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Clinical Review on Dereluctive Orphan Diseases

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Pharmaceutical (drug) and biotech companies are constantly researching and developing new medications to treat medical conditions, and new drugs come on the market frequently. People who have rare diseases or disorders, however, have not had as much research attention in past decades. This is because their numbers are small, often having such low prevalence and therefore the potential market for new drugs to treat them is also small. Orphan drugs are medicinal products intended for the diagnosis, prevention or treatment of orphan diseases. Orphan diseases are a spectrum of medical conditions with very different etiologies, the common denominator being the infrequency of their occurrence in the population. The new business model of orphan drugs could offer an integrated healthcare solution that enables pharmaceutical companies to develop newer areas of therapeutics, diagnosis, treatment, monitoring, and patient support. Incentives for drug development provided by governments, as well as support from the FDA and national organizations in special protocols are a further boost for the companies developing orphan drugs. Although there may still be challenges ahead for the pharmaceutical industry, orphan drugs seem to offer the key to recovery and stability within the market. The aim of this article is to review on the concept of orphan diseases in various countries with their status and some orphan diseases, affecting commonly among the rarity.

Keyword: Orphan Drugs, Prevalence, Incentives Etiologies, Infrequency.

1. Introduction

A disease is an impairment of health or a condition of abnormal functioning. It is a pathological condition of a part, organ, or system of an organism resulting from various causes, such as infection, genetic defect, or environmental stress, and is characterized by an identifiable group of signs or symptoms [1].

1.2 The concept of rarity

"A rare disease is a disease that occurs infrequently or rarely in the general population". In order to be considered as rare, each specific disease cannot affect more than a limited number of people out of the whole population [1]. It is important to underline that the number of rare disease patients varies considerably from disease to disease, and that most people represented by the statistics in this field suffer from even rarer diseases, affecting only one in 100,000 people or less. Most rare diseases do only affect some thousands, hundreds or even a couple of dozen patients.

2. Definitions

The concepts of rare diseases, neglected diseases, orphan diseases and orphan drugs are not clearly defined and used as interchangeable concepts. This situation has led to misperception and confusion as to precisely what each of these concepts refers to and/or as to what reality each of them covers.

2.1 Rare Diseases

Rare diseases are characterized by their low prevalence (less than 1/2000) and their heterogeneity. Because rare disease patients are a minority, there is a lack of public awareness; these diseases do not represent a public health priority. The market is so narrow for each disease that the pharmaceutical industry is reticent to invest in research to develop and to develop treatments for rare diseases. There is therefore a need for economic regulation, such as national incentives [2].

2.2 Orphan Diseases

Orphan diseases comprise both rare diseases and neglected diseases. They are "orphan" of research focus and market interest, as well as of public health policies. The World Health Organization defines orphan diseases, "as all pathological condition, affecting 0.65-1 out of every 1000 inhabitants". They are usually not studied for their pathophysiology or for newer therapeutic options, as these are not economically viable [3].

2.3 Orphan Drugs

Orphan drugs are medicinal products intended for the diagnosis, prevention or treatment of rare diseases. These drugs are called "orphan" because, under normal market conditions, it is not cost-effective for the pharmaceutical industry to develop and market products are intended for only a small number of patients suffering from rare conditions. For drug companies, the cost of bringing an orphan medicinal product to the market would not be recovered by the expected sales of the product. For this reason, governments and rare disease organizations have emphasized the need for economic incentives to encourage drug companies to develop and market medicines intended for the "orphaned" rare disease patients [4].

2.4 Orphan survey

2.4.1 United States

As defined in the United States, any drug developed under the Orphan Drug Act of January 1983 (ODA) is an orphan drug. The ODA is a federal law concerning rare diseases (orphan diseases) that affect fewer than 200,000 people in the United States or are of low prevalence (less than 5 per 10,000 in the community).

2.4.2 Europe

A disease or disorder that affects fewer than 5 in 10,000 citizens is the definition for rare in Europe (Orphan Drug Regulation 141/2000). At first glance, this may seem a small number, but by this definition, rare diseases can affect as many as 30 million European Union citizens. According to EURORDIS (European Organization for Rare Diseases), the number of rare diseases numbers from about 6,000 to 8,000 most of which have identified genetic conditions, with medical literature describing approximately five new rare conditions every week [5].

