International Journal of Medicine and Pharmaceutical Research

Journal Home Page: www.pharmaresearchlibrary.com/ijmpr

REVIEW ARTICLE

Progeria: A Genetic and Rare Disease

Anitha Nandagopal*, Naaz Nazmeen, Firdous Afshan, Anupama Koneru

Dept. of Pharmacology, Sultan-ul-Uloom College of Pharmacy, Road no.3, Banjara Hills, Hyderabad, Telangana-500034.

ABSTRACT

Hutchinson Gilford Progeria Syndrome is an extremely serious disorder characterized by rapid, premature ageing of children which can precipitate cardiovascular diseases. Progeria is caused by de novo mutation in Lamin A gene which activates splicing in donor site, resulting in short, mutant protein called as "Progerin". Generally, Lamin A is produced by detachment of 15 amino acids and farnesyl group from prelamin A. But in progeria, farnesyl group is not removed from prelamin A due to this the nuclear envelope becomes stiff. This condition is called nuclear blebbing which is a discrete feature of progeria. In affected individuals the rate of ageing is increased by 7 times that of normal. It is extensively anticipated that presence of progerin but not due to change in mature lamin A is the principle reason leading to progeria. Treatment includes farnesyl transferase inhibitors, statins, rapamycin, amino bis phosphonates and zoledronic acid. Abnormal physiology of progeria nuclei might cause DNA damage build up in progerial cells along with cellular attrition. This problem is deteriorated when the function of human mesenchymal stem cells is blocked, it will lead to change in their distinction ability and molecular identity. Thus if normal stem cells are injected into blood circulation of progerial patient may be helpful to generate normal stem cell pool. This normal cell will compete with progerial stem cells and thus healthy cells will be grown which may serve as ultimate cure.

Keywords: Progeria disease, Lamin A gene, Progerin, nuclear blebbing, farnesyl transferase inhibitors.

ARTICLE INFO

***Corresponding Author**
Ms. Anitha Nandagopal
Sultan-ul-Uloom college of Pharmacy,
Hyderabad, Telangana.
MS-ID: IJMPR3543

PAPER QR-CODE

ARTICLE HISTORY: Received 05 April 2018, **Accepted** 19 May 2018, **Available Online** 10 June 2018

Citation: *Anitha Nandagopal, et al.* Progeria: A Genetic and Rare Disease. *Int. J. Med. Pharm. Res., 2018, 6(3): 101-107.*

CONTENTS

1. Introduction

Hutchinson Gilford Progeria syndrome (HGPS) is an extremely serious disorder characterized by rapid, premature ageing of children and can precipitate cardiovascular diseases. It was first explained by Jonathan Hutchinson and Hasting Gilford in 1800's (Capell BC et al., 2005). Gilford coined the term progeria' from Greek word geros (means old) in the year 1904. This condition was further renamed by DeBusk in 1972 as Hutchinson-Gilford

Progeria Syndrome. In afflicted individuals, the rate of ageing is increased by 7 times that of normal individuals (. De Busk FL et al., 1972). HGPS is caused by de novo mutation in Lamin A, a gene which activates a splicing in donor site, resulting in short mutant protein progerin. Generally Lamin A is produced by detachment of 15 amino acids and farnesyl group from prelaminA attached to nuclear envelope. But in case of HGPS, the farnesyl group is not removed and the nuclear envelope undergoes bebbling and becomes unstable.

Genes involved in progeria

Mutations in HGPS Lamin (1824C>T, pG608G) does not change the sequence of encoded amino acid, it indicates that the mutation is of silent type. This mutation triggers a cryptic splice donor site (c. 1819-1820) in exon 11 of Lamin A gene, which results in production of prelamin A mRNA in which 150 base pairs are deleted. The resultant prelamin A is translated into a mutant form of Lamin A protein designated as progerin devoid of 50 amino acids (607-656) at carboxyl terminus end (Wang L et al., 2012), Mutations in 1868C>G (T623S) at exon 11 in lamin gene produces lamin A devoid of 35 amino acids (QI YC et al., 2013). Mutation at exon 2, 8, and 9 of Lamin A gene results in unusual cases of progeria like absence of coronary artery diseases.

