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Cystinosis: insights into the disease and its management

Cystinosis, previously known as Lignac-Fanconi disease, is a rare autosomal recessive lysosomal storage disease (LSD) caused by mutations in the CTNS gene. These mutations lead to the accumulation of cystine in lysosomes. In cystinosis, unlike other LSDs where the problem is with acid hydrolases that degrade macromolecules, the accumulation of cystine in all body tissues is due to improper efflux from lysosomes. If left untreated, this can lead to multi-organ damage, progression to end stage renal disease (ESRD), and subsequently, death within the first decade of life. Fortunately, with early diagnosis and cystine depleting therapy, patients may live up to the 5th decade of life (1).

Cystinosis affects approximately 1 in 100,000-200,000 newborns worldwide. A high incidence rate of 1 in 26,000 was found in Brittany, France (2). The highest incidence rate, 1 in 3600, was reported in a Pakistani group living in the West Midlands, UK. Moreover, higher incidence rates were reported in areas with high consanguinity (3).

The CTNS gene codes for cystinosin (Fig 1), a membrane protein responsible for transporting cystine from lysosomes into the cytosol. A dysfunctional cystinosin due to gene mutations leads to lysosomal cystine crystal deposition, which is a key pathogenic feature of the disease. A 57-kb deletion is found in more than 60% of North European cystinosis' patients (4). Outside of this population, this mutation is rarely observed. In the Middle East, this is mostly absent, and the most commonly reported is the c.681G>A (5).

Disease Forms

The disease exists in 3 forms: the infantile nephropathic form, the juvenile or late-onset nephropathic form, and the ocular non-nephropathic or benign form. The first is the most common phenotype, affecting almost 95% of cystinosis patients (6). It is also the most severe, manifesting as renal Fanconi syndrome during the first year of life with progression to ESRD by age of 10y, if not properly treated. It is caused by large deletions or insertions in the gene, for example the 57 kb deletion (4). The juvenile form also affects the kidneys, but symptoms are much less severe because of the lower intra-lysosomal cystine levels. The ocular form is the least severe, leaving the other organs spared since it is associated with the lowest concentrations of intra-lysosomal cystine. *In vitro* studies have shown a total loss of transporter activity in the infantile nephropathic form but only a partial loss in the other types (7).

Pathogenesis

Cystine accumulation

Most cystine comes from the lysosomal degradation of disulphide bearing proteins, mainly albumin. Cubilin and megalin are multi-ligand receptors found in the proximal tubule of the kidney responsible for reabsorption. The degradation of albumin along with the extracellular endocytosis of cystine through megalin provides a constant supply to the lysosomes. Normally, a low amount of cystine is retained due to cytinosin mediated exodus as well as vesicular efflux or exocytosis (8). In cystinotic patients cystinosin is dysfunctional indicating that the amount supplied to the lysosomes exceeds the amount released.

Crystal formation

The slow accumulation of cystine is the key feature of the disease first starting out as needles, which then form polyhedral crystal structures which may build up to reach dimensions greater than 10 µm in diameter, leading to lysosome deformation. These crystals (Fig 2) also impact lysosome motility, impair lysosomal fusion and fission. Although cystine crystals may lead to chronic inflammation that can drive the progression of renal Fanconi syndrome, they are not pathogenic in the initiation of the disease (9). The disconnection between the accumulation of crystals and the initiation of renal Fanconi syndrome has led to the proposal of the following three major theories that may be involved in the pathogenesis of nephropathic cystinosis: energy imbalance, increased apoptosis, and oxidative stress.

In this issue

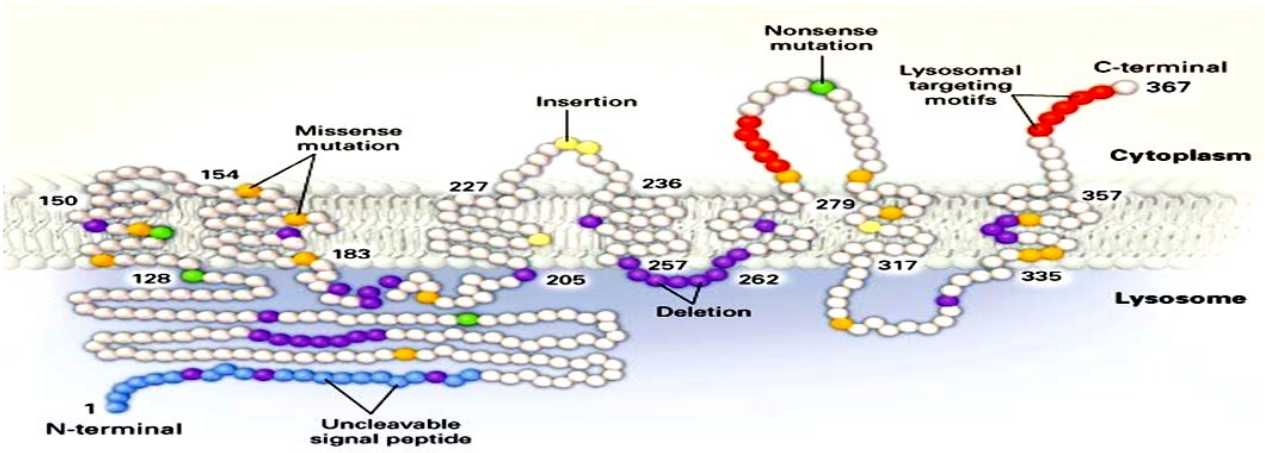

Fig 1. *Cystinosin. 7 trans-membrane protein made up of 367 amino acids located in the membrane of the lysosome. The c-terminal is in the cytoplasm while the N-terminal is located inside the lysosome. (from Ivanova , 2015)*

Energy imbalance and increased apoptosis

When renal tubules were exposed to cystine dimethyl ester (CDME), ATP levels are drastically reduced (10,11), but this was later found to be independent of lysosomal cystine accumulation.

High rates of apoptosis were found in cystinotic fibroblasts and PTCs (11,12). Renal biopsy samples from patients with cystinosis show a significantly reduced number of proximal tubules, which can be linked to the over-expression of and increased activation of the protease enzymes caspase 3 and 4, respectively (12). Although apoptosis leads to the progression of renal Fanconi syndrome, it is not a primary cause of the disease. Initially, proximal tubule integrity is maintained, with shedding of apoptotic PTCs and subsequent proliferation of neighboring PTCs. With time, this adaptive mechanism fails and leads to the development of the swan neck deformity (Fig 3) of the proximal renal tubule (13-15).

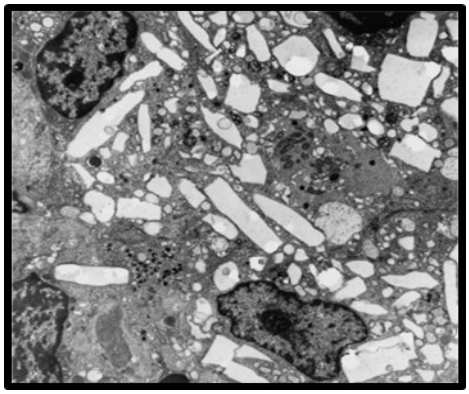

Fig 2. *Electron photomicrograph showing cystine crystals of different shapes in interstitial cells. (from ref 6)*

Impaired glutathione metabolism

One study found that PTCs from cystinotic patients had depleted GSH levels and increased apoptotic

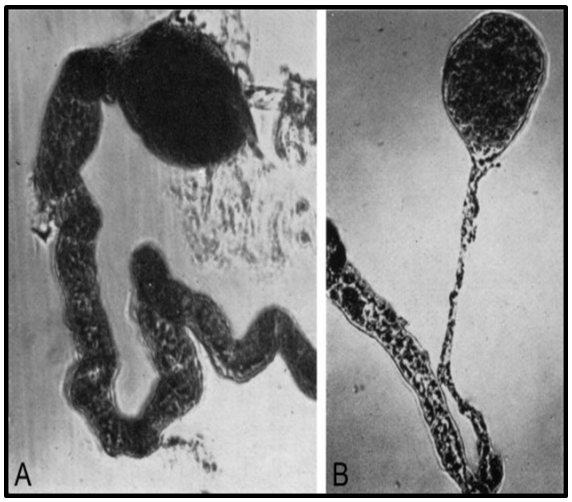

Fig 3. *The main feature of cystinosis is lysosome cystine accumulation. Cystine crystals are found in interstitial macrophages leading to the increased production of inflammatory molecules. Cystine accumulation can also lead to increased apoptosis, oxidative stress, and energy imbalance. All of these mechanisms can be corrected by administration of cysteamine. On the other hand, new pathologic mechanisms such as increased autophagy and altered mTORC1 signaling cannot be corrected by the administration of cysteamine. (from ref 15)*

rate (11,16) due to the overall decrease in cysteine, which serves as a rate-limiting factor for the production of GSH. Most cystine is usually reduced into cysteine in the cytosol. However, with cystinosis, the amount of cystine in the cytosol is reduced because of sequestration into the lysosomes. One study found that the reduction of GSH, and therefore increased oxidative stress, was corrected by the administration of cysteine (16), further supporting the theory of depleted cysteine levels in cystinotic patients. But cysteamine, the cystine depleting medication used for cystinotic patients, has limited efficacy in patients with established Renal Fanconi syndrome (17), indicating the presence of more complex underlying mechanisms. Figure 4 summarises all the proposed pathogenic mechanisms.

