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Recent research on orphan drugs: An overview

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ABSTRACT

Orphan drugs have been used to treat rare diseases since last three decades. The incidences of such diseases have been increasing at a greater pace than the speed with which drugs are researched and developed to treat such diseases. One of the major reasons is that the pharmaceutical industry is not very keen to carry out research on the development of orphan drugs as these drugs do not capture a bigger market. This is the current scenario inspite of the various incentives provided in the Orphan drug act. However, in this review, we have tried to focus on the results of few of the recently conducted clinical trials carried out towards the development of such orphan drugs.

Key words: Orphan drugs, Act, rare diseases, Clinical trials, Patient compliance.

INTRODUCTION

A medicinal product designated as an orphan drug is one that has been developed specifically to treat a rare medical condition referred to as “orphan disease.” It may be defined as drugs that are not developed by the pharmaceutical industry for economic reasons but which respond to public health need. The spiraling cost of drug development coupled with strict regulations; along with the low return on investment are some important factors that discourage pharmaceutical innovators from developing orphan drug products. Such rare diseases in small patient populations have a few approved drug treatment options available [1].

Orphan drugs are an important public-health issue and a challenge for the medical community [2]. Modern society still has a lack of options for the effective treatment of patients with rare diseases. As one of the consequences of this, the demand for public health protection has increased the economic burden of patient suffering from such diseases [3]. Scientific advances have given researchers a new tool to explore these orphan diseases, which are often more complex than common diseases. On the brighter side, these rare diseases when taken together cannot be called rare at all. There are approximately 7000 different types of rare diseases and disorders with more being discovered today. It has been reported that there are about 250 new rare cases reported every year, however the acceptable treatment is available only for 200-300 orphan diseases [4]. It is known that the 80% of these rare diseases are of genetic origin and the rest have environmental, bacterial, viral or unknown origin [5]. Overall orphan diseases are often chronic, progressive, disabling; even life threatening and most of these have effective or curative treatment, having low prevalence and high complexity [6].

The US Orphan Drugs Act (ODA) has undergone amendments in 1984 wherein it has been stated that a drug can be said to be orphan drug only when it is used to treat a condition affecting fewer than 2,00,000 persons in the US, or which will not be profitable within seven years following approval by the FDA. This act has provided incentives to various pharmaceutical industries to develop rare disease treatments recognizing the scarcity of medicines to treat rare disease with very small patient populations. Over the last 30 years more than 400 medicines representing 447

separate indications have been approved to treat rare diseases, compared to fewer than 10 in the 1970s. In 2013, FDA has granted the orphan drug designation to 2,899 potential therapies. However there are also significant challenges in the orphan drug space, including obstacles to study execution, regulatory hurdles and a changing reimbursement environment. Orphan drugs are replacing the blockbuster drugs of previous decades and have economic potential to generate as much life time revenue as drugs used for more common health conditions. In recent years, many pharmaceutical companies have begun to focus their attention on orphan drug development, and in some cases, have established business unit dedicated to rare diseases. Philanthropic and venture capital investment interest in orphan drug development has increased as well, resulting in increased lobbying for support of new legislature supporting FDA reform. Some orphan drugs approved by USFDA (2014) along with their route of administration and application; is depicted in Table 1 [7].

Ethical issues related to orphan drug include the difficulties associated with organizing clinical studies for orphan medicinal products (OMPs) are plentiful. Because of the small number of eligible patients, it can prove difficult to enroll a sufficient number of volunteers for clinical trials [8]. In such small studies, the problems that can arise are the questionable validity of the results and the risk of not being able to demonstrate the similar effect in trials with complex patient populations that are more prone to variability and statistical challenges [9]. Orphan drugs are seldom produced by pharmaceutical industries because investment in orphan drug manufacture does not give them a profitable market. Also, the under developed countries cannot afford to pay the process of such drugs [10].

Research and development on orphan drugs

Donnenfeld E.D. [11] has performed a comprehensive search on the clinical studies related to a novel potent steroid difluprednate in controlling postoperative inflammation after ocular surgery. Difluprednate as ophthalmic emulsion (0.05%) was shown to be efficacious in the treatment of postoperative inflammation in different clinical settings, including a novel perioperative regimen.

This drug is also the first one found to be more potent than prednisolone acetate which has been the standard drug of choice in cataract surgery complications.

Cataract complications are rare but still occur in about 5 % patients for which most physicians prophylactically treat patients with a standard perioperative regimen to prevent infections and reduce postoperative inflammation and pain. With the proven efficacy of difluprednate, a new standard for potency in a topical corticosteroid, with excellent anti-inflammatory properties has been generated.