Etiology

HGPS is caused due to mutation in Lamin gene (Tsiligiri M et al., 2015). Lamin A is a protein which is synthesized by gene Lamin, this protein has a layer which is attached to inner nuclear membrane which consists of many polypeptides whose main components are lamin A, B, B2 and C. Lamin A and C are produced by alternate joining copy of LMNA gene (Coutinho HD et al., 2009). Due to mutation in gene, abnormal form of Lamin A protein is produced which alter the nuclear membrane of cell resulting in tissues damage (Goldman RD et al., 2004). The disease is usually transmitted with respect to an autosomal dominant inheritance pattern (Hennekam RC et al., 2006). It was also found in siblings with autosomal recessive inheritance pattern (Khalifa MM et al., 1989).

Risk of HGPS to Family

Parents of proband are not affected. Healthy individuals suffer from this disorder due to the de novo mutations in parents with asymptomatic somatic and germ-line mosaicism which results in a progeny with progeria.

- Siblings-As HGPS occurs due to de novo pathogenic variant, the risk of progeria will be low in siblings and other family members. The risk of progeria in sibling is 1/500 according to the case report of patient in 2005. Exceptional cases of progeria of twins with HGPS are seen.
- Off spring-Classical HGPS patient have no reproductive history (Shankar P et al., 2010).

Epidemiology

Progeria research foundation database stated that at any time there are approximately 200-250 children surviving with progeria world- wide, 103 of them have been discovered in April 2013. Progeria has its impact on both sexes and on all races. HGPS cases have been identified across 40 different countries. Documented reports of 24 cases in Europe, 20 cases in Northern America, 18 cases in Asia, 16 cases in central and southern America and 4 cases in Africa are available (Hutchinson J, 1886; Gilford H, 1904).

2. Prognosis

HGPS patients have an average life of 13 years with age scope of 7-27 years. Cohorts of HGPS patients states the average survival of patients is 14.6 years but the survival rate was increased due to intermediate treatment with farnesyl tranferase inhibitor. 90% of patients experience mortality and morbidity as a result of accelerating atherosclerosis of coronary and cerebro-vascular arteries (Gordon LB et al., 2014).

Biosynthesis of HGPS based on molecular biology

Primarily HGPS was anticipated to be an autosomal recessive disorder, later it was considered as an autosomal dominant condition where the single copy of the modified gene in each cell is sufficient to develop the disease. major reason for disease as mutation in gene LMNA and not congenital. Another reason for HGPS is de novo nucleotide substitution at position 1824($c \rightarrow T$) in exon-11 of LMNA revealed by 80-90% of cases (Eriksson M et al., 2003). A three step prenylation process is involved in the production of mature lamin A from prelamin A. The process occurs very rapidly leading to the deletion of unprocessed prelamin A (Gao J et al., 2009). The CAAX closing end of Prelamin A is composed of cysteine, aliphatic serine, aliphatic iso-leucine and methionine (CSIM) (Dominici S et al., 2009). Protein prenylation process of CAAX protein includes 3 steps.

Step-1: Poly isoprenylation

In this step farnesyl transferase identifies methionine group in the CAAX of protein and 15 carbon Farnesyl group is added to the CSIM sequence, the last part of CAAX protein.

Step-2: Proteolysis

2 ZMPSTE24 endoprotease removes the SIM (AAX) portion of CSIM (CSIX) sequence by enzyme prenyl protein peptidase. This process is called proteolysis.

Step-3: Carboxymethylation: The last step of prenylation process where carboxy methylated group (O-CH3) is added to generate a carboxy methylated farnesylate prelamin A with the help of methyl transferase enzyme. Abbreviated form of prelamin A is termed progerin, that lacks ZMPSTE24 cleavage site, but still it posses cysteine C terminal which is further farnesylated and carboxymethylated (Liu Q et al., 2010). Holding of farnesyl group in the progerin (prelamin A) will cause progerin to integrate itself in the nuclear rim in an abnormal way. Thus progerin lead to increase in DNA damage by producing an abnormal heterochromatin assembly. Due to this structure of nuclear membrane will be deformed and becomes stiff; this is called nuclear blebbing which is a discrete feature of progeria (Zaremba-czogalla M et al., 2011).