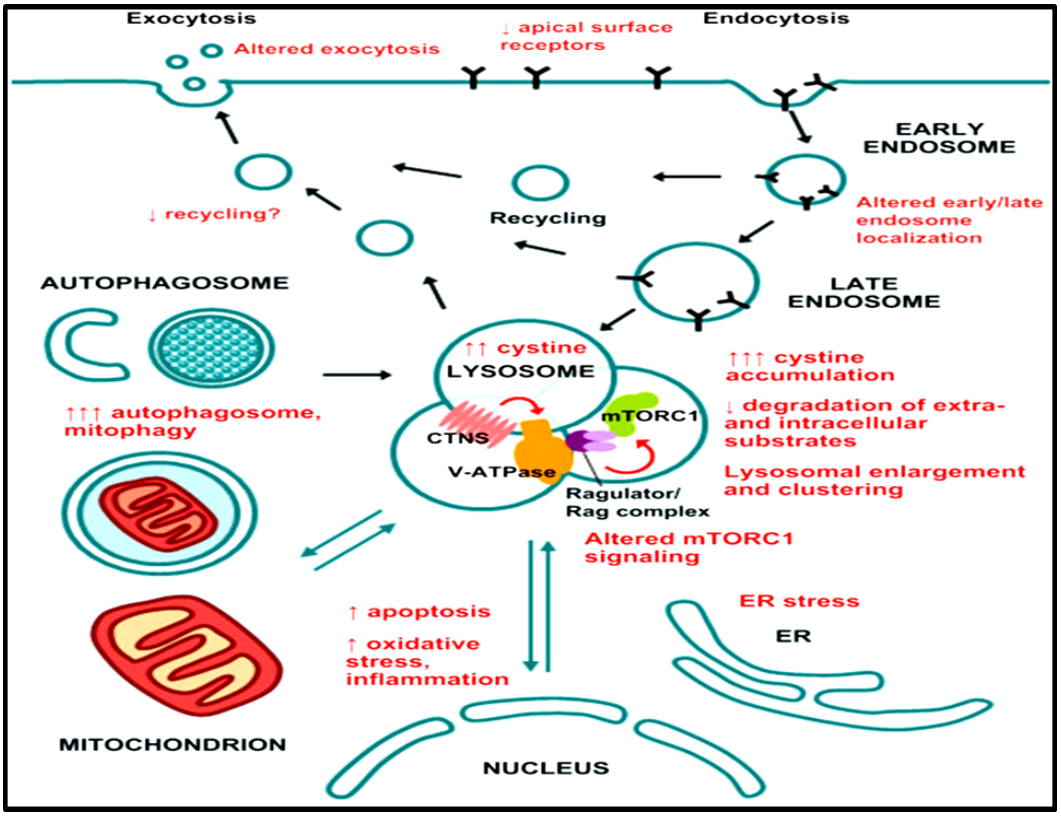

Fig 4. *The main feature of cystinosis is lysosome cystine accumulation. Cystine crystals are found in interstitial macrophages leading to the increased production of inflammatory molecules. Cystine accumulation can also lead to increased apoptosis, oxidative stress, and energy imbalance. All of these mechanisms can be corrected by administration of cysteamine. On the other hand, new pathologic mechanisms such as increased autophagy and altered mTORC1 signaling cannot be corrected by the administration of cysteamine. (from Settembre et al (2013) Nat Rev Cell Biol 14(5);283)*

Clinical Presentation

Renal manifestations

At birth, patients with infantile nephropathic cystinosis show no signs or symptoms with normal length and weight parameters (1,18). Patients may present with characteristic blonde hair and light skin, as it has recently been discovered that the availability of cystinosin was linked to melanin synthesis (19).

By the age of 6-12 months, these patients begin to show symptoms of renal Fanconi syndrome with "asymptomatic aminoaciduria" being the first manifestation (18). Other characteristics include excessive urinary losses of sodium, potassium, bicarbonate, magnesium, calcium, phosphate, glucose, and proteins (1,18,20). At this point, failure to thrive and growth retardation occur. Infants also present with episodes of polyuria, polydipsia, and vomiting, which can lead to severe dehydration and electrolyte imbalance (6, 18).

By the age of 12-18 months, vitamin D resistant rickets begin to manifest (Fig 5) due to urinary losses of phosphate and vitamin D binding protein and reduced activity of alpha 1 hydroxylase in the renal proximal tubules, which is responsible for the activation of vitamin D (21,22). Moreover, serum creatinine levels do not become abnormal until the age of 5 y (18). Therefore, patients with cystinosis should be treated immediately once diagnosed and preferably during the 1st year of life as delaying treatment may lead to the development of ESRD by the age of 10 y (23).

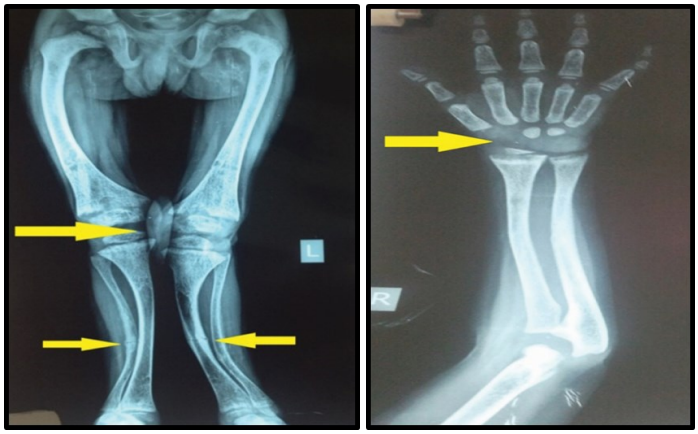

Fig 5. *X-ray of Cystinotic Patient Left: X-ray of lower limbs showing rickets. Right: X ray of wrist showing delayed bone age. (from Kanthila et al (2015) J Clin Diagn Res 9;SD05)*

Patients with the juvenile form usually develop a milder form of renal Fanconi syndrome, with the progression to ESRD occurring later during their

twenties, and some may only present with asymptomatic proteinuria with no severe growth retardation and the manifestation of extra-renal symptoms usually occur at a much later stage (18). Lastly, the adult benign form of cystinosis affects the eyes, with photophobia being the only clinical manifestation, leaving the kidneys and other organs unaffected (24).

Extra-renal manifestations

These develop mostly during adulthood because lysosomal cystine accumulation occurs in all tissues and organs. Patients with the infantile nephropathic form who do not receive treatment develop major extra-renal symptoms by the age of 30 y (17). They include mainly photophobia and blepharospasm, due to corneal cystine accumulation (18).

By the age of 18 months, all cystinosis patients show this corneal cystine deposition. Other ophthalmologic manifestations include superficial punctuate and filamentary keratopathy (24,25). Although retinopathy usually occurs during adolescence, it has been reported in patients as young as 3 y of age (25) and can lead to blindness in 10-15% of patients (24).

