Optimization of medical therapy in patients with acromegaly

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Acromegaly is a chronic multi-organ disease that negatively affects the quality and life expectancy of patients. The leading cause of the disease is GH-secreting pituitary tumors, the pathomorphological structure of which determines secretory activity, tumor growth rate, clinical course, and sensitivity to the proposed therapy. Taking into account the morphological heterogeneity of somatotrophic tumors, the search for and stratification of potential predictors, which make it possible to forecast the clinical course of the disease and the effectiveness of the treatment, is especially relevant nowadays.

The aim of this work is a clinical and morphological comparison between the effectiveness of long-term medical therapy (MT) with somatostatin analogs of the first-generation (SA1) and the immunophenotypic features of densely and sparsely granulated somatotroph adenomas (DGA and SGA) identified using immunohistochemical analysis (IHA).

Materials and methods: 65 patients (23 m) with acromegaly were included in the study. The average passport age was 45.0±13.3 years, the age of diagnosis was 41.6±13.7 years [M(s)]. All patients underwent transsphenoidal adenomectomy followed by immunohistochemical examination of fragments of the removed tumor as the first line of treatment. According to the results of IHA, DGA was detected in 27 patients, and SGA – in 38 patients. Due to the continued postoperative activity of the disease, 47 patients (16 with DGA and 31 with SGA) were prescribed secondary MT with prolonged forms of SA1 (lanreotide 120 mg / 28 days and octreotide at a dose of 10-30 mg / 28 days). The average duration of pharmacotherapy was 21±16 months. To assess the effectiveness of MT, IGF-1 index (II) [the value of exceeding the level of IGF-1 of the upper age norm (IGF-1 / UAN)] was used. The presence of biochemical remission was recorded with the value of II <1. The values of IGF-1 decrease from baseline after 3 and 6 months of SA1 treatment were compared with IGF-1 and II values after 12 months of treatment and at the last visit, as well as with the duration of ineffective and effective treatment. In a subgroup of 18 patients who did not receive SA1, postoperative activity was maintained in 3 out of 11 (27%) patients with DGA and in 4 out of 7 (57%) patients with SGA, and was associated with a large volume of adenoma. The tumor immunophenotyping data were used for retrospective clinical and morphological comparison and confirmation of the prognostic significance of the results of short-term treatment.

Results: DGAs differ in the pronounced expression of AT to GH, the 2nd subtype (s/t) of somatostatin receptors (SSR), as well as a greater difference and ratio between the 2nd and 5th s/t SSR. SGA are characterized by relatively low expression of the 2nd and increased expression of the 5th s/t SSR, a high percentage of cells with AT to cytokeratin and elevated values of the proliferative index Ki-67 (Fig. 1). Comparative analysis showed that, with similar indicators of secretory activity, patients with DGA are characterized by a relatively late the age of the diagnosis and the smaller initial size of the pituitary adenoma. There were no intergroup gender differences, the proportion of men in both groups was 35-36%. The overwhelming number of patients with DGA showed good sensitivity to MT SA1 with the achievement of early and persistent biochemical remission. A direct correlation was found between the magnitude of the decrease in the level of IGF-1 after 3 months of treatment and the expression of the 2nd s/t SSR (r=0.48; p=0.001). It is shown that the duration of effective MT SA1 directly correlates with the difference and the score ratio between the 2nd and 5th subtypes of SSR (r=0.51; p=0.004 and r=0.53; p=0.002, respectively). On the contrary, patients with SGA were distinguished by an early age of diagnosis, large pituitary adenoma with extrasellar spread and invasive growth (Fig. 2). The use of SA1 was manifested by a low level of suppression of the level of IGF-1 after 3, 6 and 12 months of treatment, as well as the absence of biochemical remission at the last visit (Fig. 3, 4). At the same time, the dose of prolonged octreotide used was significantly higher than 27±6 versus 20±7 mg/28 days (p=0.009). According to the results of multiple regression analysis, the most significant independent signs associated with the percentage decrease in the level of IGF-1 after 3 months of SA1 treatment are: 1. duration of effective MT SA1 (months) (beta=0.56; p=0.034); 2. severity of expression of the 2nd s/t SSR (beta=0.42; p=0.011); 3. the difference in the expression scores of the 2nd and 5th s/t SSR (beta=0.39; p=0.015); 4. final level of IGF-1 index during treatment (beta=-0.45; p=0.006).