Physiology of LMNA gene

Lamin A or C are officially known as LMNA or otherwise known as LMNA –HUMAN, LMNC, and LMN1. Gene LMNA is placed on chromosome 1 from base pair 154, 351, 121 to base pair 154, 376, 494. Any alterations or

mutations in the chromosome1 and Lamin gene results in many health consequences like cancers, thrombocytopenia, Charcot-Marie-Tooth disease, Hutchinson-Gilford progeria syndrome. Lamin gene (LMNA) plays a major role in the production of various proteins termed as lamins, especially lamin A and lamin C. Lamin A and C are structural proteins with same amino acid sequence. They are collectively known as intermediate filament proteins. The main function of these proteins is to maintain the stability and strength of the cell. These proteins are found in the nuclear lamina (a meshwork of proteins adhered to intrinsic membrane of nuclear envelope).The inward and outward movement of molecules and genes is governed by nuclear envelope. Prelamin A (nascent form of lamin A) experiences multiple steps while lamin C does not undergo any steps for its introduction into lamina.

Lamin A

Information for the production of lamin A and C by possible splicing is provided by Lamin gene (LMNA). Lamin A and C comprise the major component of nuclear lamina which is 20nm thread like network which is present inside the inner nuclear membrane in most distinguished cells and in nucleoplasm (Worman HJ, 2005). Lamin A interacts with chromosomes, many signaling and structural proteins. It is present throughout the nucleoplasm. Lamin A exerts essential role in preserving the shape and integrity of nuclear envelope and nuclear pore complexes. It also helps in DNA replication, cell cycle control, DNA repair, cellular differentiation, chromatin organization and regulation of transcription (Dechat T et al., 2008; Shumaker DK, et al., 2006; Dechat T et al., 2009). Lamin A is produced from prelamin A, a 664 amino acid precursor protein. A series of post translational modifications will lead to produce mature lamin A. Initially, a 15 carbon farnesyl which is a lipid, is attached to cysteine of lamin A. The AAX portion is taken from the terminal CAAX part, and then farnesyl moiety is carboxy methylated. Finally a mature lamin A is formed by removal of farnesyl cysteine methyl ester. This ester helps in targeting prelamin A to nuclear envelope.

Mutations leading to cause of Progerin production in HGPS: Mutation results in removal of proteolytic cleavage site required detach farnesyl and prelamin A which accumulates in nuclear envelope. Nuclear abnormalities due to deformation of cell nucleus are responsible for premature ageing in progeria patients (Agarwal US et al., 2010).

Progerin is the principle culprit in HGPS

The disease progresses in patients due to the presence of farnesyl group in progerin molecule (Yang SH et al., 2010). Accumulation of prelamin A along with farnesyl group in the periphery of nucleus may increase lipophilicity of membrane (Goldman RD et al., 2004; Gordon LB et al., 2007; Kieran MW et al., 2007; Coppede F, 2012).It was extensively anticipated that the presence of progerin is the principle reason leading to progeria but not due to change in mature lamin.

HGPS and associated diseases

Patients with progeria predominantly die at an age of 11-13 years by virtue of myocardial infarction, heart attack elicited by advancing atherosclerotic disease according to Coppede et al. CVS complications like interstitial fibrosis dispersed myocardial fibrosis and calcification of arotic and mitral valve have been reported. Cerebrovascular complications such as subdural hematoma, seizures, hemiplegia, and cerebral vascular infarctions have also occurred (Hennekam RC et al., 2006; Coppede F, 2012). Dysarthria, facial palsy followed by limb weakness, dizziness, and headache are the consequences of cerebral infarction and other complications are marasmus, inanitation, and loss of mobility.

Clinical features of cardiovascular system in progeria patients: According to Hennekam et al, during first 5 years, no cardiovascular complications are seen in progeria patients (Nair K et al., 2004; Sivaraman J et al., 1999). However systemic hypertension is common before 5 years of age. During 6-8 years of age, patients may eventually develop shortness of breath, fatigue and dyspnoea which are peak at the end phase. Patients also experience stroke at an age of 4-19 years. Some patients develop gangrene resulting in amputation of toes (Riechel W et al., 1970), while the others develop renal infarction. Atherosclerosis of mitral, aortic valve and left ventricular outflow tract might be the major reason for cardiovascular diseases.