More than half of all patients develop primary hypothyroidism by early adolescence and show thyroid gland atrophy and fibrosis due to cystine crystals deposition (26) due to increased apoptosis and endoplasmic reticulum stress. Male patients usually present with primary hypogonadism due to testicular cystine crystal accumulation and fibrosis. The pituitary-testicular axis is disrupted with biochemical values showing low serum testosterone levels and high serum luteinizing hormone (LH), follicular stimulating hormone (FSH), and sex hormone binding globulin (SHBG) (27). Azoospermia was found in all cystinosis patients, except in one study where spermatogenesis was documented on a testicular biopsy specimen (28).

Unlike male cystinosis patients, female patients are usually still fertile and normal pubertal development is possible. However delayed puberty till 15 y of age is not uncommon (27).

By the age of 18 y, 50% of patients develop glucose intolerance and diabetes, due to a gradual loss of insulin secretion and C-peptide production. Many cystinotic patients who have undergone renal transplantation develop hyperglycemia (29).

Hepatomegaly, due to enlargement of Kupffer cells with cystine crystals, and splenomegaly may occur in up to 40% of patients (30). Some may present with tremors, social difficulties, speech delay and fine motor impairment (31). Children with cystinosis may also have impaired visual memory and tactile recognition, but have strong auditor short-term memories, which can be considered as a compensatory mechanism (32).

Patients with cystinosis may be at high risk for Chiari 1 malformations, due to growth restriction and rickets (33). Muscle weakness and myopathy usually begin during adolescence and mainly affect the distal limbs (34) Cystinotic myopathy is also associated with pulmonary dysfunction as patients may present with signs and symptoms of restrictive lung disease (35). Myopathy is also linked to dysphagia, and subsequently aspiration pneumonia, and is inversely related with the duration of cystine depleting therapy (36).

Diagnosis

Diagnosis may be confirmed by any of the following three methods: detection of elevated cystine count in leuokocytes, molecular analysis of the CTNS gene, and detection of corneal crystals by the slit lamp examination (37).

Other methods include reflectance confocal microscopy (RCM), a non-invasive imaging technique that uses a diode laser to detect dermal cystine deposits, which are specific to cystinotic patients (38).

Prenatal diagnosis is possible during the first trimester using molecular analysis or by measuring ^{35}S-labeled cystine accumulation in cultured amniocytes or chorionic villi samples, and by a direct measurement of cystine in uncultured chorionic villi, followed by quantification of cystine using HPLC or LC-MS/MS (39). Newborn screening is currently unavailable due to technical issues such as requirements of higher volumes of blood samples (5-10 ml) to correctly quantify cystine and the problem with the spontaneous oxidation of cysteine to cystine in stored blood samples leading to false results (37).

Treatment

Symptomatic treatment

Once the patient is diagnosed with cystinosis, treatment should begin with a combination of cystine depleting therapy and symptomatic treatment aimed at correcting electrolyte and acid-base abnormalities, nutritional deficits, and managing the patient's extra-renal manifestations, such as rickets, hypothyroidism, and/or other endocrine abnormalities.

Cystine depleting therapy

Cysteamine was approved by the FDA in 1994, and in 1997 in Europe for the treatment of cystinosis and is currently the only treatment that targets cystine accumulation (20,23,41).

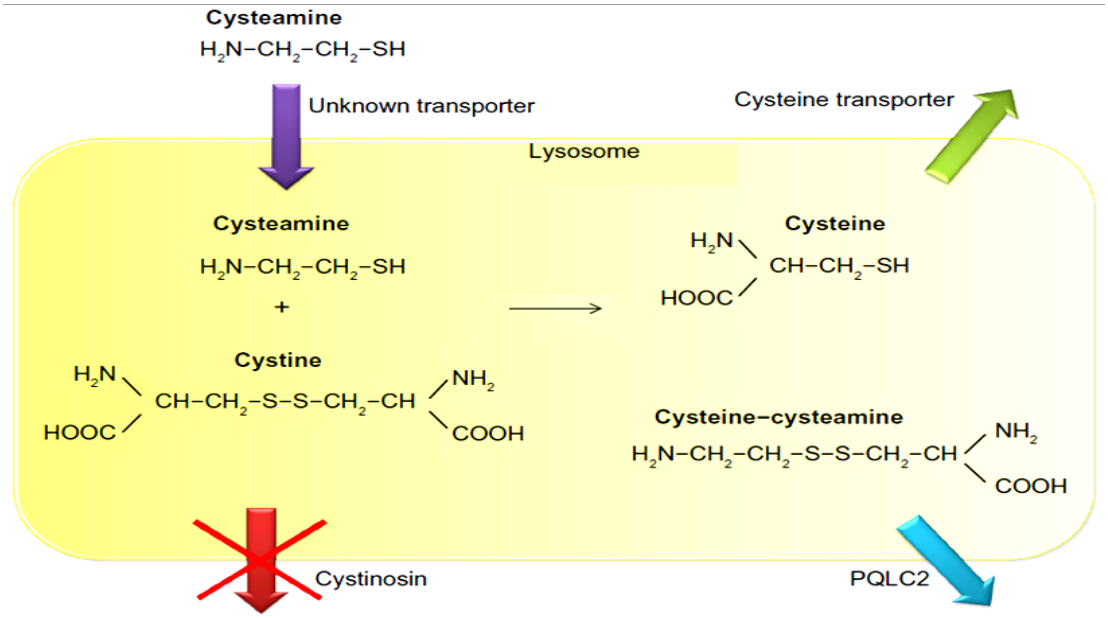

Fig 6. Mechanism of action of Cysteamine. *Cysteamine converts cystine into cysteine and cysteine-cysteamine, so that they are able to efflux from their respective channels. (from Besouw & Levtchenko (2014) Int J Nephr Renovasc Dis 7;297)*

Cysteamine depletes cystine by entering through an unknown transporter and cleaving the disulfide bond in cystine into free cysteine and cysteamine-cysteine mixed disulfide. The use of cysteamine is the cornerstone of therapy as it slows the progression to ESRD by preventing further glomerular damage and may slow or prevent the progression of extra-renal symptoms such as hypothyroidism, hyperglycemia, myopathy and pulmonary dysfunction (17, 23, 42). The best outcomes are obtained when cysteamine is initiated before age 1y and continued lifelong (23). Although cysteamine is able to prevent growth failure if initiated in early infancy, it is unable to achieve a "catch-up growth" once growth retardation has been established (21,43). In addition, oral cysteamine cannot reverse established renal Fanconi syndrome (17,43).

Side effects

Gastrointestinal side effects such as nausea, vomiting, dyspepsia and epigastric pain, are common in cystinotic patients taking the oral formulation of cysteamine, cysteamine bitartrate. Therefore, patients taking cysteamine are usually prescribed proton pump inhibitors (PPI) to reduce the risk of ulceration and manage gastric acid hypersecretion (44).

Other side effects include halitosis and bad sweat odour which occur due to the medication's metabolite, disulfide. Some patients have found oral supplements of vitamin B2, riboflavin, and chlorophyll tablets to be useful in masking this bad odour (45). Rare side effects which occur at overdose include striae rubrae, bone pain, myalgia, and symmetric angioendotheliomatosis elbow lesions (46). Seizures, hyperthermia, lethargy, neutropenia and allergic rashes have also been reported at high doses of cysteamine usage. For this reason, it is usually started at low doses and titrated up slowly (47). Female patients who are planning to become pregnant must consider discontinuing cysteamine due to its teratogenic potential.

Dose and formulations available

Cysteamine bitartrate (Cystagon®), the most commonly used oral preparation (41), is administered every 6 h, with the dose calculated based on body surface area (BSA) (1.30 g/ m^2/day; maximum of 1.95 g/ m^2/day) and not on bodyweight (50 mg/kg/day) to reduce the risk of overdose (48). Cysteamine is usually started at 1/6 of the target dose and increased every 4-6 weeks gradually to reduce the incidence of side effects, which may subsequently lead to poor compliance (47).

A delayed release formulation of cysteamine bitartrate (Procysbi®) was approved in 2013 in the USA and Europe for the treatment of cystinosis. In contrast to the immediate release formulation, which is released in the stomach, the delayed release capsule is enteric coated and consists of microspheronized beads. The modified formulation was based on the hypothesis that enteric release allowed a greater rate of absorption and less first pass metabolism, thus allowing twice daily administration. The dose of Procysbi® is exactly the same as the dose for Cystagon®, except that it is administered in 2 doses, every 12 h (49).

