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Care Pathway and Managed Access Protocol for Kanuma in the Netherlands

Summary
Kanuma® (sebelipase alfa) has received marketing authorization in the EU as an orphan drug for the treatment of lysosomal acid lipase deficiency (LALD). Early results of treatment show improved survival in infants with the severe form of LALD (also referred to as Wolman disease), in particular in those with less advanced disease. In a randomized placebo-controlled trial reductions in liver fat content by MRI and improvements in lipid profile and liver enzymes has been observed. LALD is a highly heterogeneous disease and limited information is available on the natural disease course, specifically in milder patients. In addition, long term effects of Kanuma®, in particular the ability to prevent irreversible liver damage, are insufficiently known. This protocol is intended to assist in evidence based decision making for initiation a cessation of expensive treatment with Kanuma® in the Netherlands.

Background

Deficiency of the lysosomal enzyme lysosomal acid lipase (LAL; acid cholesteryl ester hydrolase, EC 3.1.13), caused by mutations in the lysosomal acid lipase (LIPA) gene, results in storage of cholesterylesters in macrophages and hepatocytes. LAL hydrolyses cholesteryl esters and triglycerides to generate free fatty acids and cholesterol in lysosomes. The disorder is extremely rare and has an autosomal recessive pattern of inheritance.
Near or complete absence of LAL activity results in the rapidly fatal infantile-onset Wolman disease (WD) (MIM 278000). These infants have failure to thrive, diarrhea, malabsorption, massive hepatosplenomegaly and hemophagocytic lymphohistiocytosis and usually die before the age of 1 year (Jones 2016). Adrenal glands are also frequently involved. The more attenuated form, cholesteryl ester storage disease (CESD; MIM 278000) has a wide spectrum of clinical phenotypes. Severe disease symptoms with gross enlargement of liver and spleen can occur during childhood, often also accompanied by involvement of the adrenal glands. On the other end of the spectrum are adults who are without any symptoms.

Pathophysiology and phenotypes

Tissues affected by the storage of cholesterol esters and triglycerides are mainly the liver, and gut, but also the bone marrow, adrenal glands, and testis. Adrenal glands may show calcification, particularly in the severe phenotype, also referred to as Wolman disease. The infants have a severe failure to thrive due to malabsorption that results in malnutrition, severe liver disease with end stage liver failure. They also have hepato(splenomegaly) that further increases the risk of malnutrition, and adrenal gland calcification that results in adrenal cortical insufficiency. The bone marrow storage results in lymphohistiocytosis and anemia, thrombocytopenia. Untreated, infants with classic Wolman disease do not survive beyond age one year (Jones 2016). Children with milder forms, but severe manifestations may have gross hepatosplenomegaly, cytopenia, malnutrition and ultimately liver failure. In attenuated phenotypes, a typical pattern of type IIb dyslipidemia occurs in plasma with an increase in total cholesterol as well as LDL cholesterol, combined with low HDL cholesterol levels. This atherogenic profile may result in premature atherosclerosis, which is due to the enhanced production of cholesterol as well as decreased reverse cholesterol transport.
Other complications in adults with CESD are hepatic fibrosis and eventually cirrhosis. It is not completely clear what causes the fibrotic changes. Patients with progressive liver disease will become at risk for development of cirrhosis and liver cancer. (Burton 2015A; Grabowski)

Management

General treatment

Supportive care for patients with CESD consists of measures to treat the complications of liver, gut and bone marrow disease or cardiovascular complications, according to the most up-to-date standards of care. Mechanical ventilation may be needed in case of severely enlarged hepatosplenomegaly compromising pulmonary capacity. Liver transplantation has been performed for cases with end-stage liver failure. For patients with atherosclerosis, the use of statins is part of routine treatment but has received attention as it may also more specifically target the underlying lipid disorder.

Specific treatment

Hematopoietic stem cell transplantation has been performed in some cases of Wolman disease with variable success. This form of therapy is not applied in adult patients.
Since statins and cholestyramine can reduce the production of cholesterol and ApoB, several studies have focused on this type of treatment to reduce the lipid burden in CESD patients. However, while a favorable effect in plasma can be achieved, with some reduction in LDL-cholesterol, its effect on lysosomal accumulation in tissues is unclear. Lovastatin has been

reported to have some effect, although others reported no change even in plasma levels. Ezetimibe, a cholesterol absorption inhibitor, has shown to be able to reduce liver cholesterol accumulation in LIPA knock-out mice. Addition of ezetimibe to statins has been reported in a patient with CESD to further reduce LDL-cholesterol in plasma.