Pathological changes of cardiovascular system in progeria patients

Arterial Disease changes

HGPS patients experience narrowing or blockade of intramural arteries by plaque (Baker PB et al., 1981). Right coronary artery occlusion is characteristic one. Severe atherosclerosis was reported in aorta of patients followed by enhanced stiffness and reduced compliance. Thickened tunica intima, thickened tunica adventitia and unimproved tunica media with 50% loss of medial smooth muscles in ascending aorta have been reported by researchers (Olive M et al., 2010). Close review of two autopsies of progeria patients by Stehbens et al enclosed detail collagen such as type I, III, IV, V and VI in renal vessels and aorta (Stehbens WE et al., 1999).

Pulmonary hypertension and valvular changes

Life threatening pulmonary hypertension is seen in patients as consequence of medial hypertrophy of thickened pulmonary arteries and intimal fibrosis (Shiraishi I et al., 2001). Histopathological examination from autopsy of progeria patients detailed the irregular accumulation of collagen, elastic fibers on the inner walls of all pulmonary arteries along with cell proliferation (Constantinescu D et al., 2010).

Diagnosis: The various factors which are affected in HGPS were shown in Table 1.

Treatment for Progeria

Treatment for progeria is divided into pharmacological and non- pharmacological treatment. Frequent monitoring of blood vessels and heart diseases helps to control children condition. Some of the signs and symptoms can be delayed by using certain therapies.

Pharmacological treatment

Following drugs are used in the treatment of progeria

Farnesyl transferase inhibitors (FTI): Farnesyl transferase inhibitors can combat progerial symptoms although progerin, an abnormal protein is still being expressed. FTI can anticipate the binding of abnormal

protein progerin to nuclear margin and access the number of normal shaped nuclei. The cells with farnesyl tranferase inhibitors tends to participate in geranylgeranylation (Gordon LB et al., 2008), an alternate pathway mediated through geranylgeranyl transferase I instead of polyisoprenylation that employes farnesyl transferase to adhere 20 carbon of geranylgeranyl group to prelamin A. This pathway may decrease the effect of FTI treatment so combination of statins, amino bis-phosphonates and FTI which can inhibit farnesylation and geranylgeranylation pathway. Recent study pattern of HGPS patients revealed the therapeutic use of lonafarnib a farnesyl transferase inhibitor in the treatment of HGPS syndrome. The study was conducted on 25 HGPS patient for a period of 2 years to monitor the following parameters like skeletal rigidity, eyes health, hearing and weight. During the course of study there was an increase in one or more parameters out of 25 patients, single patient /child experience better CVS health. Lonafarnib is formulated as capsules; oral doses are 150,115, 90, and 70 mg/m2 the dosing starts from 150 mg/m2 orally bid. If the therapy does not work or toxicity occurs the dose of drug can be alterted (Sousa SF et al., 2008).

Rapamycin: Rapamycin is a macrolide compound, a non-toxic drug used to treat ageing in progeria, as it would suppress cellular senescence/ageing which is called as geroconversion, and it also prevents atherosclerotic retinosis (Gordon et al., 2012) and accelerated atherosclerosis in humans (Rodriguez AE et al., 2006; Mueller MA et al., 2008) which is the ultimate cause of death in progeria patients. Rapamycin also acts as an immunustimulator, clinically approved drug for the treatment of progeria whose side effects are less if used in low and intermediate doses (Zhao L et al., 2009) and it is also used for treating TSC syndrome in children (Major P, 2011).

HMG CO A reductase inhibitors

Pravastatin an HMG CO A reductase inhibitor can also be given to HGPS patients as it tends to reduce the cholesterol levels as well as checks atherosclerosis. It works by arresting farnesyl group formation, an essential procedure that precedes the disease. For child with weight ≤10 kg is 5 mg orally OD and for a child with weight of 10 kg is 10 mg orally OD.

Zoledronic acid: Zoledronic acid can prevent hypercalcemia in progeria patient. It is widely used in myelomas and bone cancers. It works similar to provastatin by arreseting farnesyl group formation. Zoledronic acid is administered as IV infusion at a dose of 0.0125 mg/kg body weight for about 30 minutes (Sousa SF et al., 2008).

CVS drugs: Nitroglycerine and regular anticongestives are prescribed in case of angina and congestive heart failure respectively. Anticoagulants are contraindicated in case of angina, stroke, ischemic attacks and vascular blockade.