Fig. 1. Immunophenotypic characteristics of DGA and SGA

	% cells with AT to GH	% cells with AT to CAM 5.2	Expres-sion of the 2nd s/t SSR (scores)	Expres-sion of the 5th s/t SSR (scores)	Difference in the expression scores of the 2nd and 5th s/t SSR	Score ratio between the 2nd and 5th s/t SSR	Ki-67 (%)
DGA	75 (17)	66 (18)	11 (2)	4 (3)	6,5 (2,6)	4,0 (3,0)	4,5 (2,6)
SGA	46 (20)	88 (15)	6 (3)	6 (3)	1,1 (4,2)	1,3 (1,2)	12,3 (17,8)
P=	0,000	0,0000	0,0000	0,0122	0,0000	0,0000	0,0277

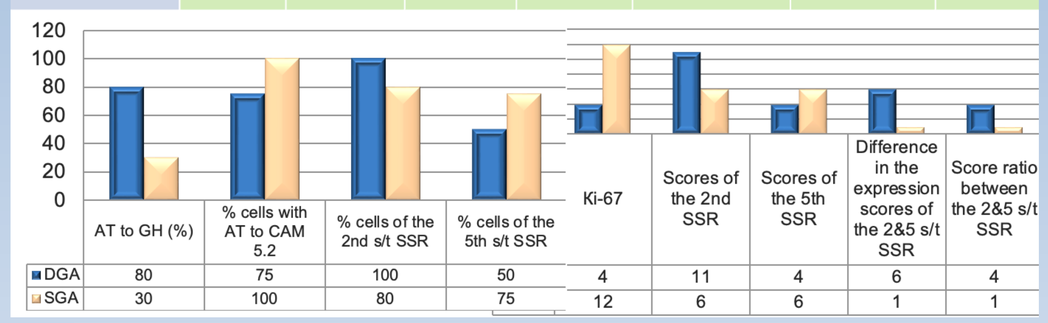


Fig. 3. Efficacy of SA1 treatment in various types of somatotrophic adenomas

Fig. 2. Clinical and morphological comparisons

M (s)	N (м)	Passport age (years)	Age of diagnosis (years)	GH (ng/ml)	Baseline of IGF-1 index	Volume of tumor (ml)	Final level of IGF-1 index during treatment
DGA	27 (9)	49 (13)	47 (12)	25 (30)	2,7 (0,9)	2,5 (4,8)	0,9 (0,4)
SGA	38 (14)	42 (14)	36 (14)	34 (54)	2,7 (0,9)	9,1 (11,9)	1,7 (0,8)
P 1-2	65	0,0245	0,0154	-	-	0,0083	0,0000

