Therapeutic effect of chimeric molecule targeting for both somatostatin and dopamine receptors on GH secreting pituitary adenoma

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The Master's Thesis
submitted to the Department of Medical Science,
the Graduate School of Yonsei University
in partial fulfillment of the requirements for the degree of
Master of Medical Science

Jean Kim

December 2017

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The Graduate School
Yonsei University

December 2017

ACKNOWLEDGEMENTS

I am grateful to my supervisor Professor Eun Jig Lee for his guidance and support throughout my study. This study would not have been possible without his assistance and cooperation. I also would like to express my sincere gratitude to my reviewers, Professor Ho Sung Kim and Cheol Ryong Ku who had the patience to read my thesis and provided helpful feedback so, I could improve and complete the paper. I am thankful to my laboratory colleagues for their supports because I learned not only laboratory techniques and knowledge but also the fact that working together could bring out a better result in experiments.

Lastly, I am thankful to my grandmother for her unwavering love and my parents for their support. Their patience and support helped me stay strong and steadfast while working on this paper.

Jean Kim

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ABSTRACT

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Acromegaly is a rare disease that is mainly caused by growth hormone (GH) secreting pituitary tumor. The medical treatment is not only costly but also sometimes unresponsive in some patients. There are efforts to develop a new drug that has better effectiveness. BIM23B065 is a chimeric molecule that works on both somatostatin receptors and dopamine receptors. In this study, the effect of chimeric molecule was investigated and compared to somatostatin receptor analogue and dopamine agonist drugs. The *in-vitro* study was carried out with GH3 cell. It decreased GH release to medium, and phosphorylation of ERK 1/2 and CREB was down regulated up to 22% and 26%. With the animal model of GH secreting pituitary adenoma, the dosage and treatment duration were tested, and the effect of drug was further investigated through analysis of IGF-1 hormone

level change in before and after treatment. The IGF-1 level was decreased to 50% after one month of treatment via osmotic pump implant. Based on MRI results, the tumor size decrement was visually observed after treatment with the chimeric molecule. Therefore, the novel chimeric molecule was proven to be effective in decrease of IGF-1 and GH level. Its effect should be explored further so that the drug could become another choice of drug for treatment of acromegaly.

Key words: GH-secreting pituitary adenoma, chimeric molecule, IGF-1, growth hormone, BIM23B065, preclinical study

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I. INTRODUCTION

Acromegaly is a disease characterized by chronic growth hormone (GH) and insulin-like growth factor-1 (IGF-1) hypersecretion[1,2]. It is mostly caused by a GH-secreting pituitary adenoma. The surgical resection of the pituitary adenoma is the first choice of treatment in most cases; however, it restores IGF-1 level in less than 60% of cases[1,2]. In patients unsuitable or unwilling to undergo surgery, or in whom surgery fails to normalize plasma GH and IGF-1 concentrations, pharmacological interventions have been used[1,2].

Somatostatin analogues and dopamine agonists are the representative medications for GH secreting pituitary adenoma[3,4]. With the background that GH secreting pituitary adenoma has prominent expression of somatostatin receptors and dopamine receptor, those target therapeutics have been widely applied in acromegalic patients[3-6]. However, they have relatively low effectiveness on controlling the biochemical activities and mass size[2,7]. Somatostatin analogs (SA)

such as lanreotide have been consistently shown to reduce hormonal hypersecretion in most patients and to normalize it depending on the level of hormone[1-3]. Dopamine agonists such as cabergoline may be effective in up to 30% of patients only with mildly elevated plasma IGF-1 concentrations[1,2]. Somatostatin and dopamine agonist are the major target therapy agent for the treatment of acromegaly however, not only the drug is costly but also its effect has continued to show unresponsiveness as well as resistance to drug[8]. Therefore, there is a need for alternative pharmacological approaches to the treatment of acromegaly.

Recently, novel chimeric molecules consisting of a somatostatin analogue and a dopamine agonist have been synthesized, is currently being tested[9-11]. The chimeric molecule used in this study works on both somatostatin receptor 2 and 5 as well as dopamine receptor subtype 2; thus, it is a promising candidate for the treatment of acromegaly and GH-secreting pituitary adenoma.

The main purpose of this study was to confirm the effect of BIM23B065 on GH-secreting pituitary adenoma and procide evidence for its approval as a new therapeutic option for acromegaly. This chimeric drug is expected to overcome the low rate of responsiveness in previously used drugs and be more efficient in the management of hormone levels including IGF-1 and GH. Results of this preclinical study provides a solid basis for conducting future clinical trials.