General anesthetics

Anesthetics are used cautiously in HGPS patients in extreme conditions like fiberoleptic intubation and regular intubations. The patients have narrow irregular air passages and stiffened vessels as a result they become hyper or hypotensive. Rather than continuing the treatment the classical solution would be total cure (Warner HR, 2007). In response to the physiologic demands, apoptosis can cause repeated cellular rubbing bring about forced reconstruction of tissue cells which will evantually result in inability of vegetative cell pool to respond to these demands (Halaschek-Wiener J et al., 2007). Failure of growth in HGPS patients at an age of 2 years can be result of above process. Abnormal physiology of progeria nuclei might cause DNA damage buildup in HGPS cells along with cellular attrition (Bridger JM et al., 2004). Cellular rubbing (damage) problem is further deteriorated when human mesenchymal stem cell function is blocked along with change in distinction ability and molecular identity. Thus if normal stem cells/somatic are injected into blood circulation of progeria patient may be helpful to generate normal stem cell pool, this normal cell will compete with progeria stem cells and thus healthy cells are grown which may serve as ultimate cure explained by Scaffidi and Misteli (Scaffidi P et al., 2008).

Table 1

Factors	Effects
Growth	Height growth will be less, Lifelong, weight gain will be ≤ 3rd percent, Thin and high pitched voice, Disproportionately large head for face
Body fat	• Eminent eyes • Prominent scalp • Prominent veins throughout the body • Absence of ear lobes in some cases
Skin/hair/nails /eyes	• Tight, dry and pigmented skin • Hard skin over lower abdomen and proximal thighs • Irregular small bulging of skin over proximal thighs and lower abdomen • Generalized alopecia • Absence of eye brows and some time eyelashes • Weak finger and toe nails • Inability to close eyes which is called as Nocturnal lagophthalmos, keratitis may lead to corneal ulcers. • Thin lips
Hearing	Low frequency
Oral /dental	• Delayed loss of primary teeth • Partial secondary tooth eruption • As a result of small mouth, dental crowding can be seen, lack of primary tooth loss and secondary tooth eruption behind primary teeth • Tongue mobility (50% affected individuals) is limited due to short and thick lingual frenum • Steeple shaped (ogival)and palatal vault (60-70% of individuals are affected)
Skeletal system/joints	• Narrow nasal bridge and pointed tip • Closure of anterior fontanelle is

	delayed • Pear-shaped thorax • Osteolysis of distal phalanges • Undersized jaw which is called as micrognathia and abnormal posterior positioning of maxilla and mandible called as retrognathia • Short and weak clavicles • Low bone density • Thin limbs • Tightened joint ligaments globally but variable in severity • Osteoarthritis • Horse- riding and unsteady gait
Cardiovascular/ neurovascular	• Cardiac manifestations • Angina, congestive heart failure, myocardial infarction. Strokes including clinical strokes, transient ischemic attacks, and silent strokes that are seen on MRI or CT scan of the head but do not manifest as clinical deficits • Raynaud phenomenon in fingers is seen in minority of affected individuals
Endocrine	• Frank diabetes is unusual, insulin resistance can be seen in 50% of individuals • Secondary sexual development is incomplete • Concentration of leptin in serum is low

Non-Pharmacological treatment

Shoe pads-Reduced body fat leads to foot discomfort. Hence shoe pads are inserted to maintain the foot strength.

Occular lubricants-Patients suffering from progeria cannot close their eyelids completely. This disorder is known as Nocturnal lagopthalmos. This disorder leads to keratitis upon exposure. This condition can be overcome by using ocular lubricants which will offer moisture to eye. Ocular lubricants must be used solely during day time and along with moisturizing ointment during sleep. Eyelids can also be closed by using skin tapes. Physical therapy-Occupational and physical therapy is employed to enhance the movement of finger, joints. Hydrotherapy along with active stretching and strengthening are also recommended.