When comparing Procysbi® to Cystagon®, Procysbi® was non-inferior to Cystagon®,- in reduc-

ing WBC cystine. Although the frequency of PPI use in patients taking Procysbi® decreased significantly (87%), the frequency of gastrointestinal side effects was similar to Cystagon®. Overall the safety and efficacy profile of both medications were comparable.

Management of corneal cystine accumulation

Oral cysteamine is unable to reverse corneal cystine accumulation, so topical cysteamine is necessary to dissolve the corneal cystine crystals and treat photophobia. Currently, 0.44% solution, Cystaran® is the formulation available and must be administered hourly while awake. However, poor compliance has been reported with topical cysteamine due to the solution's low pH, which may cause eye burning. A 0.55% gel formulation (Cystadrops®) has recently been developed and is administered 4 times daily, thus improving compliance. Ocular symptoms usually improve within a few weeks of continuous usage, but the cornea may not appear clear until 2-3 months of using the topical formulation.

Renal transplantation

Although oral cysteamine may delay the development of ESRD by 6-10 y, many patients ultimately develop renal failure. Therefore, the only cure is a kidney transplant as cystine crystals that develop on the grafted kidney are not pathogenic because they arise from host mononuclear cells. However, patients still need to continue taking cystine depleting agents to control the extra-renal symptoms (50). The 5-year graft survival rate in cystinotic patients is much longer than those who have undergone renal transplantation but do not have the disease. Patients who have undergone renal transplantation must be given immunosuppressive agents, so they should be monitored for infections, immunodeficiency and the development of diabetes mellitus (42).

Gene therapy

Gene therapy is the only novel method that has been proposed, specifically. The issue with cystinosis is that the CTNS gene is expressed in all tissues, which would therefore require a gene delivery system that is capable of efficiently transducing cells in every tissue compartment. To date, no such system exists, but hematopoietic stem cell (HSC) transplantation can theoretically integrate into every tissue compartment, which is why it has been suggested as a potential therapy for cystinosis. HSC transplanted into cystinotic mice showed significant integration into tissues. In addition, the cystine content was reduced by 57-94% in the organs tested. The progression of renal dysfunction was halted and the deposition of corneal cystine crystals significantly reduced (51). When the experiment was performed using mesenchymal stem cells, the benefit on kidney function was short-lived mainly due to poor integration of the cells into the organs tested (52). Current studies are aimed at developing safer strategies for HSC transplantation using lentiviral vectors as opposed to allogenic stem cell transplantation, which carries the risk of increased morbidity and mortality. Harrison and collaborators demonstrated that cross-correction was possible in cystinosis, with the deficient cystinosin being transferred from CTNS-expressing cells to CTNS deficient cells (53).

Therapeutic drug monitoring

Besides diagnosing cystinosis, the leukocyte cystine assay is the cornerstone of therapeutic monitoring of cystinotic patients. Although it is not the most ideal method, as cystine accumulation in blood may not accurately represent lysosomal cystine in tissues, it is the only method that is currently used to monitor cystine levels. In the past, mixed leukocytes were used but they were found to be less reliable as cystine preferentially accumulates in polymorphonuclear (PMN) leukocytes. A study by Levtchenko and co-workers showed that 15 patients required a dose increase after PMN leukocyte's cystine levels were higher than the target ranges in comparison to mixed leukocyte's cystine levels, which showed that they were within the target range (54). Samples for monitoring should be obtained at the time of trough cysteamine, 6 h after the last dose of the immediate release form of cysteamine and 12 h after the last dose of the delayed release formulation. The therapeutic target levels are <1.0 nmol ½ cystine/ mg protein (55).

Once the blood sample is obtained, it should be treated with N-ethylmaleimide to prevent sulfhydryl exchange with cysteine. PMN leukocytes should then be isolated within 24 h; however, if the assay is done on mixed leukocytes, then a differential complete blood count (CBC) should also be measured as well as the proportion of protein that comes from PMN leukocytes. Cystine content is then determined by LC-MS/MS, and the amount of protein is determined by the Lowry protein assay. LC-MS/MS is the currently used method because of its high sensitivity and specificity in distinguishing between normal cystine levels and heterozygotes (56).

Prognosis

Life expectancy has dramatically increased over the last 30y with the development of cysteamine when started at an age earlier than 5y and the availability of renal replacement therapy. Patients who are diagnosed in early infancy, receive proper treatment, and adhere to their regimens, are expected to live well into adulthood and even up to the age of 50y (17, 23, 42). A US database study examining patients between the ages of 18-45y showed that longer duration of therapy (>20y compared to <10y) also reduced the incidence of extra-renal symptoms by similar rates (17). In conclusion, since many aspects of the disease are still unclear, further research is necessary to develop a better understanding of cystinosis that may help find potential therapeutic targets.

