diplopia in primary position	$n = 7$	$n = 3$	

intrathyroid lymphocytes. With respect to the fall of microsomal antibody titre, similar results were observed in GO patients receiving cyclosporin [13].

The recent discovery in immunoglobulin preparations of anti-idiotypic antibodies against disease-associated cross-reacting idiotypes of human thyroglobulin recognizing an immunodominant α-idiotype shared by antibodies from patients with autoimmune thyroid disease and not found in antibodies from healthy subjects supports the hypothesis that i.v. immunoglobulin could be effective through anti-idiotypic suppression in patients with autoimmune diseases [14,15]. However, there is reasonable evidence that active molecules within i.v. immunoglobulin such as CD4 and other shed surface molecules from lymphocytes could be important in causing the immunomodulation. This would explain why i.v. immunoglobulin is too effective in what is after all not an antibody-mediated disease.

Immunomodulatory effects of i.v. immunoglobulin may further depend on the interaction of infused immunoglobulin with inflammatory cells and lymphocytes through Fc portions and/or interactions of i.v. immunoglobulin with circulating immunoglobulin or antigen receptors on lymphocytes through variable V regions [16–18]. Functional modulation of T lymphocytes by immunoglobulin has been demonstrated as another possible mechanism of action of i.v. immunoglobulin in an experimental model [19]. *In vitro* studies suggest that immunoglobulin has direct effects on cytokine production in T cells and monocytes/macrophages [20,21]. A prolonged elevation in levels of soluble tumour necrosis factor receptor and a marked increase in plasma levels of IL-1 receptor antagonist were observed after one bolus injection (400 mg/kg) of i.v. immunoglobulin [22]. There are also many similarities between i.v. immunoglobulin and tumour growth factor β, which has inhibitory effects on various T and B cell interactions and activities [23].

In patients with active GO, increased water content of thickened eye muscles is probably the cause of elevated T2 [24]. Reversibility of thickness and T2 in muscles with primarily elevated T2 can be explained as a therapy-induced decrease of water content. Therefore, measurement of elevated T2 might be a factor in the prediction of the reversibility of muscle thickening, and favours the choice of anti-inflammatory therapy regimens in these patients [24,25]. In this study, decrease of T2 of the eye muscles after therapy correlated significantly with the decrease of the muscle area.

In our GO patients immunoglobulin therapy was safe. The risk of transmitting viral infections with immunoglobulin, especially the newer preparations that have been treated with a solvent-detergent, is very low [26], and there has never been a documented transmission of HIV from any preparation of immunoglobulin [27]. Nevertheless, high costs and the potential risks of immunoglobulin therapy must be considered before treatment is commenced, particularly in diseases for which the benefits of therapy are not clearly established. Subcutaneous immunoglobulin which has been recently reported to be a safe, cost-effective, and convenient method of immunoglobulin administration [28], may be promising in patients with primary hypogammaglobulinaemia and autoimmune diseases.

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