Prevention of primary manifestations

- Aspirin therapy-Aspirin helps in delaying strokes and heart attack in adults at low dose hence, aspirin can be prescribed to a progeroid patient at a dose of 2-3mg/kg body weight /day. (Low dose aspirin therapy). It is contraindicated in the patient who has coexisting chicken pox or influenza as it can accelerate Ryes syndrome.
- Vitamin supplements- Standard dose of multiple vitamin tablets are adviced. Vitamin A allows the free flow of blood by dilating the blood capillaries (Kotade et al., 2015). Ascorbic acid (Vitamin C) is an antiageing vitamin which helps in removing dead skin cells along with eliminatrion of free radicles that damage the skin (Rani et al., 2013).
- Flouride supplements- Fluoride supplements are administered as per the requirements (Gordon et al., 2012).
- Hydration -During hot weather or while travelling hydration becomes essential because in this conditions, the vascularature becomes less pliable, reduced compensation and holds the risk of a CVS Complications.

3. Management of HGPS

Early signs and symptoms of progeria can be managed by assessing the following parameters.

- Standard growth chart is plotted between weight and height to evaluate growth over time.
- MRI of neck and brain
- ECG and Echocardiogram.
- Size and thickness of lumen can be determined by scanning the carotid artery.
- X ray of hips, skeletal muscle as well as DEXA(dual energy X ray absorptiometry) are performed to determine a vascular necrosis, Clavicular resorption, CoxaValga, extra- skeletal soft tissue calcification and bone mineral density.
- Joint mobility, occupational therapy and physical therapy are determined by goniometry.
- Lipid profile assessment like TG, TC, LDL, and HDL.
- Ophthalmic examinations especially the possible exposure keratopathy.
- Low frequency hearing loss can be detected by audiological examination.
- Nutritional evaluation.
- Clinical genetics consultation (Gordon LB et al 2014).

4. Conclusion

Progeria is a rare, severe disease characterized by rapid premature ageing of children. The rate of ageing in affected individuals is 7 times that of normal individuals. It is caused due to single gene mutation in lamin a gene which results in short mutant protein, progerin. This progerin adheres to the nuclear membrane resulting in irregular nuclear scaffolding and resulting in nuclear blebbing. This is the discrete feature of progeria. There is no way to prevent progeria, however clinical trials with farnesyl transferase inhibitor, namely lonafarnib resulted in improved bone structure, increased flexibility of blood vessels and additional weight gain. In addition, treatment with rapamycin, statins, zoledronic acid etc is also helpful. Hydration, physical and occupational therapy can be used for its management. Normal stem cells may be injected into blood circulation of progerial patient. This normal cell will compete with progerial stem cells and generates normal stem cells pool which serves as ultimate cure. Since few drugs are available for the management of HGPS, there is a great need for further research to investigate new drug

molecules. New techniques should also be explored to manage the symptoms of this disease and there by to improve the qualtity of life of these patients.

Conflict of Interest: There is no conflict of interest between the authors.

5. Acknowledgement

The authors are grateful to Sultan-ul-Uloom Education Society for providing us the facility to carry out this work.

6. References

[1] US Agarwal, S Sitaraman, S Mehta. Hutchinson-Gilford Progeria syndrome. Indian Journal of Dermatology Venereology and Leprology, 2010, 76(5): 591.

[2] PB Baker, N Baba, CP Boesel. Cardiovascular abnormalities in progeria. Case report and review of the literature. Archives of Pathology & Laboratory Medicine, 1981, 105(7): 384-386.

[3] JM Bridger, IR Kill. Aging of Hutchinson-Gilford progeria syndrome fibroblasts is characterized by hyperproliferation and increased apoptosis. Experimental Gerontology, 2004, 39(5): 717-724.

[4] D Constantinescu, AB Csoka, CS Navara. Defective DSB repair correlates with abnormal nuclear morphology and is improved with FTI treatment in Hutchinson -Gilford Progeria syndrome fibroblasts. Experimental Cell Research, 2010, 316(17): 2747-2759.

[5] F Coppede. Premature ageing syndrome. Advances in Experimental Medicine and Biology, 2012, 724: 317-331.

[6] HD Coutinho, VS Silva, GF Goncalves, RB Nobrega. Molecular ageing in progeroid syndromes: Hutchinson –Gilford progeria syndrome as a model. Immunity & Ageing, 2009, 6(4): 1.

[7] FL DeBusk. The Hutchinson-Gilford progeria syndrome: report of 4 cases and review of the literature. International Organization for Standardization. 1972, 80(4): 697-724.