References

1. Nesterova G, Gahl WA. Pediatr Nephr. 2013;28(1):51-9.
2. Bois E, Feingold J, Frenay P, Briard ML. J Med Genet. 1976;13(6):434-8.
3. Hutchesson AC, Bundey S, Preece MA, Hall SK, Green A.. J Med Genet. 1998;35(5):366-70.
4. Taranta A, Wilmer MJ, van den Heuvel LP, Bencivenga P, et al. Pediatr Nephrol. 2010;25(7):1263-7.
5. Sadeghipour F, Basiratnia M, Derakhshan A, Fardaei M. Hum Genome Var. 2017;4:17038.
6. Stokes MB, Jernigan S, D'Agati VD. Kidney Int. 2008;73 (6):782-6.
7. Kalatzis V, Nevo N, Cherqui S, Gasnier B, Antignac C. Hum Mol Genet. 2004;13(13):1361-71.
8. Amsellem S, Gburek J, Hamard G, Nielsen R, et al. J Am Soc Nephrol. 2010;21(11):1859-67.
9. Prencipe G, Caiello I, Cherqui S, Whisenant T, Petrini S, et al. J Am Soc Nephrol. 2014;25(6):1163-9.
10. Foreman JW, Benson LL, Wellons M, et al. J Am Soc Nephrol. 1995;6(2):269-72.
11. Laube GF, Shah V, Stewart VC, Hargreaves IP, Haq MR, Heales SJ, et al. Pediatr Nephr 2006;21(4):503-9.
12. Sansanwal P, Kambham N, Sarwal MM. Pediatr Nephrol. 2010;25(1):105-9.
13. Gaide Chevronnay HP, Janssens V, Van Der Smissen P, et al. J Am Soc Nephrol. 2014;25(6):1256-69.
14. Galarreta CI, Forbes MS, Thornhill BA, et al. Am J Physiol Renal Physiol. 2015;308(10):F1155-66
15. Darmady EM, Stranack F. Br Med Bull. 1957;13:21-6.
16. Chol M, Nevo N, Cherqui S, Antignac C, Rustin P. Biochem Biophys Res Commun. 2004;324(1):231-5.
17. Gahl WA, Balog JZ, Kleta R. 2007;147(4):242-50.
18. Gahl WA, Thoene JG, Schneider JA. N Engl J Med. 2002;347(2):111-21.
19. Chiaverini C, Sillard L, Flori E, Ito S, Briganti S, Wakamatsu K, et al. FASEB J. 2012;26(9):3779-89.
20. Gahl WA, Reed GF, Thoene JG, Schulman JD, Rizzo WB, Jonas AJ, et al. N Engl J Med. 1987;316(16):971-7.
21. Besouw M, Levtchenko E. Minerva Pediatr. 2010;62 (3):307-14.
22. Soliman NA, El-Baroudy R, Rizk A, Bazaraa H, Younan A. Saudi J Kidney Dis Transpl. 2009;20(3):436-42.
23. Brodin-Sartorius A, Tete MJ, Niaudet P, Antignac C, Guest G, et al. Kidney Int. 2012;81(2):179-89.
24. Gahl WA, Kuehl EM, Iwata F, Lindblad A, Kaiser-Kupfer MI. Mol Genet Metab. 2000;71(1-2):100-20.
25. Tsilou E, Zhou M, Gahl W, Sieving PC, Chan CC. Surv Ophthalmol. 2007;52(1):97-105.
26. Chan AM, Lynch MJ, Bailey JD, Ezrin C, Fraser D. Am J Med. 1970;48(6):678-92.
27. Winkler L, Offner G, Krull F, Brodehl J. Eur J Pediatr. 1993;152(3):244-9.
28. Besouw MT, Kremer JA, Janssen MC, Levtchenko EN. Fertil Steril. 2010;93(6):1880-3.
29. Filler G, Amendt P, von Bredow MA, Rohde W, Ehrich JH. Eur J Pediatr. 1998;157(9):738-42.
30. Gahl WA, Schneider JA, Thoene JG, Chesney R. J Pediatr. 1986;109(4):605-8.
31. Besouw MT, Hulstijn-Dirkmaat GM, van der Rijken RE, et al. J Inherit Metab Dis. 2010;33(6):787-93.
32. Nichols SL, Press GA, Schneider JA, Trauner DA. Pediatr Neurol. 1990;6(6):379-81.
33. Rao KI, Hesselink J, Trauner DA. J Pediatr. 2015;167 (5):1126-9.
34. Vester U, Schubert M, Offner G, Brodehl J. Pediatr Nephrol. 2000;14(1):36-8.
35. Anikster Y, Lacbawan F, Brantly M, Gochuico BL, Avila NA, Travis W, et al. Chest. 2001;119(2):394-401.
36. Sonies BC, Almajid P, Kleta R, Bernardini I, Gahl WA. Medicine (Baltimore). 2005;84(3):137-46.
37. Wilmer MJ, Schoeber JP, van den Heuvel LP, Levtchenko EN. Pediatr Nephrol. 2011;26(2):205-15.
38. Chiaverini C, et al. J Am Acad Derm 2013;68(4):e111-6.
39. Jackson M, Young E. Prenat Diagn. 2005;25(11):1045-7.
40. Emma F, Nesterova G, Langman C, Labbe A, et al. Nephrol Dial Transplant. 2014;29 Suppl 4:iv87-94.
41. Schneider JA, Clark KF, Greene AA, Reisch JS, et al. J Inherit Metab Dis. 1995;18(4):387-97.
42. Van Stralen KJ, Emma F, Jager KJ, et al. Clin J Am Soc Nephrol. 2011;6(10):2485-91.
43. Besouw MTP, Van Dyck M, Francois I, et al. Pediatr Nephrol. 2012;27(11):2123-7.
44. Dohil R, Fidler M, Barshop B, Newbury R, Sellers Z, Deutsch R, et al. Pediatr Nephrol. 2005;20(12):1786-93.
45. Besouw M, Blom H, Tangerman A, de Graaf-Hess A, Levtchenko E. Mol Genet Metab. 2007;91(3):228-33.
46. Besouw MT, Bowker R, Dutertre JP, Emma F, Gahl WA, Greco M, et al. J Pediatr. 2011;159(6):1004-11.
47. Corden BJ, Schulman JD, Schneider JA, Thoene JG. Dev Pharmacol Ther. 1981;3(1):25-30.
48. Bouazza N, Treluyer JM, Ottolenghi C, Urien S, et al. P Orphanet J Rare Dis. 2011;6:86.
49. Dohil R, Fidler M, Gangoiti JA, Kaskel F, Schneider JA, Barshop BA. J Pediatr. 2010;156(1):71-5 e1-3.
50. Spear GS, Gubler MC, Habib R, Broyer M. Hum Pathol. 1989;20(5):472-6.
51. Syres K, Harrison F, Tadlock M, Jester JV, Simpson J, Roy S, et al. Blood. 2009;114(12):2542-52.
52. Baer PC, Geiger H. Curr Opin Nephrol Hypertens. 2010;19 (1):1-6.
53. Harrison F, Yeagy BA, Rocca CJ, Kohn DB, Salomon DR, Cherqui S. Mol Ther. 2013;21(2):433-44.
54. Levtchenko E, de Graaf-Hess A, Wilmer M, et al. Clin Chem. 2004;50(9):1686-8.
55. Gahl WA, Schneider JA, Schulman JD, Thoene JG, Reed GF. Pediatr Nephrol. 1990;4(2):129-35.
56. Chabli A, Aupetit J, Raehm M, Ricquier D, Chadefaux-Vekemans B. Clin Biochem. 2007;40(9-10):692-8.

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TEST YOUR KNOWLEDGE

Answers on back page

1) ***One of the major theories involved in the pathogenesis of nephropathic cystinosis is***

a) Increased apoptosis
b) Decreased metabolism
c) Decreased oxidative stress
d) All of the above

2) ***The cornerstone of therapeutic monitoring of cystinotic patients is***

a) Reticulocyte cystine assay
b) Turbidimetric assay
c) Leukocyte cystine assay
d) ELISA

3) ***Currently, the only FDA-approved drug for the treatment of cystinosis and which targets cystine accumulation is***

a) Cystone
b) Cystine
c) Cystamine
d) Cysteamine

Is there a problem?

A patient is given the prescription, shown below, to treat his hypertension. Is there any major error with the prescription?

RMX HOSPITAL

Patient Name: Ahmad Ali Age: 40 years
Address: Street No: 448

Rx

Lisinopril 10mg tablet
1 tablet two times a day
Send one packet

Dr. Faisal
Signature Date: 20/6/18

Answer (Prescription Exercise)

The frequency is wrong. For hypertension, lisinopril is used once daily.

Source: British National Formulary

TOPICAL ISSUES AND CONTROVERSIES

Liquid e-cigarettes: a danger to young kids

In the previous issue we discussed an article outlining the benefits *vs* health risks of using e-cigarettes to help smokers give up smoking. A recent study published online on April 23rd in the journal *Pediatrics* addresses the equally important consideration of how e–cigarettes affect young children exposed to them.

Electronic cigarettes, known as e-cigarettes, are handheld devices that emit a vapour containing nicotine, flavouring, and solvents that are inhaled by users. As e-cigarette use has grown steadily since their introduction in the US in 2007, so has exposure to the liquid nicotine they contain.

Following an enormous jump in children's exposures to toxic liquid nicotine from electronic cigarettes, new research shows that the rate dropped in just one year. But experts say that too many young kids are still being exposed to liquid nicotine. Among cases that ended up in the emergency department, 93% had swallowed the substance. According to researchers, the annual rate of exposures in the US skyrocketed by nearly 1,400% from 2012 to 2015, then fell by 20% from 2015 to 2016.

However these exposures are still occurring and there is more that can be done to reduce exposures in young kids. One of the suggestions by the study authors is to take steps that go beyond 2015 legislation that requires child-resistant packaging for liquid nicotine, which contributed to the decline in exposures.

In their study, the researchers tracked calls to US poison centers related to exposures to liquid nicotine and e-cigarettes among children younger than 6y and found that nearly 8,270 exposures took place from

January 2012 through April 2017. That number averaged out to 129 calls per month or more than four per day. Eighty-four percent of the exposures were accounted for by children younger than 3y.

The health consequences of liquid nicotine exposure from e-cigarettes can be severe. The findings showed that affected children are more than five times as likely to be admitted to the hospital, and 2.6 times more likely to experience a serious medical effect compared to children exposed to traditional cigarettes. It is not surprising as nicotine is a very toxic substance and even in small amounts can cause severe clinical effects, including coma and seizures. It's an important poison, which many consumers don't realise. Among children exposed to liquid nicotine, 35% were treated but not admitted for further treatment, while 1.4% were admitted. There was an increase by 1398% in the annual exposure rate per 100000 children from 0.7 in 2012 to 10.4 in 2015, and subsequently decreased by 20% from 2015 to 8% in 2016.

Meanwhile, there is a need to dispel the public misconception that nicotine isn't harmful. Parents and caregivers who use e-cigarettes are urged to store them in a locked place out of reach and sight from young children.

The legislation requiring child-resistant packaging for liquid nicotine, which is often sold in fruit flavors and brightly colored packaging that appeals to children, is just the first step in the right direction for regulating the product. Some recommend that the use of "flow restrictors", such as those already in use on some children's over-the-counter fever-reducing drugs, is a measure that can be easily applied to liquid nicotine bottles. Others suggest that the amount and/or concentration of liquid nicotine in each package could be reduced, as even a small amount can be a lethal dose to children.

The US FDA should consider regulating the labeling used on liquid nicotine packages and limiting the flavours available. There is a need to limit access and decrease the attractiveness of liquid nicotine to young children.