Enzyme replacement therapy.
Enzyme replacement therapy with recombinant LAL (sebelipase alfa; Kanuma®), has recently received marketing authorization in the EU and USA. This therapy offers especially great hope for children severely affected by this disorder, as they are at risk of liver failure and early death that can currently only be prevented by liver transplantation, and gut failure that is very difficult treat. In an ongoing study in nine infants presenting with early-onset LALD (Wolman disease), open-label treatment with sebelipase alfa significantly improved 1-year survival compared with historical controls (Jones 2016). The results of a placebo-controlled trial of sebelipase alfa, administered every 2 weeks at a dose of 1 mg/kg have been published in 2015 (Burton 2015B). Treatment for 20 weeks in a primarily pediatric group of 66 patients with CESD resulted in normalization of alanine aminotransferase levels in 31% of patients compared with 7% in the placebo group, and improvement in the abnormal lipid profile. In 32 patients, liver biopsies were performed. Although sebelipase alfa undoubtedly positively affects key features of LAL deficiency, reversal of liver damage and prevention of cirrhosis or early death remain to be established. Once active screening for LAL deficiency is performed, more patients with potentially benign phenotypes are likely to be identified (Stitziel). For this group of patients, the natural disease progression and relevant clinical endpoints should be defined for appropriate use of sebelipase alfa.

The high costs of treatment cause a threat to healthcare budgets that results in further hesitance to reimburse therapy in many countries. NICE recently rejected the use of Alexion's Kanuma® for the treatment of adults and children with the more attenuated phenotype of LAL-D, but also for treatment of infants who usually die within weeks to months after diagnosis if not treated by Kanuma®, because of considerably uncertainties about the longer term benefits of Kanuma® and its very high cost (McKee).

Centers in the Netherlands
AMC
The Academic Medical Center is involved in the diagnosis and follow-up of patients with LAL-D. AMC (Dr. Hovingh) participates in the Lysosomal Acid Lipase (LAL) Deficiency Registry (ALX-LALD-501) (https://clinicaltrials.gov/ct2/show/NCT01633489)

UMCG
The UMCG is involved in the diagnosis of patients with LAL-D and takes care of 2 patients with infantile LAL-D (Wolman disease). Prof van Spronsen has initiated an international meeting supported by Alexion addressing combined specific and supportive care. He is invited to act as member to the Scientific advisory Committee for infantile LAL-D.

<u>Purpose of the proposed protocol:</u>
The protocol aims to provide conditional access to treatment with Kanuma® for Dutch patients with LAL-D for at least 5 years. Conditions are:

1. Patients in the Netherlands will only be treated with sebelipase alfa following the strict start and stop criteria as laid down in this protocol.
2. AMC and UMCG will act as the centers of excellence for diagnosis, follow-up and treatment of LAL-D patients: AMC as general lysosomal center will support juvenile and older patients. The UMCG as center for metabolic diseases with severe liver disease as

consequence, and center for severe liver and gut disease with possibility to perform liver or gut transplantation in children will treat patients with the infantile form.
3. An agreement should be made between healthcare insurers and Alexion on a substantially reduced price for sebelipase alfa for the time of the evaluation period.
4. Representatives from AMC and/or UMCG will actively engage with the LALD Registry to be able to provide up to date knowledge and new insights into the appropriate use of sebelipase alfa.

Protocol

Each year, the centers of expertise will perform an analysis of data on effectiveness and safety, which will be the basis for a report to ZIN. ZIN will decide on the added value of sebelipase alfa, based on all available data (i.e. data obtained from this study as well as from available peer-reviewed publications).

Indication committee:

Before initiation of treatment, each patient will be discussed in the indication committee. The agreed criteria for treatment are shown below. In urgent (infantile) cases, the discussions will be held by phone or e-mail to avoid any delay.
Apart from this, meetings are held to discuss cases in Groningen or Amsterdam, including expert physicians (pediatricians, internists), clinical genetics, pharmacist, hepatologist and immunologist.
An anonymized resume of discussed cases and decisions will be submitted in the yearly report to ZIN.

Diagnosis:

A definite diagnosis will be made in a symptomatic patient with confirmed lysosomal acid lipase deficiency and mutation analysis showing two pathogenic mutations.