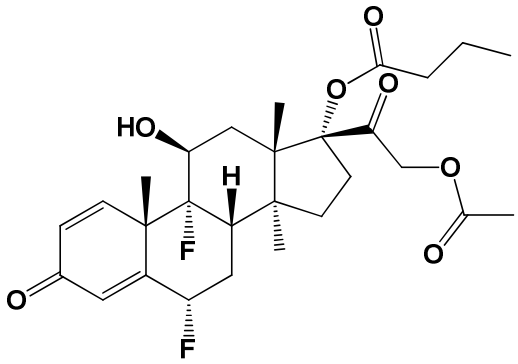


Fig. 11: Difluprednate

Mette *et al*. [12] have conducted a randomized clinical trial to assess whether bezafibrate increases fatty acid oxidation (FAO) and lowers heart rate (HR) during exercise in patients with carnitine palmitoyltransferase (CPT) II and very longchain acyl-CoA dehydrogenase (VLCAD) deficiencies. The primary outcome measures were changes in FAO, measured with stable-isotope methodology and indirect calorimetry, and changes in HR during exercise. It was suggested from these studies that bezafibrate does not improve clinical symptoms or FAO during exercise in patients with CPT II and VLCAD deficiencies. We hypothesized that a clinical improvement due to bezafibrate in vivo would be associated with an increase in FAO during exercise and a better exercise tolerance in patients with disorders of FAO.

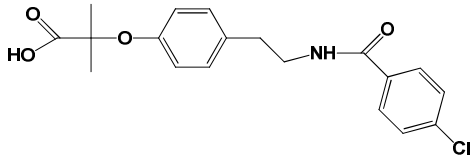


Fig. 12: Bezafibrate

Blight [13] has studied an extended-release formulation of dalfampridine which has been recently approved by the US Food and Drug administration to improve walking in patients with multiple sclerosis (MS). The drug is reported as potassium channel blocker and has long been considered a potential therapeutic strategy for treatment of multiple sclerosis (MS) based on the pathophysiology of demyelinated axons. Randomized, double-blind, placebo-controlled trials, with dalfampridine extended release tablets were conducted and was revealed that average walking speed in patients on therapy was increased to about 25% above baseline.

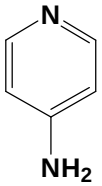


Fig. 13: Dalfampridine

Beal *et al*. [14] has studied the role of gabapentin in treatment of post-herpetic neuralgia which results from an insult to the peripheral and central nervous systems caused by the varicella zoster virus. It has been found that a majority of cases occur in patients over the age of 50 years. Gabapentin is a structural analog of gamma aminobutyric acid that binds to the α_2-δ site of voltage-dependent calcium channels and modulates the influx of calcium, with a resulting reduction in excitatory neurotransmitter release. Gabapentin is needed to be given at least three times per day, but has a short half-life. It also has dose-limiting side effects that prevent some patients from achieving therapeutic plasma levels. Hence, an extended-release formulation of gabapentin has been developed which can be given once daily by the use of acuform technology. This is a polymer-based drug delivery system that retains the tablet in the stomach and upper gastrointestinal tract for a sustained period of time.

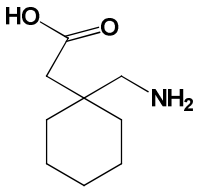


Fig. 15: Gabapentin

Widemann *et al*. [15] has assessed the role of the recombinant bacterial enzyme, glucarpidase (carboxypeptidase-G2), leucovorin, and thymidine in the management and outcome of patients with high-dose methotrexate (HDMTX) –induced nephrotoxicity. The various toxicities were also monitored, and the relationship of baseline characteristics to the development of severe toxicity and death was established by using logistic regression analysis. Also, early intervention with the combination of leucovorin and glucarpidase was found to be highly effective in patients who developed HDMTX-induced renal dysfunction. Extreme toxicity and death occurred in patients in whom glucarpidase rescue was delayed and occured inspite of thymidine administration.