References

1)https://www.drugs.com/news/e-cig-liquid-remains-poisoning-danger-young-kids-73763.html utm_source=ddc&utm_ medium=email&utm_campaign=Monthly+News+Roundup+-+Vol +164%2C+April+2018

2) Govindarajan P et al. E-Cigarette and Liquid Nicotine Exposures Among Young Children. Pediatrics. 2018;141 (5):e20173361

Botanical dietary supplements

To be classified as a dietary supplement, a botanical must meet the definition given below. As defined by the US Congress in the Dietary Supplement Health and Education Act, which became law in 1994, a dietary supplement is a product (other than tobacco) that

1. is intended to supplement the diet
2. contains one or more dietary ingredients (including vitamins; minerals; herbs or other botanicals; amino acids; and other substances) or their constituents
3. is intended to be taken by mouth as a pill, capsule, tablet, or liquid
4. is labeled on the front panel as being a dietary supplement.

Botanicals are sold in many forms: as fresh or dried products; liquid or solid extracts; tablets, capsules, powders; tea bags; and other forms. A particular group of chemicals or a single chemical may be isolated from a botanical and sold as a dietary supplement, usually in tablet or capsule form. An example is phytoestrogens from soy products. Common preparations include teas, decoctions, tinctures and extracts.

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Are botanical dietary supplements standardised?

Standardisation is a process that manufacturers may use to ensure batch-to-batch consistency of their products. The standardisation process can also provide a measure of quality control.

Dietary supplements are not required to be standardised in the US. In fact, no legal or regulatory definition exists for standardisation as it applies to botanical dietary supplements. Some manufacturers use the term standardisation incorrectly to refer to uniform manufacturing practices; The presence of the word "standardised" on a supplement label does not necessarily indicate product quality.

Ideally, the chemical markers chosen for standardisation would also be the constituents that are responsible for a botanical's effect in the body. In

this way, each lot of the product would have a consistent health effect. However, the components responsible for the effects of most botanicals have not been identified or clearly defined. For example, the sennosides in the botanical senna are known to be responsible for the laxative effect of the plant, but many compounds may be responsible for valerian's relaxing effect.

Are botanical dietary supplements safe?

Many people believe that products labeled "natural" are safe and good for them. This is not necessarily true because the safety of a botanical depends on its chemical makeup, how it works in the body, how it is prepared, and the dose used.

The action of botanicals range from mild to powerful (potent). A botanical with mild action may have subtle effects. Some mild botanicals may have to be taken for weeks or months before their full effects are achieved. For example, valerian may be effective as a sleep aid after 14 days of use but it is rarely effective after just one dose. In contrast a powerful botanical produces a fast result. Kava, as one example, is reported to have an immediate and powerful action affecting anxiety and muscle relaxation.

The dose and form of a botanical preparation also play important roles in its safety. Teas, tinctures, and extracts have different strengths. The same amount of a botanical may be contained in a cup of tea, a few teaspoons of tincture, or an even smaller quantity of an extract. Also, different preparations vary in the relative amounts and concentrations of chemical removed from the whole botanical. For example, peppermint tea is generally considered safe to drink but peppermint oil is much more concentrated and can be toxic if used incorrectly. It is important to follow the manufacturer's suggested directions of use and not exceed the recommended dose without the advice of a health care provider.

Does a label indicate the quality of a botanical dietary supplement product?

The degree of quality control depends on the manufacturer, the supplier, and others in the production process.

In 2007, the FDA issued Good Manufacturing Practices (GMPs) for dietary supplements to ensure quality. The GMPs aim to prevent the inclusion of the wrong ingredients, the addition of too much or too little of a dietary ingredient, the possibility of contamination (by pesticides, heavy metals such as lead, bacteria, etc.), and the improper packaging and labeling of a product.

What methods are used to evaluate the health benefits and safety of a botanical dietary supplement?

Scientists may investigate history of use, conduct laboratory studies using cell or tissue cultures, and experiment with animals. Studies on people (e.g., individual case reports, observational studies, and clinical trials) provide the most direct evidence of a botanical supplement's effects on health and patterns of use. Some botanicals have been evaluated in scientific studies. For example, research shows that St. John's wort may be useful for short-term treatment of mild to moderate depression. Like other dietary supplements, botanicals are not required by federal law to be tested for safety and effectiveness before they are marketed, so the amount of scientific evidence available for their ingredients varies widely.

Source

https://ods.od.nih.gov/factsheets/BotanicalBackground-HealthProfessional/

New 'biologic' drug for severe asthma

Asthma is a chronic lung disease. An estimated 15% of asthma patients cannot control the disease with current inhaled medications. Such patients have severe disease with persistent airway inflammation, which causes continuous symptoms of breathlessness and exercise intolerance, and puts them at risk of severe attacks for which they have to be hospitalized. They suffer greatly, and have very poor quality of life, and have much difficulty in functioning and cannot go to work.

A biologic drug in development to treat severe asthma, reduces the rate of serious attacks by about two-thirds compared to a placebo. If approved, the drug tezepelumab could join a group of costly medications that appear to offer relief when nothing else curbs respiratory distress. The new research was funded by the drug developers, Amgen and MedImmune, a subsidiary of AstraZeneca. Tezepelumab, an injectable drug, is a monoclonal antibody.

In this phase 2, randomised, double-blind, placebo -controlled trial, they compared subcutaneous tezepelumab at three dose levels with placebo over a 52-week treatment period. The primary end point was the annualised rate of asthma exacerbations (events per patient-year) at week 52. Researchers

wanted to understand the effects of tezepelumab on asthma patients who had suffered at least one asthma attack that required hospitalisation within the past year, or two attacks that forced physicians to increase their medication level.

Overall, 918 patients were screened and 584 underwent randomization: 145 were assigned to low-dose tezepelumab, 145 to medium-dose tezepelumab, 146 to high-dose tezepelumab, and 148 to placebo. The 584 study patients with severe asthma were nonsmokers, aged 18 to 75, who used asthma inhalers.

The use of tezepelumab at a dose of 70 mg every 4 weeks (low dose; 145 patients), 210 mg every 4 weeks (medium dose; 145 patients), or 280 mg every 2 weeks (high dose; 146 patients) resulted in annualized asthma exacerbation rates at week 52 of 0.26, 0.19, and 0.22, respectively, as compared with 0.67 in the placebo group (148 patients).

Thus, exacerbation rates in the respective tezepelumab groups were lower by 61%, 71%, and 66% than the rate in the placebo group. Three serious adverse events were considered by the researchers to be related to the trial agent; two (pneumonia and stroke) occurred in the same patient in the low dose tezepelumab group and one (the Guillain– Barré syndrome) in the medium-dose tezepelumab group.

Tezepelumab appears to be the broadest and most promising biologic for the treatment of persistent uncontrolled asthma to date. The drug blocks a molecule that's key to the development of swelling in the airway, and is therefore effective in different subtypes of asthma. As a result, the chances that the drug will work in severe asthma patients are higher than with the available monoclonals that are more selective for a specific subtype of patients. It's too early to estimate how much the drug may cost. However, similar biologic asthma drugs cost $25,000 to $30,000 a year.

The authors recommend further studies involving large, ethnically diverse populations of patients with uncontrolled asthma, and using the “best available small-molecule therapies”, including high-dose inhaled glucocorticoids plus LABAs. This is necessary to demonstrate the clinical importance of their findings.

References

1) https://www.drugs.com/news/new-biologic-may-help-severe-asthma-66924.html?utm_source=ddc&utm_medium=email&utm_campaign=Newsletter+Vol+157+-+September+2017

2) Corren J. N Engl J Med 2017;377:936-46.

NEWS from the FDA

Sweeping changes to opioid policies unveiled by FDA

In response to the ongoing opioid abuse epidemic, top officials at the US FDA announced plans to reassess the agency's approach to opioid medications.

They are determined to help defeat this epidemic through a science-based and continuously evolving approach. The plan contains real measures the agency can take to make a difference in the lives of so many people who are struggling under the weight of this terrible crisis. The plan is further outlined in an article published online in the *New England Journal of Medicine (N Engl J Med 2016; 374:1480-1485).*

In the US, the annual number of deaths from opioid overdoses now exceeds the number of deaths caused by motor vehicle accidents. Regardless of whether these issues are viewed from the perspective of patients, physicians, or regulators, the status quo is clearly not acceptable. As the public health agency responsible for over-sight of pharmaceutical safety and effectiveness, FDA recognises that this crisis demands solutions, and urges all concerned to join FDA in this area. The multi-component plan will focus on policies aimed at reversing the epidemic, while still providing pain patients access to effective medication.