II. MATERIALS AND METHODS

1. Ethical Statement

The Institutional Animal Care and Use Committee (IACUC) of Yonsei University Health System (approval number: 2015-0403) reviewed and approved all animal procedures. Experiments were carried out under strict guidance of the Association for Assessment and Accreditation of Laboratory Animal Care. Animals were kept under standard conditions including light with 12-hour light and 12-hour dark cycle of which lights were turned on at 07:00 h and temperature ranged 22–24℃. Animals always had free access to standard rodent chow and water except for intended fasting for the experiment. All mice were maintained in accordance with American Association of Laboratory Animal Care guidelines.

2. Cell culture

For in-vitro experiment, a rat pituitary tumor GH3 cell (American Type Culture Collection) was used. GH3 cell line was grown in Dulbecco's modified Eagle's medium (DMEM)/high glucose media with 10% FBS and penicillin-streptomycin solution (Hyclone Co., Logan, UT, USA). Cells were kept in a culture incubator that maintained the atmospheric condition of 37℃ and 5% CO_2. Media was changed within 3 days and the cell line was split with trypsin/EDTA every week.

3. Experimental animals

An animal model that was used in this study was previously developed mouse model, which expressed phenotype of GH secreting pituitary adenoma[7]. Somatotroph specific aryl hydrocarbon receptor interacting protein (AIP) knock-

out (sAIPKO) mouse model was made using rGHp-Cretg/+; Aiplox/lox mice[12]. All animals in this study were over 40 weeks old male because most sAIPKO mice developed GH secreting pituitary adenoma as it aged (above 40 weeks).

4. Cell proliferation assay

To test the toxicity of the drug to cell, MTS assay was performed. 100μl of GH3 cells will be seeded in a 96-well plate in a ratio of $4x10^3$ cells/well. After 24 hours of incubation in 37℃, 5% CO_2 incubator, growth media was changed with DMEM/high without serum for starvation. After 12 hours, medium treated with three different drugs including lanreotide, cabergoline, BIM23B065 were prepared in different concentrations. The control group was treated with DMSO. After treated with drugs, cells were grown for 24, 48 and 72 hours in the incubator.

MTS solution (Promega, Madison, WI, USA) was diluted in a ratio of 150μL/1ml media. The cells were treated with MTS media for 1 hour and 30 minutes in the incubator. Using spectrophotometer, the optical density was observed under 495nm.

5. GH and IGF-1 ELISA

Media taken from the cell culture was tested for GH level change before and after treatment of drugs. To see the drug effect on normalizing growth hormone and IGF-1 levels in animal model, blood serum samples from before and after treatment were also tested. For measurement of growth hormone and IGF-1, Rat/Mouse Growth Hormone ELISA Kit 96-Well Plate (Millipore, Billerica, MA, USA) and Mouse IGF1 ELISA Kit (Abcam, Cambridge, UK) were used for and performed according to the manufacturer's instructions.

6. Western blot

Before treating with drugs, cells were seeded and stabilized for 24 hours. After treatment of drugs for 15 minutes, plates were washed twice with 1x DPBS (Dulbecco's Phosphate-Buffered Saline).

Samples plates were kept on ice from this moment and treated with protein lysis buffer, which is composed of 10% glycerol, 50mM Na3VO4, 100mM NaF, 100mM phenylmethylsulfonyl fluoride, and 100mM dithiothreitol mixed in RIPA buffer. Using a cell scraper, cells were collected into 1.5ml Micro centrifuge tubes and kept on ice for 1 hours with frequent mixing in between. Samples were then centrifuged for 20 minutes in 14,000rpm and the supernatant will be transferred to new EP tubes.

Concentration of protein were measured by running a Bradford assay. Protein concentrations will be set to 50μM for all samples. Then, samples were prepped with 10% SDS-PAGE buffer and denatured in a heating block at 95℃ for 5 minutes.

Proteins were separated by sizes using a gel electrophoresis and transferred to Immoblion PVDF membrane by wet transfer technique. Obtained membranes were blocked with 5% skim milk for 1 hour to prevent non-specific binding with antibodies. Targets included biomarkers that are involved with cell proliferation and GH secretion. First, antibody of interest were diluted to 1:1000 ratio and the membrane was sealed with the antibody solution overnight in 4℃. The membrane was washed in 1x TBS-T solution and reacted with secondary antibody in ratio of 1:4000 for another hour at room temperature. After TBS-T washing, proteins on membrane were detected using a West Save Up Western Blot detection kit (AbFrontier #LF-QC0101) on ECL film.