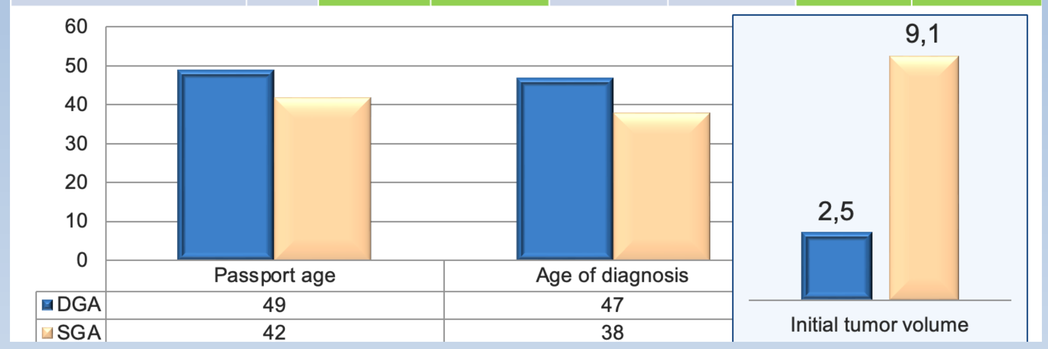
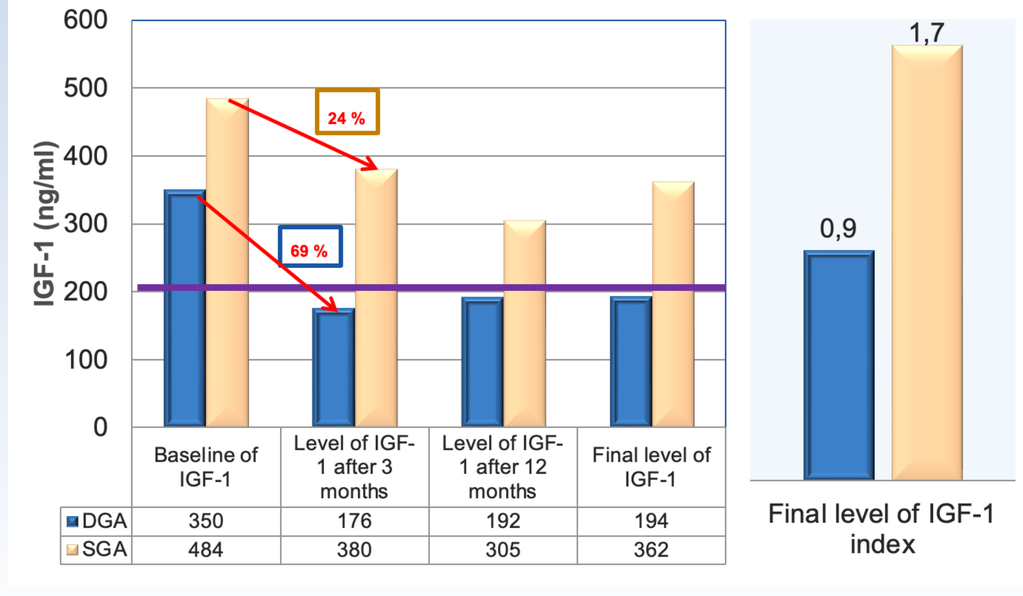
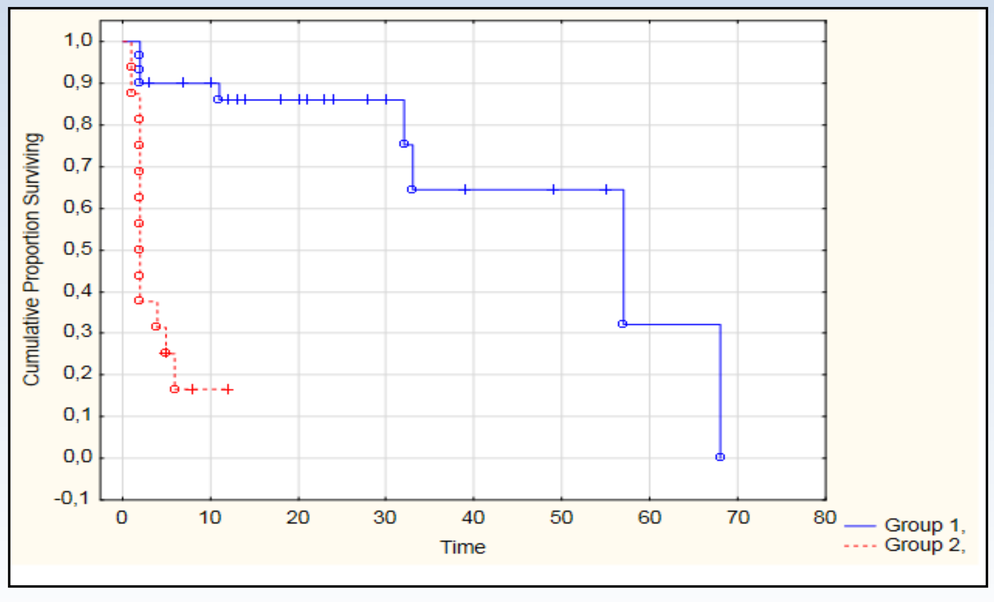


Fig. 4. The time to achieve treatment control depending on the tumor morphotype (Gr.1 – SGA, Gr. 2 – DGA)





Conclusion:

1. The presence of fundamental clinical and morphological differences between DGA and SGA was confirmed, as well as the need for a differentiated approach to secondary MT of patients with acromegaly.
2. The magnitude of the decrease in the level of IGF-1 after 3 months of treatment correlates with the severity of expression of the 2nd subtype of SSR and can be used as a cut-off point for predicting the effectiveness of long-term primary or secondary therapy for SA1.