2.4.3 Australia

The Therapeutic Substances Regulations does not define a rare disease or orphan indication in terms of the number of patients, but rather indicates that it must not be intended for use in more than 2000 patients a year if it is a vaccine or *in vivo* diagnostic. In order to attain the orphan designation, "the application must show why the medicine is an orphan drug." In Australia, orphan drugs are drugs used to treat diseases or conditions affecting fewer than 2,000 individuals at any one time (0.2%) [6].

2.4.4 Canada

Canada has no official "orphan disease" status; however, based on international standards, it could be defined as diseases with a potential patient population numbering between 3,300 (Australian standards) to 22,500 (US definition).

2.4.5 Japan

A drug must meet the following three conditions in order to be considered for orphan drug designation in Japan. Any disease with fewer than 50,000 prevalent cases (0.4%) is Japan's definition of rare. The drug treats a disease or condition for which there are no other treatments available in Japan or the proposed drug is clinically superior to drugs already available on the Japanese market. The applicant should have a

clear product development plan and scientific rationale to support the necessity of the drug in Japan.

2.4.6 India

The need for such an act is thus evident from the initiative by the Indian Pharmacists and the Government to implement Laws, which would strengthen the health infrastructure and provide relief to the numerous rare disease sufferers throughout the country. A group of pharmacologists at a conference held by the Indian Drugs Manufactures Association in 2001 requested the Indian Government to institute the Orphan Drug Act in India. The national orphan drug regulation should offer lucrative incentive, economic outcome and market exclusivity rights to the rare drug manufacturer to enjoy the reasonable profit and interest for investment in the R&D of rare drugs [7].

3. Statistics of Rare Diseases

About 6000-8000 rare diseases have been affecting 7% of population worldwide. 95% of medical conditions included in rare list have no FDA approval treatments [8]. 80% of rare diseases have been identified to genetic origins. Other rare diseases are the result of infections (bacterial or viral) and allergies, or are due to degenerative and proliferative causes According to San Orphan SA, Geneva, Switzerland, around 65 per cent of rare diseases are serious and disabling. More interestingly, about 250 new rare diseases are discovered each year, corresponding to five new rare diseases per week [9].

3.1 Orphan Designation

The Orphan Designation is a legal procedure that allows for the designation of a medicinal substance with therapeutic potential for a rare disease, before its first administration in humans or during its clinical development. The Office of Orphan Products Development(OOPD) evaluate requests for orphan drug designation, and once a drug is designated, acts as an internal FDA advocate interfacing with the FDA review division to help facilitate progress. The OOPD is separate from the FDA therapeutic review divisions [10]. A sponsor may request orphan drug designation for a previously unapproved drug or a new indication for an already marketed drug. The drug product may be a new formulation and the requisite information for a new drug product required by International Conference on Harmonization (ICH)/FDA would need to be provided in a marketing application. If the sponsor is able to provide valid evidence that their drug may be clinically superior to the drug already has orphan drug status, the new drug can be designated as orphan drug. In either of the above scenarios, the sponsor would need to include patent certification in the marketing application that demonstrates that there are no patent infringement issues [11].

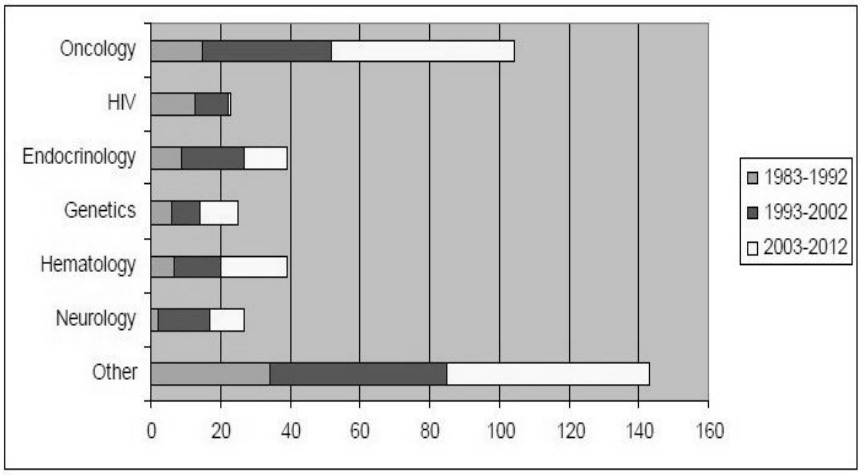

Fig 1: Orphan drug designations by therapeutic area 1983-2012

4. Orphan Drug Status

In 1982, The U.S. Food and Drug Administration (FDA) recognized the lack of incentive for pharmaceutical companies to develop cures for rare diseases and established the Office of Orphan Product Development. This branch of the FDA provides incentives to companies that work toward curing rare diseases by exercising the rights given to them under the Orphan Drug Act of January 1983. One type of incentive is the orphan drug status, which provides tax reductions and the exclusive right to develop the cure for a specific condition for a period of seven years to companies attempting to cure rare diseases [12].