7. Osmotic pump implantation

Animals were confirmed as knock-out model by genotyping. The dosage had to be decided for the new chimeric molecule drug. Therefore, three different dosages of the drug were tested on sAIPKO mice. Each group had 4 animals as well as vehicle group thus, total 16 animals that were over 40-week old male.

Using Alzet mini-osmotic pumps (Durect co, Cupertino, CA, USA), the drug was delivered for 7 days. Preparation of osmotic pump was followed according to the manufacturer's protocol. The drug concentration was calculated based on animals' weight individually. For implantation surgery, animals were undergone anesthesia using isoflurane. After the blood was taken via retro-orbital bleeding, the pump was implanted under the epidermis on dorsal posterior side of animal as the incision wound was clipped. Blood glucose level and weight were measured daily to observe animals condition.

After the concentration was set, four groups of animals including vehicle, lanreotide, cabergoline and the chimeric molecule were tested for a month. The test concentration of lanreotide was set at the same molar concentration as BIM23B065 and the cabergoline concentration was set based on information from previously done animal study[13,14]. The procedure and protocols were the same as the previous experiment except for the pump type and the monitoring frequency. The pump type was changed to 14-day duration so that the pump was changed to a newly prepped pump after 2 weeks. In addition, animal's condition was monitored every other day.

Lanreotide and BIM23B065 were provided by IPSEN (Boston, MA, USA) and cabergoline was purchased at Dongkoo Bio&Pharma (Seoul, South Korea).

8. MRI

All MRI experiments were performed on a 9.4T Bruker BioSpec 94/20 USR small animal imaging system (Bruker BioSpin MRI GmbH, Ettlingen, Germany) equipped with 1H mouse body coil. The T2-weighted MRI scan were performed, and tumor size was measured using OsiriX DICOM viewer before and after the treatment of the chimeric molecule. The tumor volume was estimated by the equation of which tumor volume is (length x width^2)/2^{15}. All procedures were approved by the Animal Care and Use Committees at Yonsei University College of Medicine.

9. Statistical analyses

Statistical analysis was performed using Microsoft excel. Results were expressed as mean ± SEM of results from three independent experiments with similar patterns. Differences were assessed by ANOVA.

III. RESULTS

1. Proliferation assay

In GH3 cells, the half maximal inhibitory concentraton (IC50) was measured to determine the effect of the chimeric molecule as well as positive controls including cabergoline and lanreotide. After 72 hours of drug treatment, the cell population decreased to 43% at 250μM BIM23B065. Cell viability decreased to 53% and 49% after 72 hours of treatment of 250μM lanreotide and 15μM cabergoline, respectively (Fig. 1A).

2. CREB and ERK 1/2 phosphorylation change

After the proliferation assay, IC80 of each drug was used to see how drugs had effect on GH3 cells by checking CREB and ERK 1/2 phosphorylation. After 15 min of treatment with each drug, cells were harvested and prepared for protein lysis.

As a result, phosphorylation of CREB was decreased about 26% with the chimeric molecule treatment showing the most decreased among treatment groups. CREB phosphorylation decreased about 16% and 18% in Lanreotide and the mixture treatment respectively. Cabergoline decreased CREB phosphorylation by 9%. BIM23B065 and lanreotide also down-regulated p-ERK 1/2 by 22% compared to control. However, cabergoline and combination of lanreotide and cabergoline up-regualted p-ERK level by 14% compared to control. (Fig. 1C).

3. Growth hormone in cell medium

After treatment with each drug groups based on the result of proliferation test information, the media at 48 hours was used to test the level of growth hormone change. When comparing with the vehicle, GH level in media decreased in all drugs. It decreased by 3% with lanreotide. Cabergoline showed the greatest decrement about 13%; the combination of cabergoline and lanreotide exhibited a result similar to that of cabergoline. BIM23B065 also decreased GH level in the medium by about 10% (Fig. 1B).