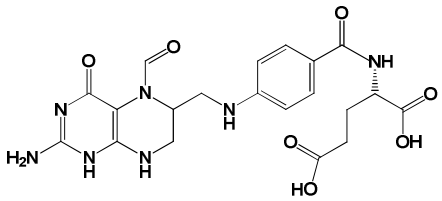


Fig. 16a: Leucovorin

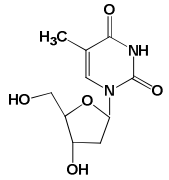


Fig. 16b: Thymidine

Gibod *et al*. [16] have evaluated the efficacy and safety of icatibant self-administration in human volunteers with hereditary angioedema (HAE). There were no occurrences of emergency hospitalization and adverse events were also mild. Also, the patients reported that carrying icatibant with them gave them greater confidence in managing their condition indicating good patient compliance.

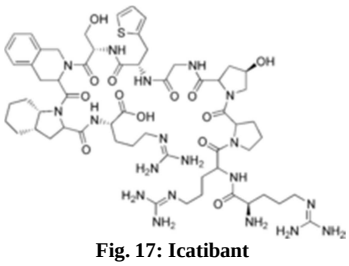


Fig. 17: Icatibant

Colao *et al*. [17] have studied an approach to monitor and treat hyperglycemia in pasireotide-treated patients with Cushing's disease which presents a number of management challenges. Pasireotide is a novel agent for the treatment of Cushing's disease with proven efficacy. It also improves outcomes and expands treatment options. It is deduced that patients on pasireotide treatment should be monitored for changes in glucose metabolism and hyperglycemia. In case of diabetics suffering from Cushing's disease, hyperglycemia should be managed by initiation of medical therapy with metformin and / or initiation of insulin. However, it has been suggested that further research into hyperglycemia following pasireotide treatment will aid in refining the best strategy to treat Cushing's disease.

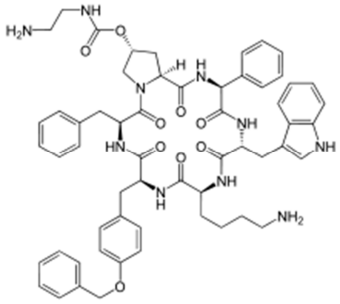


Fig. 18: Pasireotide

Elisei *et al*. [18] have conducted a double-blind, phase III trial comparing cabozantinib with placebo to study its effect in progressive medullary cancer of thyroid gland (MTC). This drug exhibited good activity in human volunteers with MTC in phase I clinical trial. Cabozantinib in a dose of 140 mg per day showed significant improvement in patients with progressive metastatic MTC. Hence, it can be an important alternative for patients with this rare disease.

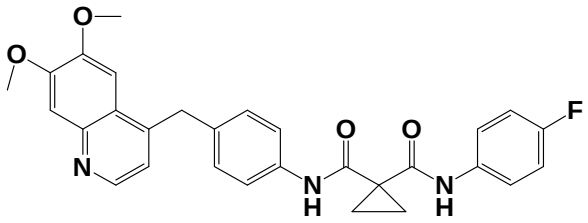


Fig. 20: Cabozantinib

VanderMolen *et al*. [19] have screened romidepsin, a selective inhibitor of histone deacetylases (HDACs). This drug has been approved by the USFDA for the treatment of cutaneous T-cell lymphoma. It is isolated Japanese soil sample and obtained from cultures of gram negative bacteria *Chromobacterium violaceum.* Due to the synthetic complexity of the compound, as well as the low yield from the producing organism, analogs are sought to create

synthetically accessible alternatives. It high efficacy and manageable toxicity are helpful for both patients receiving treatment and doctors prescribing it.

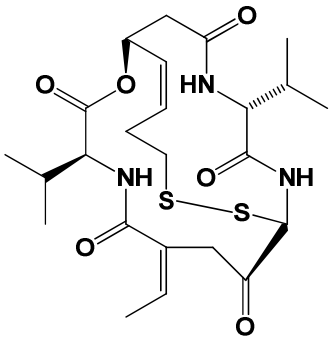


Fig. 21: Romidepsin

Jeppesen [20] has conducted clinical trials on the drug teduglutide, which is a novel glucagon-like peptide 2 analog, in the treatment of patients with short bowel syndrome. In such patients, parenteral support (PS) is lifesaving because they are unable to compensate for their malabsorption by metabolic or pharmacologic adaptation. These complications altogether may impair the quality of life of patients. Hence, the treatment is to increase intestinal absorption, decrease the diarrheal bouts, and reduce the need for PS to achieve the best possible quality of life for the patient. Conventional treatments include multiple drug administration which is inconvenient. However, teduglutide improves intestinal rehabilitation by promoting mucosal growth and possibly by restoring gastric emptying and secretion, thereby reducing intestinal losses and promoting intestinal absorption. Phase II balance study has revealed that this drug reduced diarrhea by and appears to be safe and well tolerated upto 24 weeks.