From a business perspective, having a large market ensures that a company can quickly recuperate the cost of development and can also realize the largest possible gain [16]. For this reason, there is little incentive for pharmaceutical companies to develop cures for rare diseases - those that affect fewer than 200,000 people in the United States - because the small market and high cost associated with finding these types of cures discourages these companies from entering this market [13].

5. List Of Some Orphan Diseases

5.1. Retinitis Pigments

Retinitis pigmentosa is an inherited retinal dystrophy caused by the loss of photoreceptors and characterized by retinal pigment deposits visits on fundus examination. The most common form of retinitis pigmentosa (RP) is a rod-cone dystrophy, in which the first symptom is night blindness, followed by the progressive loss in the peripheral visual field in day light, and eventually leading to blindness after several decades [14].

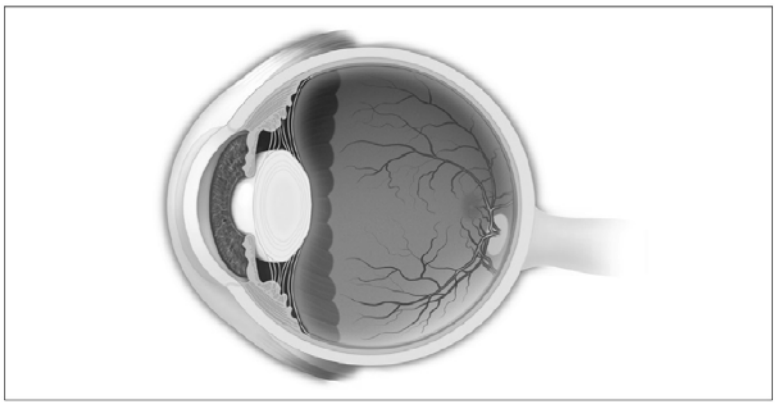

Fig 2(a): Cross section of Retina of normal individual

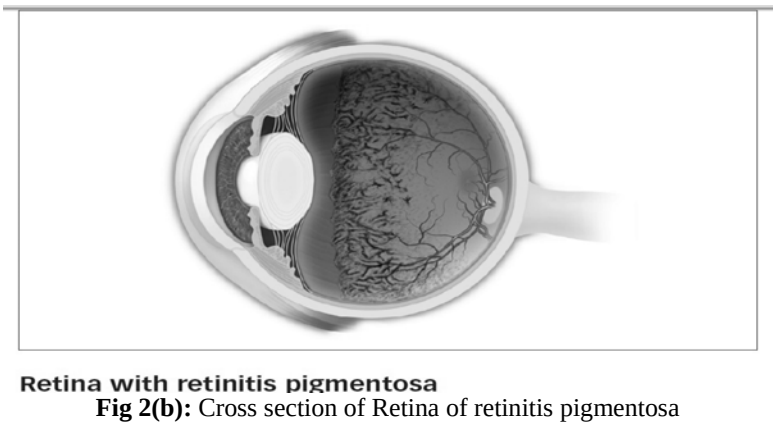

Fig 2(b): Cross section of Retina of retinitis pigmentosa

The probable order for the development of degenerative changes in retinitis pigmentosa patients is as follows:

- Migration of nuclei from the outer nuclear layer to the rod and cone layer.
- Degeneration and loss of photoreceptors and their nuclei in the outer nuclear layer.
- Loss of connecting fibers in the outer plexiform layer.
- Migration of the retinal pigment epithelium (RPE) into the retina.
- Adhesion of the retinal to the retinal pigment epithelium in broad areas and possible transneuronal degeneration of some cells in the inner nuclear and ganglion cell layers [15].

Orphan drugs designated by FDA:

Human Retinal Progenitor Cells - The particular stem cells from the retina, known as progenitor cells, are capable of rescuing photoreceptors from degeneration following transplantation to the eye [16]. These same cells are also highly efficient at becoming rod photoreceptors and this provides another more sustained pathway by which they preserve the crucial cone photoreceptors.