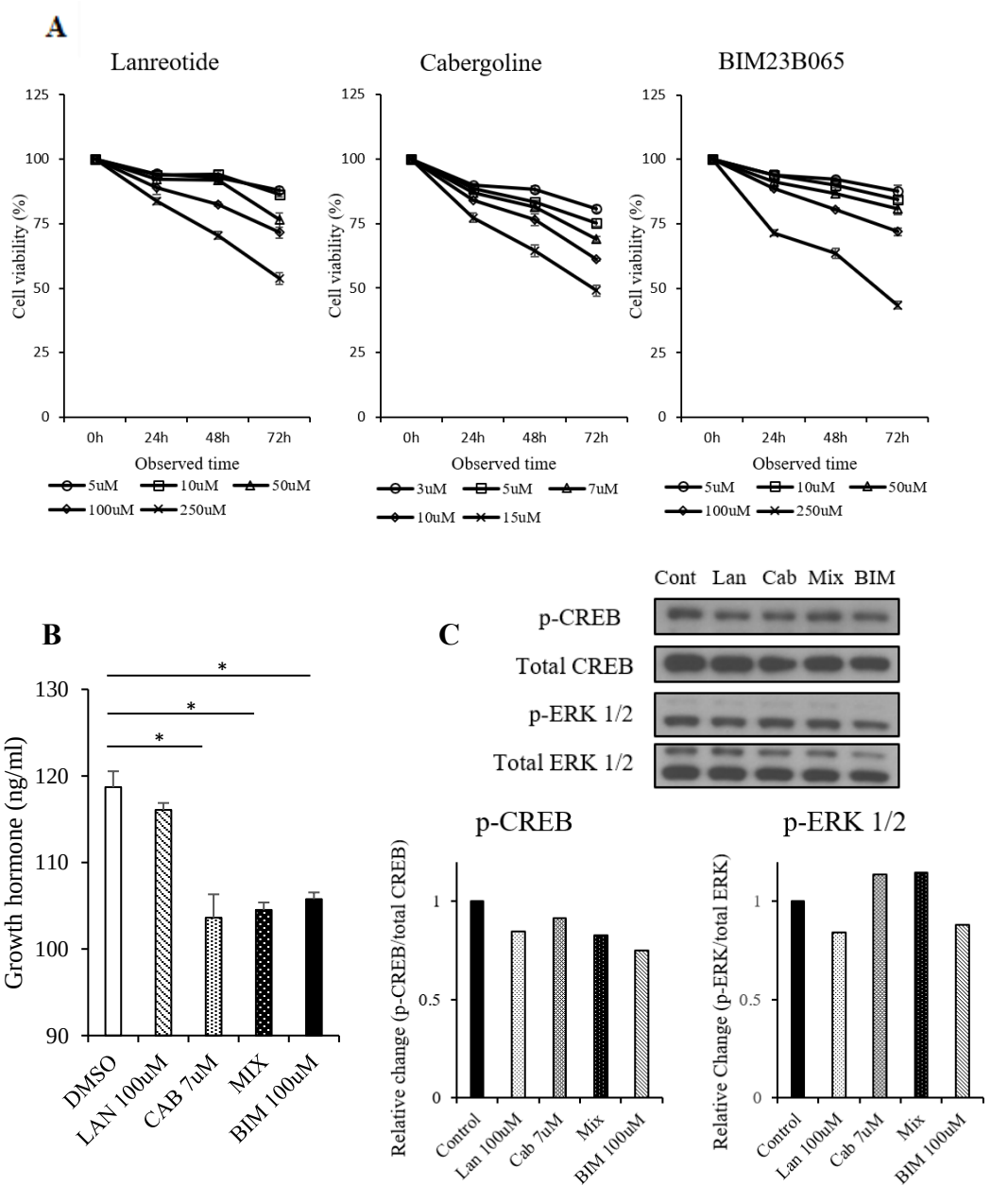

Figure 1. Effects of lanreotide, cabergoline and BIM23B065 on GH3 cell. Proliferation test **(A)**. Growth hormone release change in medium after 48 hours of treatment **(B)**. * indicates p-value < 0.05. p-CREB and p-ERK 1/2 change after 15 minutes of drug treatment (C).

4. Effects of BIM23B065 in sAIPKO mouse by different concentrations0

sAIPKO mice that were 40 weeks or older were used because most tumor incidences are reported at this age[7]. Because sex affects the onset of pituitary adenoma, female mice were excluded from the experiment, and the effect of estrogen was avoided[7].

There was no scientific research information about this chimeric molecule tested on the animal model of GH-secreting pituitary and adenoma. Thus, BIM23B065 was evaluated at 3, 4.5, and 6 mg/kg/day based on discussion with IPSEN Pharmaceutical Co.

After the 7-day experiment, most animals showed decreased IGF-1 level. All drug treated groups showed decrement of IGF-1 level after the treatment. The hormone level decreased more as the concentration of the drug was increased. Compared to the control group, IGF-1 level decreased by 10% after treatment at a dose of 3 mg/kg/day. It decreased by 20% at doses of 4.5 and 6 mg/kg/day (Fig. 2A).

body weight and blood glucose level remained constant during the treatment (Fig. 2B and C).