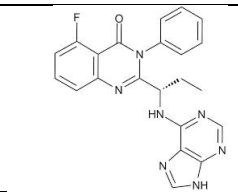
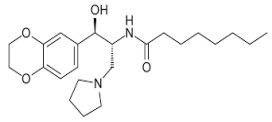
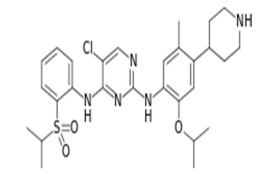
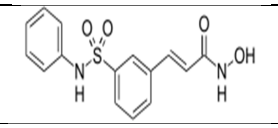
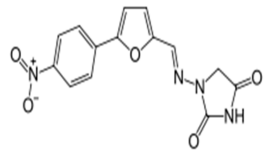
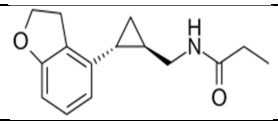
Bhatt *et al*. [21] have performed animal studies using brentuximab vedotin which is an anti-CD30 monoclonal antibody conjugated by a protease-cleavable linker to a microtubule-disrupting agent, monomethyl auristatin E. This drug complex is a novel therapeutic approach to treat primary effusion lymphoma (PEL). PEL is an aggressive subtype of non-Hodgkin lymphoma characterized by short survival with current therapies. These researchers have demonstrated that PEL cell lines and primary tumors express CD30 and thus may serve as potential targets for brentuximab vedotin therapy. In vitro studies with this drug revealed decrease in cell proliferation and, in vivo studies in mice showed promotion in tumor regression and prolonged survival.

Vincenti *et al*. [22] have performed phase II trials on the drug belatacept; which is used for prevention of acute rejection and protection of renal function in kidney transplant recipients. However, the incidence of post transplantation lymphoproliferative disorder was higher. This trial was extended with an aim to assess long-term safety and efficacy of belatacept. This study showed high patient persistence with intravenous belatacept, stable renal function, predictable pharmacokinetics, and good safety with belatacept over 5 years.

Panaccione *et al*. [23] have reviewed the clinical perspectives of infliximab which is an anti-tumour necrosis factor-alpha antibody. It is known to be effective for patients with Crohn's disease who do not respond to conventional treatments. Also, randomized controlled trials have demonstrated that infliximab is also beneficial for the treatment of moderate to severe ulcerative colitis in patients who are either intolerant or refractory to immunosuppressant agents or steroids.

Seifried *et al*. [24] has studied a case report of a patient with treatment resistant gout who was prescribed pegloticase and developed a severe reaction. He was treated with aspiration and corticosteroid injections, colchicine and nonsteroidal anti-inflammatory drugs, but then required allopurinol. Despite aggressive therapy, the patient continued to have hyperuricemia and tophi developed even after treatment with febuxostat and probenicid. The patient was later on treated with pegloticase and it was observed that this drug can be an effective alternative therapy in patients with tophaceous gouty arthritis that is resistant to conventional treatments. Before starting this drug, G6PD deficiency, serum uric acid levels also should be checked before each infusion and pegloticase should be discontinued if the serum uric acid level is greater than 6mg/dL.

Table 1: Some orphan drugs approved by USFDA (2014)

Sl. no.	Generic name	Treatment of Disease(s)	Route of administration	Chemical Structure/Formula	Pharmacological activity
1.	Idelalisib	Chronic lymphocytic leukemia and small lymphocytic lymphoma	Oral use		Phosphoinositide 3-kinase inhibitor
2.	Eliglustat	Type I Gaucher disease	Oral use		Inhibitor of glucosylceramide synthase
3.	Ceritinib	Non-small cell lung cancer which is anaplastic lymphoma kinase(ALK)-positive	Oral route		Anaplastic lymphoma kinase inhibitor
4.	Miltefosine	Leishmaniasis	Oral route		Interaction with membrane lipids inhibition of cytochrome C oxidase
5.	Belinostat	Peripheral T-cell lymphoma	Intravenous route		Inhibitor of histone deacetylase
6.	Dantrolene sodium	Malignant hyperthermia syndrome	Intravenous route		Activator of catabolism
7.	Tasimelteon	Non-24-hour sleepwake disorder in blind individuals without light perception	Oral route		Melatonin MT1 and MT2 receptor agonist
9.	Recombinant human acid alpha-glucosidase;	Pompe Disease	Intravenous route	$C_{4758}H_{7262}N_{1274}O_{1369}S_{35}$	Degradation of lysosomal glycogen
10.	Ecallantide	Angioedema	Subcutaneous route	$C_{305}H_{442}N_{88}O_{91}S_8$	Suppressor of pathogenetic mechanism caused by mutation of the C1-inhibitor gene.
11.	Siltuximab	Treatment of Castleman's disease	Intravenous route	$C_{6450}H_{9932}N_{1688}O_{2016}S_{50}$	Inhibitor of IL-6, thus restoring CYP450 activities to higher levels
12.	Ramucirumab	Gastric cancer	Intravenous route	$C_{6374}H_{9864}N_{1692}O_{1996}S_{46}$	Inhibitor of ligand-induced proliferation and migration of human endothelial cells