Epitalon- Epitalon (Ala-Glu-Asp-Gly) is obtained by targeted chemical synthesis. Epitalon therapy in patients with degenerative retinal lesions results in a positive clinical effect in 90% of the cases [17].

5.2. Cystic Fibrosis

Cystic fibrosis (also known as CF or mucoviscidosis) is an autosomal recessive genetic disorder that affects most critically the lungs, and also the pancreas, liver, and intestine. It is characterised by abnormal transport of chloride and sodium across an epithelium, leading to thick, viscous secretions [18].

The name *cystic fibrosis* refers to the characteristic scarring (fibrosis) and cyst formation within the pancreas. Difficulty breathing is the most serious symptom and results from frequent lung infections that are treated with antibiotics and other medications. CF is caused by a mutation in the gene for the protein membrane (CFTR). This protein is required to regulate the components of sweat, digestive fluids, and mucus. CFTR regulates the movement of chloride and sodium ions across epithelial membranes, such as the alveolar epithelia located in the lungs.

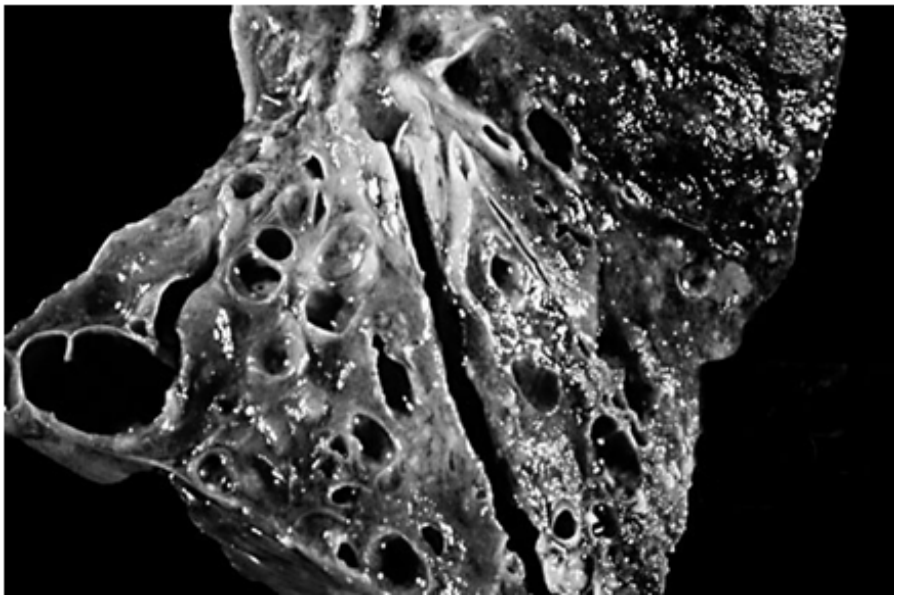

Fig 3: Cross section of lung in Cystic Fibrosis

Besides the general treatment for relieving one or other symptoms, FDA approved orphan drugs for potential treatment of cystic fibrosis [19].
Orphan drugs designated by FDA:

Ivacaftor - Ivacaftor, a CFTR potentiator, improves the transport of chloride directly to induce a non-conventional mode of gating which in turn increases the probability that the channel is open.

Fenretinide - Fenretinide (4-hydroxy (phenyl) retinamide; 4-HPR) (INN) is a synthetic retinoid derivative. Retinoids are substances related to vitamin A [20].

5.3. Pompe Disease

Pompe disease, also referred to as acid maltase deficiency (AMD) or glycogen storage disease type II (GSDII) is an autosomal recessive disorder caused by a deficiency of the lysosomal enzyme acid-glucosidase (GAA). It was the first recognized lysosomal storage disease and is the only glycogen storage disease that is also a lysosomal storage disease. In Pompe disease, lysosomal glycogen accumulates in many tissues with skeletal, cardiac, and smooth muscle most prominently involved [21].

Mutations in the *GAA* gene cause Pompe disease. The *GAA* gene provides instructions for producing an enzyme called acid alpha-glycosidase (also known as acid maltase). This enzyme is active in lysosomes, which are structures that serve as recycling centers within cells. The enzyme normally breaks down glycogen into a simpler sugar called glucose, which is the main energy source for most cells [22].

Mutations in the *GAA* gene prevent acid alpha-glucosidase from breaking down glycogen effectively, which allows this sugar to build up to toxic levels in lysosomes. This buildup damages organs and tissues throughout the body, particularly the muscles, leading to the progressive signs and symptoms of Pompe disease [23].