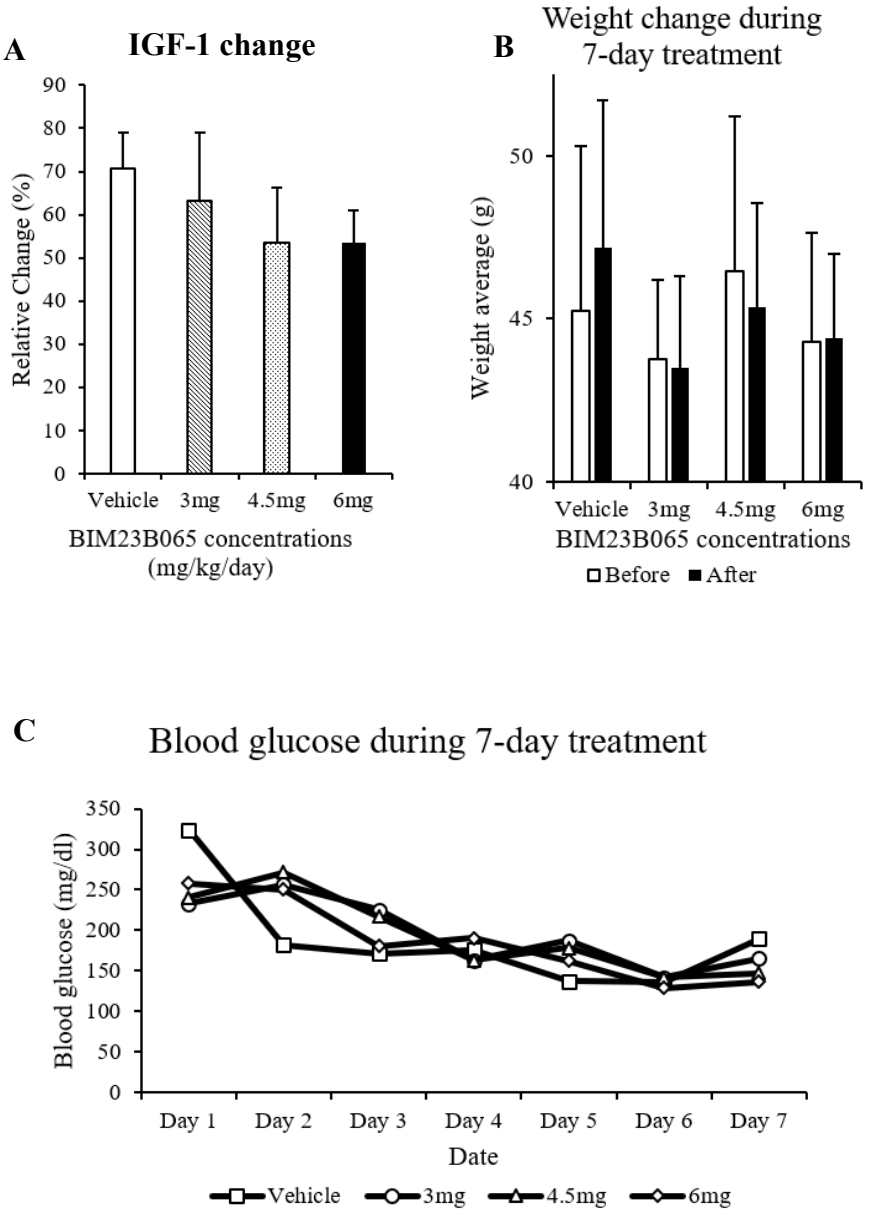

Figure 2. 7-day treatment of BIM23B065 with different concentrations. IGF-1 level change in each group after the treatment **(A)**. Weight change before and after the treatment **(B)** and daily blood glucose level record during the treatment **(C)**.

5. 4-week treatment of BIM23B065, lanreotide and cabergoline

Going through insertion and removal surgeries of pump within 7 days could have been stressful to the animals. To reduce stress as much as possible, the pump type was changed to 14-day duration instead of 7-day duration. The maximum drug concentration that could be used for the 14-day duration model was 3mg/kg/day since higher drug concentration would not completely dissolve in the vehicle solution. To examine longer exposure to the drug, mice were treated for four weeks with vehicle, BIM23B065, lanreotide, or cabergoline. Lanreotide was used at the same molar concentration as BIM23B065; therefore, its dosage was set to 2.257mg/kg/day. Cabergoline concentration was set to 0.82mg/kg/day based on previous reports.