[8] T Dechat, SA Adam, RD Goldman. Nuclear Lamins and chromatin: when structure meets function. Advances in Enzyme Regulation, 2009, 49(1): 57-66.

[9] T Dechat, K Pfleghaar, K Sengupta. Nuclear Lamins: major factors in the structural organization and function of the nucleus and chromatin. Genes & Development, 2008, 22(7): 832-853.

[10] S Dominici, V Fiori, M Magnani. Different prelamin A forms accumulate in human fibroblasts. A study in experimental models and progeria. Europeon Journal of Histochemistry, 2009, 53(1): 43-52.

[11] M Eriksson, WT Brown, LB Gordon, MW Glynn, J Singer, L Scott. Recurrent de novo point mutations in lamin A cause Hutchinson–Gilford progeria syndrome. Nature, 2003, 423(6937): 293-298.

[12] J Gao, J Liao, GY Yang. CAAX-box protein, prenylation process and carcinogenesis. American Journal of Translational Research, 2009, 1(3): 312-325

[13] H Gilford. Progeria: A Form of senilism. Practitioner, 1904, 73: 188-217.

[14] RD Goldman, DK Shumaker, MR Erdos, M Eriksson, AE Goldman, LB Gordon, et al. Accumulation of mutant lamin A causes progressive changes in nuclear architecture in Hutchinson Gilford progeria syndrome. Proceedings of the National Academy of Sciences of the United States of America, 2004, 101(24): 8963-8968.

[15] LB Gordon, C Harling-Berg, FG Rothman. Highlights of the 2007 progeria research foundation scientific workshop: progress in translational science. The Journals of Gerontology, 2008, 63(8): 777-787.

[16] LB Gordon, Kleinman, E Monica. Clinical trial of a farnesyl transferase inhibitor in children with Hutchinson-Gilford progeria syndrome. Proceedings of National Academy of Sciences, 2012, 109 (41): 16666-16671.

[17] LB Gordon, J Massaro, RB D'Agostino, SE Cambell, J Brazier, WT Brown, et al. Impact of farnesylation inhibitors on survival in Hutchinson gilford progeria syndrome. Circulation, 2014, 130(1): 27-34.

[18] LB Gordon, KM McCarten, A Giobbie-Hurder, JT Machan, SE Campbell, SD Berns, et al. Disease progression in Hutchinson –Gilford progeria syndrome: impact on growth and development. Pediatrics, 2007, 120(4): 824-833.

[19] J Halaschek-Wiener, A Brooks-Wilson. Progeria of stem cells: stem cell exhaustion in Hutchinson-Gilford progeria syndrome. The journals of Gerontology. Series A, Biological sciences and medical sciences, 2007, 62(1): 3-8.

[20] RC Hennekam. Hutchinson –Gilford progeria syndrome: review of the phenotype. American Journal of Medical Genetics Part A, 2006, 140(23): 2603-2624.

[21] Hutchinson J. Congenital absence of hair mammary glands with atrophic condition of skin and its appandages, in a boy whose mother had been almost wholly bald from alopecia areata from the age of six. Medico-chirurgical Transactions journal, 1886, 69: 473-477.

[22] MM Khalifa. Hutchinson –Gilford progeria syndrome: Report of a Lybian family and evidence of autosomal recessive inheritance. Clinical Genetics, 1989, 35(2): 125-132.

[23] MW Kieran, L Gordon, and M Kleinman. New approaches to progeria. Pediatrics, 2007, 120 (4): 834-841.

[24] KB Kotade, SV Wagh, VD Wagh. Wheat Grass as Green blood therapy: A Review. International Journal of current trends in Pharmaceutical Research, 2015, 3(6): 1128-1134.

[25] Q Liu, DI Kim, J Syme, P LuValle, B Burke, KJ Roux. Dynamics of lamin-A processing following precursor accumulation. Peer-reviewed open access scientific journal, 2010, 5(5): 10874.

[26] P Major. Potential of mTOR inhibitors for the treatment of subependymal giant cell astrocytomas in tuberous sclerosis complex. Aging, 2011, 3(3):189-191.

[27] MA Mueller, F Beutener, D Teupser, U Ceglarek, J Thiery. Prevention of atherosclerosis by the mTOR inhibitor everolimus in LDLR-1-mice despite severe hypercholesterolemia. Atherosclerosis, 2008, 198(1): 39-48.