5.3.1 Orphan drugs designated by FDA:

ALGLUCOSIDASE ALPHA - The U.S. Food and Drug Administration approved Lumizyme an enzyme replacement therapy (ERT) orphan drug for patients ages 8 years and older with late-onset (non-infantile) Pompe disease[24].

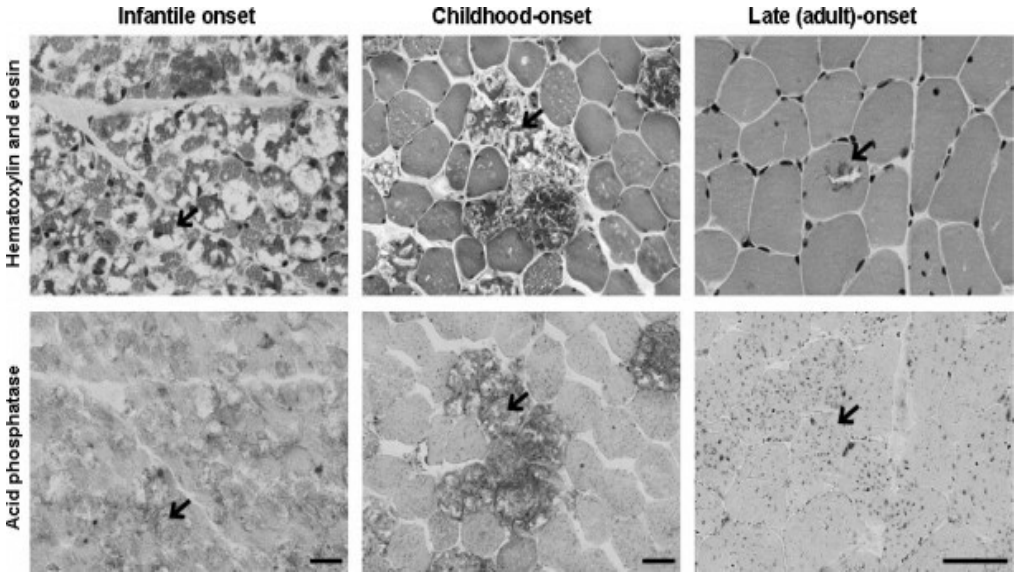

Fig 4: Histology Of Muscle In Pompe Disease

5.4. Raynaud's Phenomenon

Raynaud's phenomenon (RP) is a condition resulting in a particular series of discolorations of the fingers and/or the toes after exposure to changes in temperature (cold or hot) or emotional events. Skin discoloration occurs because an abnormal spasm of the blood vessels causes a diminished blood supply to the local tissues. Initially, the digit(s) involved turn white because of the diminished blood supply. The digit(s) then turn blue because of prolonged lack of oxygen. Finally, the blood vessels reopen, causing a local "flushing" phenomenon, which turns the digit(s) red. This three-phase color sequence (white to blue to red), most often upon exposure to cold temperature, is characteristic of RP [25].

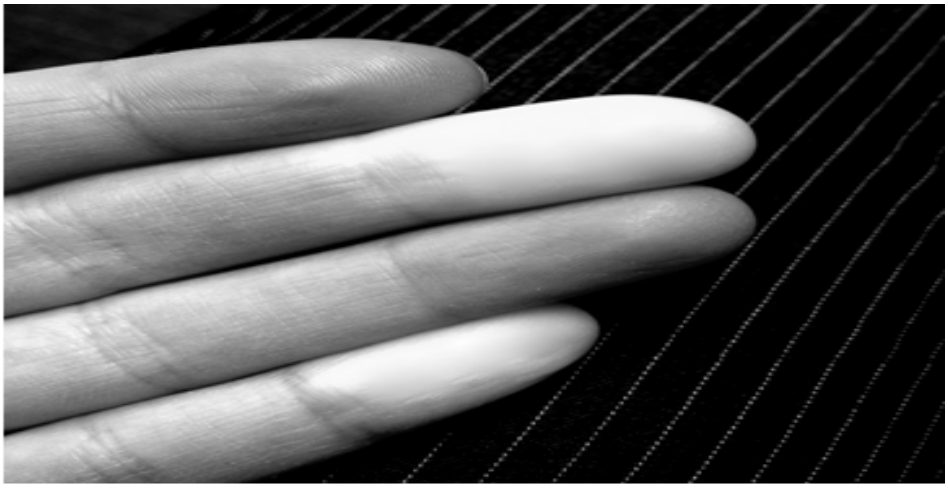

Fig 5: Raynauds Phenomenon Observed On Fingers

5.4.1 Orphan drugs designated by FDA:

Iloprost Solution For Infusion - Iloprost is a synthetic analogue of prostacyclin PGI_2. Iloprost dilates systemic and pulmonary arterial vascular beds. It also affects platelet aggregation. The two diastereo isomers of iloprost differ in their potency in dilating blood vessels, with the 4*S* isomer substantially more potent than the 4*R*isomer.