After a month of treatment, IGF-1 levels decreased by 1-% in the vehicle control group compared to pre-treatment level. It decreased by 18%, 50%, and 49% in the cabergoline, lanreotide, and BIM23B065 groups (Fig. 3A). No change in body weights and blood glucose levels were observed throughout the experiment (Fig. 3B and C).

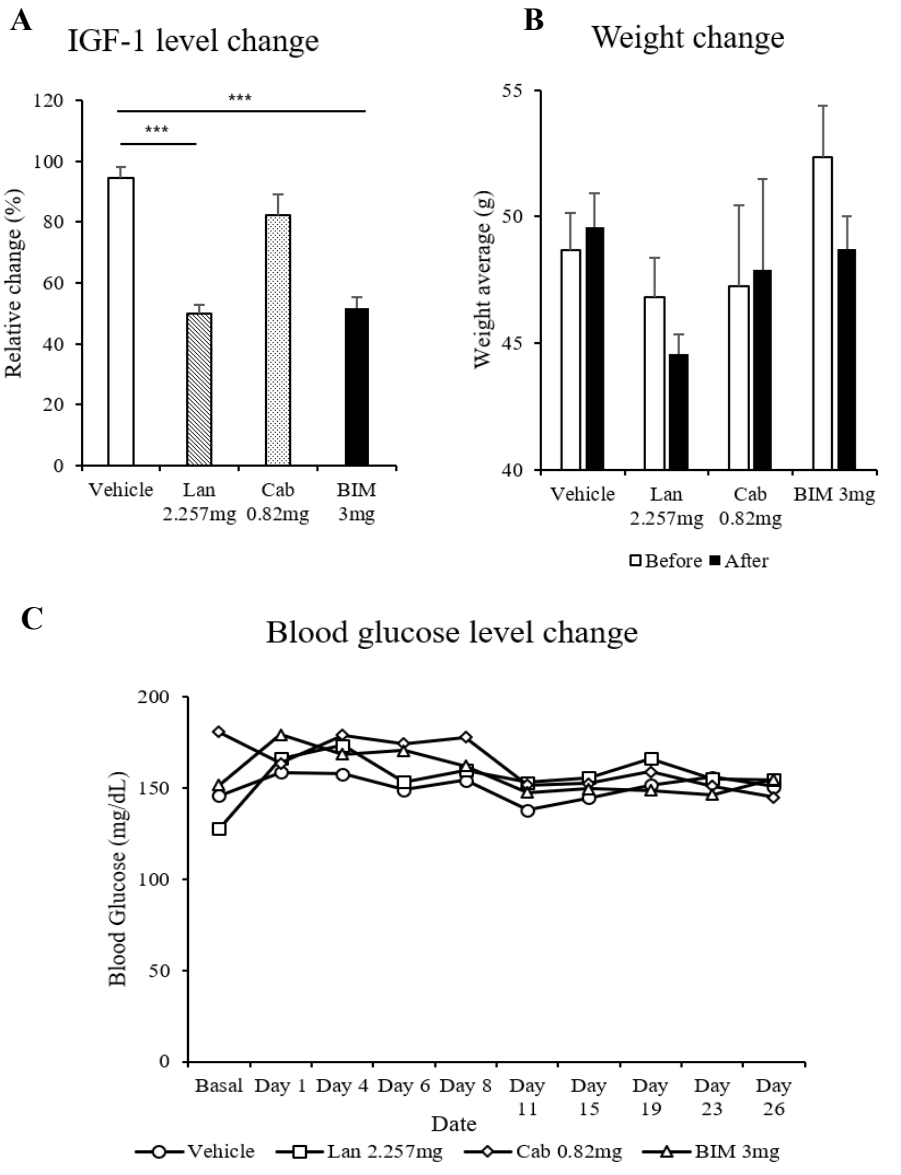

Figure 3. Effects of lanreotide, cabergoline and BIM23B065 4-week treatment in sAIPKO mouse. IGF-1 level change after 4-week treatment in each group with p-value < 0.001 in lanreotide and BIM23B065 **(A)**. Average weight change before and after the treatment **(B)**. Blood glucose level change record throughout the treatment **(C)**. *** indicates p-value < 0.001.

6. MRI result of tumor volume size before and after

To determine the effect of BIM23B065 on tumor size shrinkage, MRI was performed before and after the four-week treatment in five sAIPKO mice, of which three animals showed pituitary tumor. MRI picture were analyzed to measure the size and volume of tumor and pituitary gland.