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Specifically, the FDA plans to:

* Re-examine the risk-benefit paradigm for opioids and ensure that the agency considers their wider public-health effects;
* Convene an expert advisory committee before approving any new drug application for an opioid that does not have abuse-deterrent properties;
* Assemble and consult with the Pediatric Advisory Committee regarding a framework for pediatric opioid labeling before any new labeling is approved;
* Develop changes to immediate-release opioid labeling, including additional warnings and safety information that incorporate elements similar to those of the extended-release/long-acting (ER/LA) opioid analgesics labeling that is currently required;
* Update Risk Evaluation and Mitigation Strategy requirements for opioids after considering advisory committee recommendations and review of existing requirements;
* Expand access to, and encourage the development of, abuse-deterrent formulations of opioid products;
* Improve access to naloxone and medication-assisted treatment options for patients with opioid-use disorders; and
* Support better pain-management options, including alternative treatments.

The FDA says they will seek guidance from outside experts in the fields of pain management and drug abuse. The agency has already asked the National Academy of Medicine to assist in developing a framework for opioid review, approval, and monitoring that balances an individual's need for pain control with considerations of the broader public-health consequences of opioid misuse and abuse. They will convene independent advisory committees made up of physicians and other experts when considering approval of any new opioid drug that does not contain abuse-deterrent properties. The agency will also convene a meeting of its standing Pediatric Advisory Committee to provide advice on a framework for pediatric opioid labeling and use of opioid pain medications in children.

The FDA also plans to tighten requirements for drug companies to generate post market data on the long-term impact of using ER/LA opioids, an action, they say, that will generate the "most comprehensive data ever collected in the field of pain medicine and treatments for opioid use disorder. The data will further the understanding of the known serious risks of opioid misuse, abuse, overdose and death."

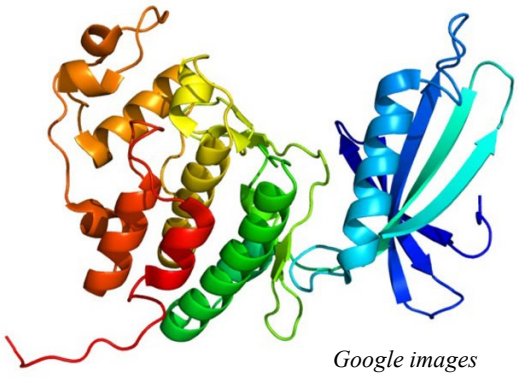
Drug overdose deaths, driven largely by overdose from prescription opioids and illicit drugs like heroin and illegally-made fentanyl, are now the leading cause of injury death in the United States. The FDA is a vital component to combating this epidemic, and the innovation and modernization they have committed to undertaking is an important part of the overall efforts at HHS. The HHS had announced a major initiative to address the opioid abuse epidemic in the US. The initiative focuses on informing opioid prescribing practices, increasing the use of naloxone, and using medication-assisted treatment to move people out of opioid addiction. The FDA says it will provide updates on progress with the goal of sharing timely, transparent information on a regular basis.

Source

http://www.medscape.com/viewarticle/858411

FDA approves new treatment for certain advanced or metastatic breast cancers

In late 2017 the US FDA approved Verzenio (abemaciclib) to treat adult patients who have hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative advanced or metastatic breast cancer that has progressed after taking endocrine therapy. Verzenio was approved to be given in combination with the anti-estrogen fulvestrant, after the cancer had re-grown. It was also approved to be given on its own if patients were previously treated with endocrine therapy and chemotherapy after the cancer had metastasised.



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Verzenio works by blocking cyclin-dependent kinases 4 and 6, involved in promoting the growth of cancer cells. There are two other drugs in this class that are approved for certain patients with breast cancer, palbociclib approved in February 2015 and ribociclib approved in March 2017.

The safety and efficacy of Verzenio in combination with fulvestrant were studied in a randomised trial of 669 patients with HR-positive, HER2-negative breast cancer that had progressed after treatment with endocrine therapy and who had not received chemotherapy once the cancer had metastasised. The study measured the length of time tumours did not grow after treatment (progression-free survival). The median progression-free survival for patients taking Verzenio with fulvestrant was 16.4 months compared to 9.3 months for patients taking a placebo with fulvestrant.

The safety and efficacy of Verzenio as a stand-alone treatment were studied in a single-arm trial of 132 patients with HR-positive, HER2-negative breast cancer that had progressed after treatment with endocrine therapy and chemotherapy after the cancer metastasised. The study measured the percent of patients whose tumours completely or partially shrank after treatment (objective response rate). In the study, 19.7% of patients taking Verzenio experienced complete or partial shrinkage of their tumors for a median 8.6 months.

Common side effects of Verzenio include diarrhea, low levels of certain white blood cells (neutropenia and leukopenia), nausea, abdominal pain, infections, fatigue, low levels of red blood cells (anaemia), decreased appetite, vomiting and headache.

Serious side effects of Verzenio include diarrhea, neutropenia, elevated liver blood tests and blood clots (deep venous thrombosis/pulmonary embolism). Women who are pregnant should not take Verzenio because it may cause harm to a developing foetus.

Source
www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm578071.htm

Gene therapy for arthritis approved in Korea

South Korea approved the world's first gene therapy for arthritis in 2017. The product, Invossa™ (TissueGene) is based on a line of allogenic human chrondrocytes that have been transduced with a retrovirus encoding transforming growth factor-beta1. The transduced cells are first irradiated at a dose that prevents cell division without limiting transgene expression. This is done to avoid possible insertional mutagenesis. Before being shipped to the doctor for injection into the knee of patients, who had unsuccessful pharmacologic and physical therapy, the cells are mixed in a 1:3 ratio with nontransduced, non-irradiated chondrocytes from the same donor. It is claimed that the product holds additional potential for repair of cartilage because genetically modified chondrocytes can be allografted into the sites of cartilage damage where they express transgenes continuously.

Kolon Life Science, TissueGene's exclusive licensee for Asia, including Korea, had received marketing approval from the Korea Ministry of Food and Drug Safety. The approval is important as it is the first critical step towards a worldwide launch for this gene therapy technology that will address one of the most pressing medical needs of millions of people suffering from osteoarthritis.

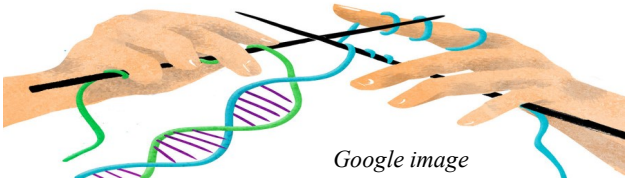
Invossa™ had completed Phase II trials in the United States, and phase III trials are expected to begin in early 2018 under a special protocol assessment agreement with the US FDA.

The clinical trials completed in Korea, and ongoing in the US, have demonstrated pain relief, increased mobility, and improvements in joint structure, which offered significant convenience and relief for osteoarthritis patients who would otherwise had to undergo surgery.

TissueGene will be using the results obtained from its national US Phase III clinical trials, to seek a disease-modifying osteoarthritis drug (DMOAD) designation for Invossa™ from the US FDA, potentially making Invossa™ the first and only cell and gene therapy for osteoarthritis of the knee.

There are only four other gene therapies that have been authorized: two for cancer and two for rare genetic diseases. The concept of gene therapy for arthritis was first published 25 years ago, and over a decade ago, the first human clinical trial was published. The progress has been slow for arthritis gene therapy. However it is gaining momentum and is catching the attention of all stakeholders.

