



# Hutchinson Gilford Progeria Syndrome (HGPS): Potential Treatments

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## ABSTRACT

The Hutchinson-Gilford Progeria syndrome (HGPS) is a rare genetic disease that causes an early accelerated aging in children; clinically characterized by manifestations affecting the skin, musculoskeletal system and blood vessels, also other features supporting aging processes. This disease affects 1 in 4 - 8 million newborns all over the world without any race and gender preferences. The clinical features of HGPS usually appear at the age of two and will be discovered through clinical diagnosis. It then will be followed by health problems like coronary atherosclerosis that can be life-threatening. The life-span is usually 14,6 years. This review will discuss some emerging potential treatment such as FTI (Farnesyltransferase inhibitors).

**Keywords:** FTI, HGPS, progeria, treatment

## ABSTRAK

Sindrom Hutchinson-Gilford Progeria adalah penyakit genetik langka berupa penuaan lebih cepat pada usia anak-anak ditandai beberapa manifestasi di antaranya kulit, sistem muskuloskeletal dan pembuluh darah, serta hal lain sesuai proses penuaan. Penyakit ini terjadi pada 1 di antara 4-8 juta bayi baru lahir di seluruh dunia tanpa preferensi ras dan *gender*. Gambaran klinis HGPS biasanya muncul di usia dua tahun, diikuti masalah kesehatan seperti aterosklerosis pembuluh darah koroner yang dapat mengancam jiwa. Rentang hidup pasien HGPS biasanya 14,6 tahun. Ulasan ini mengenai beberapa pengobatan potensial seperti FTI (*inhibitor Farnesyltransferase*). **Dias Rima Sutiono, Fransiska Adeline.** *Hutchinson Gilford Progeria Syndrome (HGPS): Pengobatan Potensial.*

**Kata kunci:** FTI, HGPS, pengobatan, progeria

## INTRODUCTION

One of few genetic diseases in the world is progeria syndrome; two types of progeria syndrome are Hutchinson-Gilford Progeria syndrome (HGPS) and Werner syndrome. Hutchinson-Gilford syndrome is the progeria syndrome which typically develops in children whereas Werner syndrome is the progeria syndrome which does not appear until teen-years. HGPS is considered a rare genetic disease that causes an early accelerated aging in children clinically characterized by some manifestations affecting the skin, musculoskeletal system, and blood vessels, also other features similar to aging processes.<sup>1-3</sup>

HPGS name means "prematurely old" was derived from Greek; "progeros" and named after the doctors who first described it: Dr. Jonathan Hutchinson in 1886 and later in 1897 by Dr. Hastings Gilford. Children with HPGS will not be discovered until the first to third

year. They will look normal at birth and early infancy but then start to grow more slowly, fail to thrive and develop specific physical features such as characteristic facial appearances, with hair loss, prominent eyes, receding mandible, narrow nasal bridge and pointed nasal tip. Other key abnormalities include delayed dentition, a thin and high pitched voice, a pyriform (pear-shaped) thorax, and a 'horse riding' stance. This condition is also followed by decreasing health condition. HGPS people tend to have serious complications such as accelerated atherosclerosis of cerebral and coronary arteries that can be worse over time and are life-threatening generally between ages 6 and 20 years. The average life span is approximately 14.6 years; at least 90% HGPS subjects dying from progressive atherosclerosis of the coronary and cerebrovascular arteries.<sup>4-6</sup> One of the oldest person with progeria syndrome known as Meg Casey, who died at 29 years old.<sup>7</sup>

The causes of this syndrome laid in the mutation of a gene called LMNA that result in an unstable and damaged nucleus.<sup>10</sup> The diagnosis of HGPS is usually for 2-year-old child. It is first based on the identification of common clinical features (features that exist and appears in aging people); genetic testing in the aforementioned mutation of LMNA can confirm the diagnosis.<sup>2</sup>

Since the condition was first recorded in 1886, there were already more than 130 cases have been reported. The reported incidence of HGPS is 1 in 4 - 8 million newborn baby.<sup>2,5</sup> HGPS cases have been found in both sexes equally, in a diversity of ethnic and races from 40 countries all over the world including Indonesia.<sup>6,8,9</sup> In this review, the potential emerging treatments of HGPS are discussed.

## Discussion

There is no specific cure for premature aging.

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People with HGPS can only depend on the treatments that can prolong their lifespan but not to cure. A regular health monitoring, such as on their cardiovascular and other old-aged disease is needed to maintain their health and to delay some signs and symptoms. There are still many ongoing researches to find the cure, focusing on the molecular level. Research showed that HGPS gene must lie within a 4.82Mb region on chromosome 1q. This region contains approximately 80 known genes, including LMNA. LMNA gene sequencing revealed that 18 out of 20 classical cases of HGPS harbored an identical de novo (that is, newly arisen and not inherited) single-base substitution, G608G (GGC > GGT), within exon 11.<sup>11</sup> The mutation causes a splice site in exon 11 and resulting in a protein called abnormal lamin A protein (progerin) that deletes 50 amino acids near the carboxy terminus. The abnormal lamin A protein causes abnormalities in the nuclear membrane of cells, contrast with the function of the normal lamin.