5.5. Hutchinsom Gilford Progeria Syndrome (Progeria)

Progeria is a rare genetic disease with striking features that resemble accelerated aging. The inheritance pattern, paternal age effect, and lack of consanguinity argue that it is due to a sporadic dominant mutation. We have observed elevated levels of hyaluronic acid (HA) excretion in progeria patients. In several

progeria patients we observed normal levels of growth hormone (GH) but very low levels of insulin-like growth factor I along with very high basal metabolic rates (BMRs). A trial of GH treatment was begun, which resulted in a marked increase in linear growth and a paradoxical drop in BMRs in these two patients [26].

Children born with HGPS typically do not appear normal at birth, but within a year they begin to display the effects of accelerated aging [27]. Typical facial features include micrognathia (small jaw), craniofacial disproportion, alopecia (loss of hair), and prominent eyes and scalp veins. Children experience delayed growth and are short in stature and below average weight. Due to a lack of subcutaneous fat, skin appears wrinkled and aged looking [28].

No effective treatment is currently available to cure the disease. Neverthless, symptomatic treatment should be proposed for all its complications, including orthopedic complications. The main complication of progeria is coronary artery bypass surgery or percutaneous transluminal angioplasty has been reported. Non aggressive nutritional therapy was proposed in a study and slightly improved weight gain and growth. Since delayed loss of primary teeth is common, extractions may be required to avoid crowding or development of two rows of teeth [29].

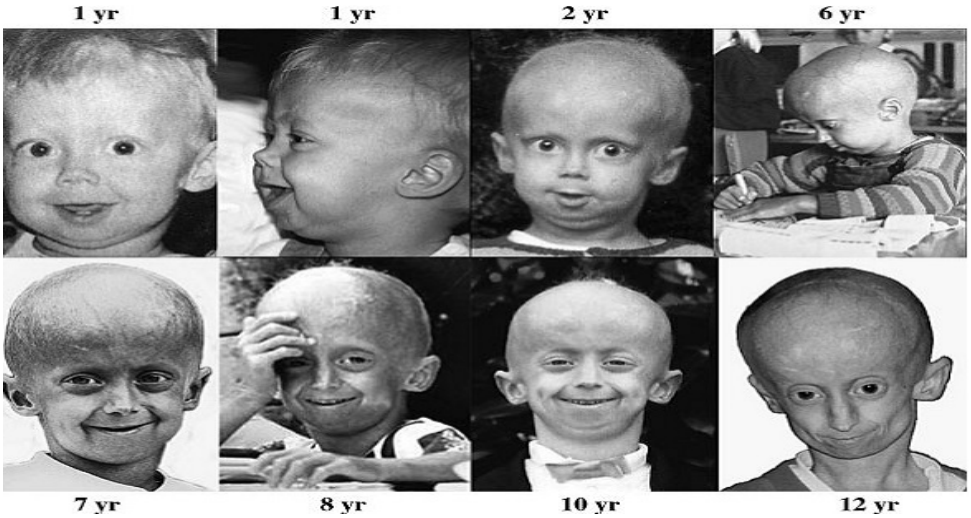

Fig 6: Dutch Patient 2 at the age of 1 year, 1 year, 2 years, 6 years, 7 years, 8 years, 10 years, and 12 years

6. Conclusion

The success of orphan drug designation for neglected rare diseases shows that companies using orphan drug programs can generate profits and recoup their R&D investments even with relatively small markets in the developed world. The orphan drug designation mainly encourages investments and initiatives by small science-oriented companies. In general, orphan drugs have been developed by small biotech firms focused on niche markets or by academic investigators combining solid scientific expertise in a specific medical area with good entrepreneurial skills. The orphan drug designation should be promoted in various countries, not having their regulations for such categories of diseases, to promote the treatment for sufferers with rare diseases.

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