The effects of radioiodine therapy on peripheral blood lymphocyte subpopulations in patients with Graves’ disease. Preliminary report

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Abstract

BACKGROUND: Treatment of Graves’ disease patients with radioactive iodide (¹³¹I) is becoming the standard therapy in an increasing group of cases but can induce alterations in immune response, like increasing levels of thyroid autoantibodies, and, in part, exacerbation of ophthalmopathy. The aim of this study was to assess the changes in peripheral blood (PB) lymphocyte subpopulations after ¹³¹I treatment of patients with Graves’ disease.

MATERIAL AND METHODS: The study was carried out in a group of 30 patients with Graves’ disease (23 f; 7 m) 49.5 ± 10.0 years of age, 26 with different subjective ocular signs like gritty sensation, increased lacrimation, orbital pain, and exophthalmos. PB lymphocyte subsets were analysed by cytofluorometry, serum concentration of TSH and fT4 were evaluated before and 6 weeks after radioiodine treatment.

RESULTS: After ¹³¹I treatment a significant increase in CD3⁺, CD4⁺, CD3⁺HLA-DR⁺ and a decrease in CD19⁺ percentages of lymphocyte subsets were found in comparison with the initial evaluation. No significant changes in percentage of CD8⁺ and NK (CD3⁻CD16⁺ CD56⁺) cells were observed during this study. A significant increase in TSH and a slight decrease in fT4 concentration took place in the 6th week after ¹³¹I application. The patients without subjective improvement of ocular signs during the therapy initially had a percentage of CD3⁺, CD8⁺ lymphocytes which was significantly lower compared with those with regression of ocular signs observed after ¹³¹I treatment.

CONCLUSIONS: The changes in PB lymphocyte subsets caused by ¹³¹I treatment of Graves’ disease confirm the involvement of acquired cellular immunity after radiation damage of the thyroid gland. The decreased initial percentage of CD8⁺ and CD3⁺ lymphocytes could help make a prediction of ocular symptoms persisting after radioiodine treatment in some patients with ophthalmopathy.

Key words: ¹³¹I, lymphocytes, Graves’ disease

Introduction

Mechanisms of acquired immunological response play a dominant role in the pathogenesis of Graves’ disease (GD). The autoimmune process is probably initiated by activation of autoreactive T lymphocytes by antigens derived from thyrocytes, such as TSH receptor (TSHR) and thyrocyte peroxidase (TPO). Intrathyroidal T lymphocytes seem to be especially involved in this process through thyroid antigen recognition and release of cytokines. Some patients with Graves’ disease develop orbital infiltrative disease and infiltrative dermathopathy. Extrathyroidal manifestations of GD have been explained by cell-mediated effector mechanisms involving cross-reacting antigens between the thyroid and orbital connective tissue, like TSHR protein expression in orbital fibroblastic preadipocytes [1]. However the spreading of autoimmunological reactivity beyond the thyroid gland and the association of Graves’ disease with other autoimmune diseases suggest a generalised immune disregulation and genetic background of the GD.

T helper cells (CD4⁺) activate B lymphocytes to autoantibodies production by interleukin-4 (IL-4) and stimulate cytotoxic T
Radioiodine kills thyroid cells by β radiation and leads to the release of antigens into the circulation; at this time a dramatic increase in cell-mediated reactivity (T cells) and in humoral-mediated reactivity (B cells and autoantibodies) to different thyroid antigens is observed. Therefore RAI treatment of hyperthyroidism could be associated with secondary immunological disturbances sharing primary autoimmune response [6].

Recent discussions have focused on the possible association of 131I therapy of Graves’ disease with the development or progression of thyroid-associated opthalmopathy (TAO) [7,8].

Several large retrospective studies have found no effects of radioactive iodine therapy on the clinical course of eye disease [9,10], whereas other investigators observed a worsening (exacerbation) of TAO after RAI therapy [11]. These latter reports suggest a role of circulating autoreactive activated T cells in the development of TAO in the course of radioiodine treatment of Graves’ disease patients. But whether it is a primary (associated with immunological response) or secondary (influence of radioiodine therapy on the clinical course of eye disease) or secondary (influence of RAI treatment) event has not yet been resolved.

The main goal of this study was to assess the changes in peripheral blood lymphocyte (PBL) subpopulations after 131I treatment of patients with Graves’ disease as manifestations of immunological response activation.

The additional aim was to find prognostic factors of TAO based on the above immunological parameters by comparing initial (before 131I treatment) values of PBL subpopulations, depending on the regression or progression of subjective ocular symptoms after RAI treatment.

Material and methods

The study was carried out on a group of 30 patients with Graves’ disease (23 f, 7 m; 49.5 ± 10.0 years of age) recognised from typical clinical and laboratory symptoms. 23 of them had different subjective ocular signs such as gritty sensation, increased lacrimation, orbital pain and exophthalmos suggesting ophthalmopathy development before 131I treatment.