[28] K Nair, P Ramachandran, KM Krishnamoorthy. Hutchinson –Gilford syndrome with calcific aortic valve stenosis and calcific mitral valve. The Journal of Heart Valve Disease, 2004, 13(5): 866-869.

[29] M Olive, I Harten, R Mitchell, JK Beers, K Djabali, K Cao. Cardiovascular pathology in Hutchinson –Gilford progeria; correlation with the vascular pathology of aging. Arteriosclerosis, Thrombosis and Vascular Biology, 2010, 30(11): 2301-2309.

[30] YC Qi, XH Xie. Hutchinson-Gilford progeria syndrome and its relevance to Cardiovascular Diseases and Normal Ageing. Biomedical and Environmental Sciences, 2013, 26(5): 382-389.

[31] B Rani, RK Maheshwari, M Sharma, S Parihar, U singh. Miraculous Therapeutic potential of Indian Goose berries. International Journal of Medicine and Pharmaceutical Research, 2013, 1(2): 218-225.

[32] W Riechel, R Garcia-Bunuel. Pathological findings in Progeria: Myocardial fibrosis and lipofuscin pigment. American Journal of Clinical Pathology, 1970, 53(2): 243-253.

[33] P Scaffidi, T Misteli. Lamin A- dependent misregulation of adult stem cells associated with accelerated ageing. Nature Cell Biology, 2008, 10(4): 452-459.

[34] P Shankar, P Vishwanath, VD Nath, N Chella,YK kumar, P Venkateshwarlu. Progeria-A brief review. International Journal of Pharma and Bio Sciences, 2010, 1(2): 1-14.

[35] I Shiraishi, S Hayashi, E Hirai. Fatal pulmonary hypertension associated with atypical case of Hutchinson -Gilford progeria. Pediatric Cardiology, 2001, 22(6): 530-533.

[36] DK Shumaker, T Dechat, A Kohlmaier. Mutant nuclear lamin A leads to progressive alteration of epigenetic control in premature ageing. Proceedings of the National Academy of Sciences of the United States of America, 2006, 103(23): 8703-8708.

[37] J Sivaraman, MD Thappa, M D'Sauza. Progeria (Hutchinson –Gilford): A case report. The Journal of Dermatology, 1999, 26(5): 324-328.

[38] WE Stehbens, SJ Wakefield, E Gilbert-Barness. Histological and ultrastructural features of atherosclerosis in progeria. Cardiovascular Pathology, 1999, 8(1): 29-39.

[39] SF Sousa, PA Fernandes, MJ Ramos. Farnesyl transferase inhibitors: A detailed chemical view on an elusive biological problem. Current Medicinal Chemistry, 2008, 15(15): 1478-1492.

[40] M Tsiligiri, C Fekos, E Theodoridou, M Lavdaniti. An Overview of Hutchinson Gilford Progeria Syndrome. British Journal of Medicine and Medical Research, 2015, 5(12): 1527-1533.

[41] L Wang, W Yang, W Ju. A proteomic study of Hutchinson -Gilford progeria syndrome: Appication of 2D –chromatography in a premature aging disease. Biochemical and Biophysical Research Communications, 2012, 417(4): 1119-1126.

[42] HR Warner. Is cell death and replacement a factor in aging? Mechanisms of ageing and development. Mech Ageing Dev, 2007, 128(1): 13-16.

[43] HJ Worman. Components of the nuclear envelope and their role in human disease. Novartis Foundation Symposia, 2005, 264: 35-42.

[44] SH Yang, SY Chang, DA Andres. Assessing the efficacy of protein farnesyl transferase inhibitor in mouse models of progeria. Journal of Lipid Research, 2010, 51(12): 400-405

[45] M Zaremba-Czogalla, M Dubiska-Magiera, R Rzepecki. Laminopathies: The molecular background of the disease and the prospects for its treatment. Cellular & Molecular Biology Letters, 2011, 16(1): 114-148.

[46] L Zhao, T Ding, T Cyrus, Y Cheng, H Tian, M Ma et al. Low dose oral sirolimus reduces atherogenesis, vascular inflammation and modulates plaque composition in mice lacking the LDL receptor. British Journal of Pharmacology, 2009, 156(5): 774-785.