When comparing before and after treatment, the tumor volume decreased 50% in average of three animals (Fig. 4A). Pituitary gland also decreased in all animals but, especially for the two animals that had tumors showed about 59% of significant decrease in pituitary gland size change (Fig. 4B). The before and after MRI pictures of a tumor model is included below (Fig. 4C).

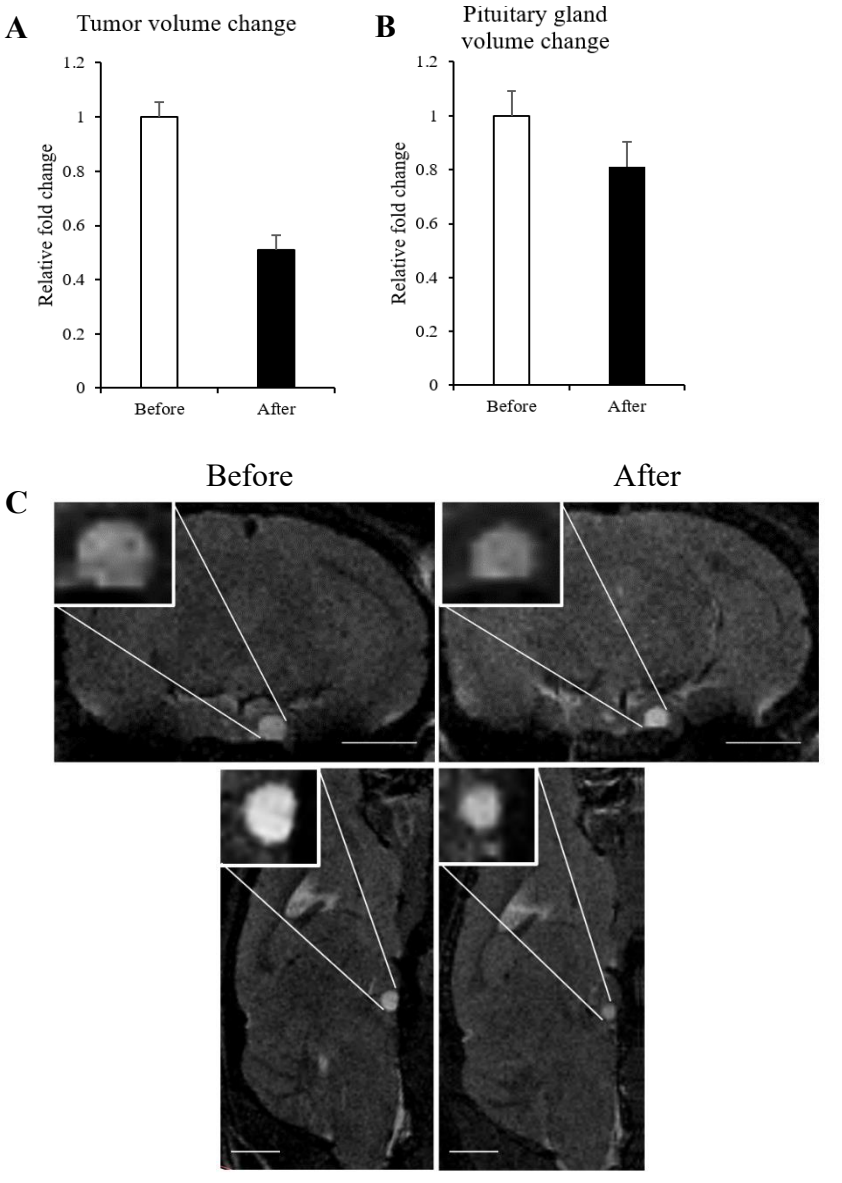

Figure 4. Effects of BIM23B065 in sAIPKO mouse in tumor size and pituitary gland size. Tumor volume change in average after 4-week treatment **(A)**. Piuitary gland size change in average after the treatment **(B)** and MRI pictures **(C)** before and after the treatment showing decrement of tumor in axial and sagittal ways (white bar shows 2mm).

IV. DISCUSSION

Resistance to somatostatin analogues has reduced available treatment options. To resolve this dilemma, new types of drugs are getting developed and tested nowadays. There had been many efforts to make chimeric drugs in response to unresponsiveness to existing drugs[9-11]. Combined with two commonly used drugs for the treatment of pituitary disease, this new chimeric molecule is a possible drug candidate.

According to the study that tested the effects of an earlier version of this chimeric molecule, it suppressed GH and prolactin secretion from human acromegaly tumor cell cultures significantly better than individual somatostatin analogues and dopamine agonists as well as their combination, indicating that it acts on receptors other than somatostatin receptors[16].