Source
https://www.prnewswire.com/news-releases/korea-approves-the-worlds-first-cell-and-gene-therapy-for-knee-osteoarthritis-300486969.html



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STATE OF KUWAIT
Pharmaceutical & Herbal Medicines Control and Registration Administration

New Pharmaceutical products approved from February to May 2018

Ampicillin Powder for Solution for Injection 250m, 500mg, 1g; Ampicillin (as Sodium) 250mg, 500mg, 1g; Golden Care; S.C. Antibiotice S.A./Romania

Antipan Solution for Injection 20mg/ml; Hyoscine-N-Butylbromide – 20mg/ml; Fourth Dimension Medi cal Co; Arwan Pharmaceutical Industries Lebanon s.a.l./Lebanon

Arixtra Solution for Injection 10mg/0.8ml; Fondaparinux sodium – 7.5mg/0.8ml; Al-Hajery; Aspen Pharma Trading Ltd./Ireland

Arixtra Solution for Injection 5mg/0.4ml; Fondaparinux sodium – 5mg/0.4ml; Al-Hajery; Aspen Phar ma Trading Ltd./Ireland

Arixtra Solution for Injection 7.5mg/0.6ml; Fondaparinux sodium – 7.5mg/0.6ml; Al-Hajery; Aspen Phar ma Trading Ltd./Ireland

Ator Tablets 20mg; Atorvastatin (as calcium) – 20mgAl-Wazzan; Egyptian International Pharmaceutical Industries Co./Egypt

B-Com Injection; Vitamin B1 – 10mg Vitamin B2 phosphate – 5.47mg Nicotinamide – 40mg Vitamin B6 – 4mg D. Pantenol – 6mg; Al-Hafez; Amoun Pharmaceuticals A.R.E./Egypt

Bifril Plus Film Coated Tablets 30/12.5mg; Zofenopril calcium – 30mg Hydrochlorothiazide – 12.5mg; Maseela Pharmaceuticals; Menarini International Operations Luxembourg SA/Luxembourg

Clavomox Suspension 457mg/5ml;Amoxicillin (as trihydrate) – 400mg Clavulanic acid (as potassium salt) – 57mg; KSPICO

Clavomox Tablets 1g; Amoxicillin (as Amoxcillin trihydrate) – 875mg; KSPICO

Co-Varotin Tablets; 160/12.5mg Valsartan – 160mg Hydrochlorothiazide – 12.5mg; KSPICO

Co-Varotin Tablets 80/12.5mg; Valsartan – 80mg Hydrochlorothiazide – 12.5mg; KSPICO

Dalman AQ Nasal Spray; Fluticasone Propionate – 0.05mg;Alghanim Healthcare; Drogsan Ilaclari San Ve Tic. A.S./Turkey

Defal Drops; Deflazacort – 22.75mg/ml; Al-Wazzan; Faes Farma S.A//Spain

Dificlir Film Coated Tablets; Fidaxomicin – 200mgAl-Mojil; Astellas Pharma Europe B.V./The Nether lands

Emmetre Tablets 20mg ; Pipethanate Ethobromide – 20mg; Ali Abdulwahab; ABC Farmaceutici S.p.A./ Italy

Episopt Eye Drops; Timolol (as maleate) – 5mg Dorzolamide (as HCl) – 20mg; Al-Wazzan; Egyptian In ternational Pharmaceutical Industries Co./Egypt

Ferrasil Solution for IV Injection/Infusion; Iron as Iron sucrose – 100mg/5ml; Fourth Dimension Medical Co; Arwan Pharmaceutical Industries Lebanon s.a.l./Lebanon

Genotropin Go Quick Powder and Solvent for Solution for Injection 5.3 and 12mg; Somatropin – (rDNA) – 5.3 and 12mg; YIACO; Pfizer SA/Belgium

Humalog KwikPen 200U/ml; Insulin lispro (rDNA) – 200U/ml; Bader Sultan; Eli Lilly and Company/ USA

Iris Tablets 5mg; Desloratadine – 5mg; Al-Hajery; The United Pharmaceutical Manufacturing Co. Ltd./ Jordan

Jadenu Tablets 90,180,200 and 360mg; Deferasirox – 90,180,200 and 360mg; Al-Mojil; Novartis Pharma AG/Switzerland

Kisqali Tablets 200mg; Ribociclib (as succinate) – 200mg; Al-Mojil; Novartis Pharmaceutical Corpor- tion/USA

Lavigard Tablets 75mg; Clopidogrel (as hydrogensulphate) – 75mg;Al-Homaizi; Gulf Pharmaceutical In dustries (JULPHAR)//UAE

Lezodex Film Coated Tablets; Letrozole – 2.5mg;Alghanim Healthcare; Apotex Inc./Canada

Linezolid Normon Solution for Infusion 2mg/ml; Linezolid – 2mg/ml ;Biomedix; Laboratorios Normon S.A./Spain

Livatam Oral Solution; Levetiracetam – 100mg/ml; Al-Rwani;Med Pharma Pharmaceutical & Chemicals/UAE

Lotemax 0.5% Ophthalmic Gel; Loteprednol etabonate – 0.5%;Ali Abdulwahab; Baush and Lomb Inc./ USA
Matador Solution for Infusion 500mg/100ml; Levofloxacin (as hemihydrate) – 500mg; Safwan; Dar Al Dawa Dev. Invest. Co. Ltd./Jordan
Matador Tablets 750mg; Levofloxacin (as Hemihydrate) – 750mg; Safwan; Dar Al Dawa Dev. Invest. Co. Ltd./Jordan
Meropenem/Anafarm Powder for Sol. for Injn./Infusion 500 and 1000mg; Meropenem (as trihydrate) – 500 and 1000mg; Alfa Gulf Trading Co; Anafarm Hellas S.A./Greece
Metoram Solution for Injection 10mg/2ml; Metoclopramide HCl – 10mg Fourth Dimension Medical Co; Arwan Pharmaceutical Industries Lebanon s.a.l./Lebanon
Mometix AQ Nasal Spray; Mometasone furoate (as monohydrate) – 50mcg; Alghanim Healthcare; Drog san Ilaclari San Ve Tic. A.S./Turkey
Neomet Tablet 850 and 1000mg;Metformin Hydrochloride – 850 and 1000mg; Al-Wazzan; Neopharma/ UAE
Panadol Cold + Flu Early Symptoms, Effervescent Tablets; Paracetamol – 500mg Caffeine – 65mg; YIA CO Medical; SmithKline Beecham (SWG) Ltd. T/A
Glaxo SmithKline Consumer Healthcare/UK
Primovist Solution for Injection 0.25mmol/ml; Gadoxetate disodium – 0.25mmol/ml; Alghanim Healthcare; Bayer Vital GmbH/Germany
Ravivo Solution for Infusion 500mg/100ml; Levofloxacin (as Hemihydrate) – 500mg; Alghanim Healthcare; Drogsan Ilaclari San Ve Tic. A.S./Turkey
Ravivo Tablets 750mg; Levofloxacin (as Hemihydrate – 750mg; Alghanim Healthcare; Drogsan Ilaclari San Ve Tic. A.S./Turkey
Resova Tablets 10 and 20mg; Rosuvastatin (as calcium) – 10 and 20mg; Al-Hajery; Jazeera Pharma ceutical Industries/Saudi Arabia
Rutaine Capsules 20mg; Isotretinoin – 20mg; Al-Hajery; The United Pharmaceutical Manufacturing Co. Ltd./Jordan
Salcrozine Tablets 500mg; Mesalazine – 500mg; Al-Wazzan; Faes Farma S.A//Spain
Stravis Tablets 50 and 100mg; Losartan Potassium – 50 and 100mg; Safwan; Medical & Cosmetic Prod uct Co. Ltd. (Riyadh Pharma)/Saudi Arabia
Vemlidy Tablets 25mg; Tenofovir alafenamide (as fumarate) – 25mg; Warba Medicals; Gilead Sciences International Ltd./UK
Votron Solution for Injection; 250mcg/5ml Palonosetrone as HCl; YIACO; Beim Ilac San ve Tic A.S./ Turkey
Xalafil Tablets 5 and 10mg; Tadalafil – 5 and 10mg; KSPICO; KSPICO/Kuwait
Xultophy Solution for Injection 100 IU/3.6mg/ml; Insulin degludec – 100 U Liraglutide – 3.6mg; Safwan; Novo Nordisk A/S/Denamrk

Answers to: Test your knowledge

Correct answers:
1-a; 2-c; 3-d

The *Kuwait Pharmacy Bulletin* (ISSN 1028-0480) is published quarterly by the Faculty of Pharmacy, Kuwait University, and includes a list of recently approved drugs from the MOH. It aims to provide instructive reviews and topical news items on a range of drug related issues. It is widely distributed free within the university, to hospitals, polyclinics & private pharmacies as well as to other universities within the Gulf & Middle East region.

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