CONCLUSION

Orphan drug development continues to remain an under researched area because it does not provide any higher financial business for the pharmaceutical industry. However, various incentives provided by the Orphan drug act have promoted its research and development to a smaller extent. The review highlights some orphan drugs under various phases of clinical trials which have given promising results for treating special and rare disease states. Still

more research is required to be conducted in this area to treat orphan diseases, although for a lower population of society.

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REFERENCES

[1] Sharma A, Jacob A, Tandon M, Kumar D, *J. Pharm. Bioallied Sci.*, **2010**, 2(4), 290-299.
[2] Schieppati A, Henter J, Daina E, Aperia A, *Lancet*, **2008**, 371, 2039-41.
[3] Haffner ME, *The New Journal of Medicine*, **2006**, 354, 445-447.
[4] Stakisaitis D, *Medicina Kaunas*, **2007**, 43(6), 441-446.
[5] Song P, *Biosci Trends*, **2012**, 6(2), 48- 51.
[6] Wastfelt, *Journal of Internal Medicine*, **2006**, 260, 1-10.
[7] Goldstein AL, *Frontiers in biomedicine*, Kluwer Academic, Plenum publishers, New York, **2001,** pp 347.
[8] Wilcken B, *J Inherit Metab Dis.*, **2001**, 24 , 291–298.
[9] Gerss JWO, Kopcke W, *Rare Dis Epidemiol*, **2010**, 686, 173–190.
[10] Gericke CA, Riesberg A, Busse R, *J Med Ethics*, **2005**, 31, 164-168.
[11] Donnenfeld ED, *Clinical Ophthalmology*, **2011**, 5, 811-816.
[12] Mette, Orngreen, Madsen KL, Preisler N, Andersen G, Vissing J, Laforate P, *Neurology*, **2014**, 82, 607-613.
[13] Blight AR, *Therapeutic Advances in Neurological Disorders*, **2011**, 4(2), 99–109.
[14] Beal B, Bertram TM, Schilling JM, Wallace MS, *Journal of Clinical interventions in ageing*, **2012**, 7, 249-255.
[15] Widemann BC, Balis FM, Kim A, Boron M, Jayaprakash N, Shalabi A, *Journal of Clinical Oncology*, **2010**, 28(25), 3979-3986.
[16] Gibod B, Bouillet L, *Clinical and Experimental Immunology - The Journal of Translational Immunology*, **2012**, 168(3), 303-307.
[17] Colao A, Block C, Gaztambide MS, Kumar S, Seufert J, Casanueva FF, *Pituitary*, **2014,** 17(2), 180-186.
[18] Elisei R, Schlumberger MJ, Muller SP, Schoffski P, Brose MS, Shah MH, *Journal of Clinical Oncology*, **2013**, 31(29), 3979-3986.
[19] VanderMolen K, McCulloch W, Pearce CJ, Oberlies NH, *The Journal of Antibiotics*, **2011**, 64, 525 -530.
[20] Jeppesen PB, *Therapeutic Advances in Gastroenterology*, **2012**, 5(3), 159-171.
[21] Bhatt S, Ashlock BM, Natkunam Y, Sujoy V, Chapman JR, Ramos JC, Mesri EA, Lossos IS, *Blood*, **2013**, 122(7), 1233-1242.
[22] Vincenti F, Blancho G, Durrbach A, Friend P, Philip JG, Halloran F, *Journal of the American Society of Nephrology*, **2010**, 21(9), 1587-1596.
[23] Panaccione R, Fedorak RN, Aumais G, *Canadian Journal of Gastroenterology*, **2008**, 22(3), 261-272.
[24] Seifried RM, Roberts J, *Hawaii Journal of Medicine & Public Health*, **2013**, 72(7), 220-223.