The chimeric molecule (BIM23B065) in this study was made of a somatostatin analogue and a dopamine agonist in a 1:1 ratio. Being a novel agent itself, and not just a mixture of two drugs, it was observed to be significantly more effective in vitro than a mixture of lanreotide and cabergoline. The goal of this study was to find out the mechanism of action of this drug in GH3 cells by checking cell proliferation at different concentrations, CREB and ERK 1/2 phosphorylation, and changes in GH release.

According to the result of proliferation assay with GH3 cells, the chimeric molecule and lanreotide showed similar level of toxicity to cells. Cabergoline on the other hand, was effective at a much lower concentration than those of the other two drugs. Assuming that the chimeric molecule is made of a direct combination of a somatostatin analogue and a dopamine agonist, the lanreotide concentration for the animal experiment was set equivalent to that of the chimeric molecule.

After seven days of treatment with BIM23B065 in sAIPKO acromegalic mice, IGF-1 level was not uniformly decreased in each dosage group. It was assumed that IGF-1 level was influenced by mechanical stress induced in the mice during the pump implant surgery. Additionally, the duration of the pump could have been too short for the drug to show its full effect. However, no change in the body weight was observed, indicating that the drug was not toxic. Based on the results of this experiment, a second four-week study was performed with the duration of the pump changed to 14-day, so that surgical intervention was required only once during the entire treatment. BIM23B065 was delivered via the 14-day pump at a dose of 3 mg/kg/day.

Results of the second animal experiment were relatively uniform. Body weights and blood glucose levels were stable throughout the entire experiment duration. The hormone level showed that the chimeric molecule had a dramatic effect on decrement of IGF-1 level. Compared to other positive control groups like cabergoline and lanreotide, the IGF-1 level of most BIM23B065-treated mice was cut half compared to the before treatment.

The chimeric molecule not only decreased the IGF-1 hormone level but also showed the shrinkage of tumor mass in pituitary gland. There were three sAIPKO mice with pituitary adenoma and two had hyperplasia. After 4 weeks, the tumor size decreased noticeably, and pituitary gland size also showed possibility of shrinkage. Therefore, the chimeric molecule had shown enough promising evidence of which it could be the next candidate of the medicinal choice for acromegaly.

V. CONCLUSION

The chimeric molecule was shown to effectively down-regulate IGF-1 level in the GH-secreting pituitary adenoma mouse model, and decrease GH release in GH3 cells. In addition, the chimeric molecule showed distinct effects compared to those of a combination of lanreotide and cabergoline, indicating that this is a novel drug and not just a mixture of two drugs. Based on the results of this study, BIM23B065 holds potential to be developed into a novel treatment agent; however, further studies are needed.

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ABSTRACT (IN KOREAN)

성장호르몬 분비 성 뇌하수체 종양에서 somatostatin analogue 와 dopamine agonist로 이루어진 키메라 물질의 치료 효과

<지도교수 이은직>

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김 지 인

말단비대증은 성장 호르몬 분비성 뇌하수체 종양으로 인하여 지속적인 성장호르몬과 IGF-1 과다분비로 인하여 생기는 질병이다. 치료방법으로는 수술적인 요법과 약물치료가 있으나 수술을 통해 호르몬 정상화가 이루어 지지 않는 경우에는 약물치료에 의존하게 된다. 하지만 기존 약물에 반응하지 않는 경우가 생겨나고 있어 새로운 약물의 필요성이 절실하다. 따라서, 기존 약물을 토대로 새로운 약물들이 현재 개발 중에 있으며, 그 중 BIM23B065는 소마토스타틴 유사체와 도파민 작용물질이 1:1 로 들어간 키메라 물질이다. 본 실험은 신 물질 약물을 이용하여

GH3 cell 에서 독성 검사, CREB 와 ERK 1/2 인산화 변화 및 호르몬 감소효과를 확인하였다. 그리고 쥐 동물 모델을 이용하여 약물의 용량을 결정하고 IGF-1 호르몬 변화를 확인하였다. 또한, 약물 투여 전후 MRI를 찍어 뇌하수체 종양의 크기 변화도 관찰할 수 있었다. 그러므로 실험에 쓰인 신 물질은 말단비대증을 치료하는 또 하나의 약물 로서의 가능성을 보였음을 확인하였다.

핵심 되는 말: 성장호르몬분비성 뇌하수체종양, BIM23B065, 성장호르몬, IGF-1, 전임상시험