Some potential treatment for this disease:

1. FTI

The prior work in mouse models and in people (both adults and children) found that FTIs may be a viable treatment for progeria but with no 100% safety assurance.<sup>6</sup> HGPS is caused by progerin protein. The progerin can be activated if a molecule called farnesyl group is attached to progerin. FTI is Farnesyltransferase inhibitors, small molecules that reversibly bind to the farnesyltransferase CAAX binding site to inhibit the attachment of farnesyl group to the progerin. FTI can normalize both the structure and function of the progerin cell. Some studies also showed that FTIs can improve cardiovascular function and increase the lifespan. This class of drug may be used for possible treatment for children with progeria.<sup>12-14</sup>

Currently, there are 3 types of FTI still in the processes of trial and research: Lonafarnib, Pravastatin, and Zoledronate. All of them inhibit post-translational farnesylation of progerin as the target action. Clinical trials for these 3 drugs are currently being done.<sup>2</sup> The first clinical trial was done for 2 years. The results have revealed benefits for the incidence of stroke, TIA and headache, skeletal and audiologic

functions, improvement of weight gain, vascular distensibility as measured via pulse wave velocity and vascular echodensity, bone rigidity, neurosensory and increasing life span.<sup>12-15</sup>

In 2009, PRF and the National Heart, Lung and Blood Institute co-founded the second and currently ongoing trial. The trial includes two additional medications to lonafarnib, also aimed at inhibiting progerin farnesylation. Pravastatin inhibits HMG-CoA reductase and the bisphosphonate zoledronate inhibits farnesyl-pyrophosphate (PP) synthase; each enzyme functions along the protein prenylation pathway.<sup>14</sup>

The first study results are showing that children with progeria receiving lonafarnib treatment had an 80 percent lower risk of death compared to the untreated cohort. Unfortunately, the study was not really dependable as the clinical trial was done with several ages and treatment duration, also various stages of disease upon treatment initiation. In addition, the children were treated with three drugs (2 years on lonafarnib monotherapy and 3.5 years on combination therapy), therefore the analysis did not distinguish individual drug. The researchers speculate that lonafarnib is the one that has large responsibility to the estimated life extension because lonafarnib is the drug-exposed to all subjects, and for the longest period of time in most instances.<sup>12-15</sup>

2. Rapamycin via increasing of autophagy

Rapamycin can improve the cellular phenotypes in HGPS fibroblasts and extend lifespan in a lamin A-deficient mouse model. Rapamycin act as a novel inhibitor of progerin that decreases protein levels through a mechanism involving autophagic degradation. Rapamycin lowers progerin, as well as wild-type prelamin A levels, and rescues the chromatin phenotype of cultured fibroblasts, including histone methylation status and BAF and LAP2 $\alpha$  distribution patterns.<sup>16,17</sup>

3. Antisense oligonucleotides

Decrease the progerin protein levels, enhance life expectancy, improving disease phenotype, and cellular phenotypes in an HGPS mouse model.<sup>18</sup>

4. Resveratrol

Improvement of cellular phenotype in HGPS fibroblasts, improvement of lamin A function via a SIRT-1 dependent manner and extended lifespan in a Zmpste24-/- mouse model.<sup>19</sup>

5. Nat10 inhibition by a chemical named remodeling that is not yet developed for clinical use corrected phenotypes in HGPS fibroblasts.<sup>20</sup>

6. Methylene blue alleviates nuclear and mitochondrial abnormalities in progeria. MB treatment not only alleviated the mitochondrial defects but also rescued the hallmark nuclear abnormalities in HGPS cells. Additional analysis suggested that MB treatment released progerin from the nuclear membrane, rescued perinuclear heterochromatin loss and corrected miss-regulated gene expression in HGPS cells.<sup>21</sup>

7. Aminopyrimidines

Monoaminopyrimidines target two key enzymes of the farnesylation process: farnesyl pyrophosphate synthase and farnesyl transferase, and rescue *in vitro* phenotypes associated with HGPS.<sup>22</sup>

8. ICMT

The reduced ICMT activity caused prelamin A changes its location within the nucleus and triggered prelamin A-dependent activation of the AKT-mammalian target of rapamycin (mTOR) signaling, which abolished the premature senescence of Zmpste24-deficient fibroblasts. Inhibition increased AKT-mTOR signaling and proliferation and delayed senescence in human HGPS fibroblasts but did not reduce the levels of misshapen nuclei in mouse and human cells.<sup>23</sup>

9. An antioxidant present in broccoli appears to give the protein-clearing system a boost, potentially reducing the effects of the disease.<sup>24</sup>

CONCLUSION

Based on the recent studies and clinical trials, FTI has a potential for HGPS treatment. Although many researches still have to be done to support FTI to be the drug for curing and treating HGPS children, it has a big potential. Many other studies try to find new



agents for potential treatment for this disease. Further research and studies are still needed to be done.

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