What is the best parameter to decide the initial dose of depot leuprolide acetate in girls with idiopathic central precocious puberty?

Dogus Vuralli[1], Ayfer Alikasifoglu[1], Irem Iyigun[2], Dicle Canoruc[2], Alev Ozon[1], Nazli Gonc[1], Nurgun Kandemir[1]
[1]Division of Pediatric Endocrinology, [2]Department of Pediatrics, Hacettepe University Medical School, Ankara, Turkey.

INTRODUCTION AND OBJECTIVE

Formulations and doses of GnRH analogues used to treat idiopathic central precocious puberty (iCPP) may vary with clinician preference or local approvals. Aim of this study is to define factors that affect initial depot leuprolide acetate (LA) dose which suppress hypothalamo-pituitary-gonad (HPG) axis in girls with iCPP.

SUBJECT AND METHODS

A total of 220 girls receiving LA for iCPP were included. LA is started in the dose of 3.75 mg/28 days, and suppression is examined using GnRH test at the 3rd month of treatment. Dose of LA is increased to 7.5 mg/28 days in those who fail the test (peak LH>2 IU/L). Higher dose is similarly tested for suppression of HPG 3 months later. We retrospectively compared clinical and hormonal characteristics of the two populations whose HPG axis was suppressed with low vs high dose of LA. ROC curves were used to determine thresholds for factors (age, body weight [BW], BMI, BMI-SDS, basal LH and estradiol, peak stimulated LH) with an impact on the suppressing dose of LA. We analyzed whether thresholds differentiate the two populations with low or high dose LA, using univariate logistic regression. Pubertal stages were grouped into early (Tanner 2&3) vs advanced (Tanner 4 &5), and impact of pubertal stages were also analyzed. Significant factors in univariate analysis were reevaluated in multiple logistic regression.

RESULTS

Peak stimulated LH in 88.6% of the patients was <2 IU/L under treatment with 3.75mg LA. Age did not differ between the two different dose populations. The best threshold values that differentiate the two doses were 36.2 kg for BW (AUC:0.934), 20.7 kg/m^2 for BMI (AUC: 0.964), +1.64 for BMI-SDS (AUC:0.914), 1.5 mIU/mL for basal LH (AUC:0.71), 41pg/ml for basal estradiol (AUC:0.898), 17.6 mIU/mL for peak stimulated LH (AUC:0.710) (p<0.001). Univariate analysis indicated BW, BMI and BMI-SDS as well as advanced stage of puberty were associated with higher dose of LA (p <0.001, <0.001, <0.001, 0.02, respectively). Basal LH, estradiol and stimulated LH peak did not differentiate necessity for low or high dose. Multiple logistic regression showed that BW, BMI, and BMI-SDS above the thresholds indicated requirement of high dose LA (p<0.001).

Table 1. Initial clinical and laboratory characteristics of the patients receiving LA at a dose of 3.75 mg /28 days and at a dose of 7.5 mg/28 days

	3.75 mg LA	7.5 mg LA	p value
Age at diagnosis (years)	8.2±1.0	8.3±0.5	0.535
Bone age (BA) (years)	10.2±0.9	10.3±0.9	0.422
Body weight (kg)	32.1±6.1	44.9±7.1	<0.001
BMI (kg/m2)	18.7±3.3	27.5±8.4	<0.001
BMI-SDS	1.1±1.2	2.4±1.2	<0.001
Height (cm)	135.2±9.2	136.2±10.0	0.172
Height-SDS	1.1±1.2	1.1±1.3	0.991
Height-SDS for BA	-0.6±1.0	-0.5±1.2	0.833
Basal FSH (IU/L)	4.5±2.1	5.3±2.5	0.121
Basal LH (IU/L)	1.2±0.7	1.9±1.2	<0.001
Basal Estradiol (pg/ml)	30.6±14.4	52.5±9.1	<0.001
Peak stimulated LH (IU/L)	11.7± 5.0	16.7±9.4	<0.001

Table 2. Evaluation of the factors affecting treatment dosage based on a univariate logistic regression analysis

Variables	Odds Ratio	95% CI		*P*-value
Body weight ≥ 36.2 kg	1,619	1,330	1,914	<0,001
BMI ≥ 20.7 kg/m^2	1,941	1,515	2,488	<0,001
BMI-SDS ≥ 1.64	2,165	1,735	2,690	<0.001
Basal LH ≥ 1.5 IU/L	1,084	0,898	1,309	0,401
Basal Estradiol ≥ 41 pg/ml	1,004	0,995	1,014	0,330
Peak stimulated LH ≥ 15.7 IU/L	1,240	0,742	1,726	0,421
Pubertal Stage (Advanced vs early)	2,516	0,877	7,215	0,020

Table 3. Evaluation of the factors affecting treatment dosage based on a multivariate logistic regression analysis

Variables	Odds Ratio	95% CI		*P*-value
Body weight ≥ 36.2 kg	1,821	1,242	3,214	<0,001
BMI ≥ 20.7 kg/m^2	2,310	1,285	4,043	<0,001
BMI-SDS ≥ 1.64	2,524	1,126	4,321	<0,001
Pubertal Stage (Advanced vs early)	2,767	0,455	16,846	0,269

CONCLUSION

Low dose monthly injections of LA is an effective treatment in majority of girls with iCPP, however higher initial dose may be preferred in patients with a body weight ≥36.2 kg or BMI≥20.7 kg/m^2 for effective suppression of HPG axis.

REFERENCES

1. Carel JC, Eugster EA, Rogol A, Ghizzoni L, Palmert MR, Antoniazzi F, Berenbaum S, Bourguignon JP, Chrousos GP, Coste J *et al*: **Consensus statement on the use of gonadotropin-releasing hormone analogs in children**. *Pediatrics* 2009, **123**(4):e752-762.
2. Bertelloni S, Baroncelli GI: **Current pharmacotherapy of central precocious puberty by GnRH analogs: certainties and uncertainties**. *Expert opinion on pharmacotherapy* 2013, **14**(12):1627-1639.

57ESPE 3--RFC9
Pituitary, neuroendocrinology and puberty
Dogus Vuralli
Poster presented at: 57th ESPE 2018 Meeting ATHENS GREECE 27-29 September 2018
PosterSessionOnline.com