7 patients had not presented any subjective ophthalmopathy symptoms before the study. In 3 of them symptoms of TAO appeared after 131I treatment. So finally 26 examined persons had subjective signs of TAO during the study.

Figure 1. Subsets of CD4+ and CD8+ peripheral blood lymphocytes in cytofluorometry: B1 – CD4–CD8+, B4 – CD4+CD8–.
served in total group (n = 30) in comparison with the initial evaluation: (median ± quartiles values) 69.8 (67.9–73.7)% vs. 74.2 (71.7–75.8)%, p < 0.0001 for CD3+, 44.6 (38.7–47.4)% vs. 48.5 (44.6–51.6)%, p < 0.00001 for CD4+ and 3.5 (3.5–7.2)%, p < 0.005 for CD3+HLA-DR+. Contrary, significant decrease in percentage of CD19+ cells was noticed during the study: 13.3 (10.3–15.7)% vs. 9.3 (7.9–13.0)%, p < 0.00001.

No significant changes in the percentage of cytotoxic (CD8+) and NK (CD3–CD16+CD56+) cells were observed during this study in whole group (Fig. 3).

In patients with present ocular symptoms (n = 26), lymphocyte subsets were compared between groups with and without ocular signs improvement after RAI.

The patients with worsening or no regression of TAO (n = 7) had initial percentages of CD3+ and CD8+ lymphocytes significantly lower in comparison to the patients with subjective improvement (regression) of TAO (n = 19) after 131I treatment (Fig. 4):

67.9 (60.6–71.9)% vs. 70.6 (66.6–72.9)%, p < 0.05 for CD3+ and 24.8 (18.5–29.3)% vs. 30.9 (26.3–37.4)%, p < 0.05 for CD8+ subsets respectively.

Discussion

Our study indicates distinct immunological response involvement after 131I administration in patients with hyperthyroidism of Graves’ disease.

The relative increase of CD4+ (Th) population seems to be a dominant feature in the picture of immunological changes 6 weeks after 131I application. It is associated with a relative increase in CD3+HLA-DR+ lymphocytes which correspond to activated T cells.

The parallel increase of both T cell subsets suggests that it would be the same lymphocyte population but further investigations are needed. These events were associated with an adequate decrease in CD19+ (B cells) population, which is either a relative change or results from their redistribution beyond blood vessels to secondary lymphoid organs, like lymphonodules and spleen or the affected thyroid gland. Changes in PB lymphocyte subsets caused by 131I treatment of Graves’ disease observed in our study are similar to results of other investigators, showing the involvement of acquired cellular immunity after radiation damage of thyroid gland [4]. Lack of any response in CD8+ cytotoxic lymphocytes and NK cells suggests that they do not participate directly in immunological disturbances after radioiodine therapy. It is likely that 131I transiently activate Th2 cell-mediated processes with increase in IL-4 production and B cells stimulation next to non-specific inflammatory processes with increase in IL-6 and TNFα production [13].

Different retrospective and prospective studies have produced conflicting data on the effect of the radioiodine therapy on the development or exacerbation of TAO [14, 15]. Some investigators conclude that the appearance or worsening of ophthalmopathy occurs more often in radioiodine treated patients than in antithyroid drugs treated patients but this is often transient and can
be prevented by the administration of prednisone [16]. In our study we observed subjective ocular symptoms in 26 patients during the study. Improvement (progression) of TAO was noticed in 19 patients. Appearance or maintenance of TAO in 6th week after RAI treatment was found in 7 persons.

Analysis of orbital T cell infiltration indicates that CD4+ lymphocytes dominate in the retrobulbar space of patients with TAO [5, 17]. Directly comparing those data with results obtained in peripheral blood could produce interpretation problems. We have not observed any differences in CD4+ population which could reflect alterations in orbital infiltrates. But significantly lower percentages of CD3+ and CD8+ lymphocytes in the group of patients with persisted subjective ocular signs after RAI treatment which were observed before 131I administration in comparison to the group with improvement of ophthalmopathy could express impairment mechanisms of immunological suppression exerted by some CD8+ T cell clones [3]. According to this hypothesis, the decreased percentages of CD3+ and CD8+ lymphocytes could help make a prediction of ocular symptoms persisting after radioiodine treatment in patients with Graves’ disease.

Conclusions

The changes in peripheral blood lymphocyte subsets caused by 131I treatment of Graves’ disease indicate involvement of acquired cellular immunity after radiation damage of thyroid gland. The decreased initial percentage of CD8+ and CD3+ lymphocytes could help make a prediction of ocular symptoms persisting after radioiodine treatment in some patients with ophthalmopathy.

References