Methods:

1. Treatment of patients in the Netherlands

Patients treated with bone marrow or liver transplantation do not follow the criteria below. These very exceptional cases are not currently present in the Netherlands and unlikely to emerge, but the possibility deserves to be mentioned. These patients should be carefully considered as candidates for ERT on an individual basis.

Eligibility 1. To receive treatment, patients, or legal representatives, must sign up to this Managed Access Protocol 2. Patients are required to attend their clinics at least 2-4 times a year for assessment. 3. Children under the age of 5 may not be able to complete all baseline and subsequent assessments. Clinically relevant assessments should be attempted at least once every 12 months until the age of 5, at which point all assessments become compulsory. 4. Sebelipase alfa will not be started if any of the following apply: · The patient is diagnosed with an additional progressive life limiting condition where treatment would not provide long term benefit; or · The patient has advanced disease and has a poor performance status; or · The patient is unwilling to comply with the associated monitoring criteria:
Start Criteria All of the following are required before treatment is started: · All patients must have a confirmed diagnosis of LALD with confirmed LAL enzyme deficiency and mutation analysis. In infantile LALD patients enzyme analysis or genotyping alone is sufficient to start

treatment · There has to be unanimous agreement in the indication committee for start of treatment: 1. infantile cases (diagnosis <6 months and severe disease) will start treatment as soon as possible 2. children < age 12 years with severe and/or progressive disease will start treatment as soon as possible 3. later onset patients will **not** be treated unless there is progressive disease AND no effect of lipid lowering therapy · In addition patients aged 5 and over can only start once a full set of baseline assessments has been obtained
Dosing: the starting dose will be determined on an individual basis, starting with 1 mg/kg/week in less severe cases. Patients not responding to 1 mg/kg/week can be dose increased to 3 mg/kg/week according to the response criteria below and in accordance with the officially registered dose. In infantile cases with severe disease, early case-based evidence suggests that for optimal response these infants may need doses of up to 5 mg/kg/ up twice weekly.
Stop Criteria Patients will cease enzyme therapy if any of the following apply: · The Patient is non-compliant with assessments for continued therapy (non-compliance is defined as fewer than two attendances for assessment in any 12 month period or missing of > 50% of infusions); · The Patient is unable to tolerate infusions due to infusion related severe adverse events that cannot be resolved. In severe infantile patients, enzyme replacement therapy will be stopped if there is severe brain damage Patients who are taken off treatment will continue to be monitored for disease deterioration and supported with other clinical measures. These patients should continue to be assessed to allow gathering of important information.
<u>Treatment of Naïve Responder (for patients who have never received treatment)</u> A responder following the first year of treatment for a treatment naïve patient will demonstrate at least three out of four of the response criteria for children > 5 years and two out of three for adults (excluding nr 2) or infants (excluding nr 1), otherwise they will have to stop treatment with ERT: 1. Improvement of liver involvement as assessed by MRI and fibroscan 2. Improvement growth and achievement of developmental milestones 3. Reduction from abnormal baseline LDL and total cholesterol levels of > 20% or normalization 4. Reduction from abnormal baseline liver enzymes of > 20% or normalization
<u>Patients who are on treatment for more than 1 year:</u> Patients who are on treatment for more than 1 year are defined as: (i) clinical trial patients; (ii) patients otherwise already receiving treatment. To remain on treatment patients must fulfill three out of four of the response criteria for children >5 years and two out of three for adults (excluding nr 2) or infants (excluding nr 1): 1. No progression of liver involvement as assessed by MRI and fibroscan 2. Continuation of improved growth and achievement of developmental milestones 3. Maintenance of reduced LDL and total cholesterol levels or normal levels 4. Maintenance of reduced liver enzymes or normal levels 5. Maintenance of reduced or normal levels of ferritin

2. Analysis of data

Detailed follow-up data of treated patients will be kept at the treating center and shared with the LALD registry.

Representatives from one or both of the centers of expertise will be in contact with the LALD registry. Alexion should make data and/or reports from the registry available upon request

within 3 months after the request to support the yearly report by the centers of expertise to ZIN and the decision making in the Netherlands.

On a yearly basis, a report will be prepared and shared with healthcare insurers/ZIN. This report will consist of
- updated number of identified, treated and untreated patients with LALD in the Netherlands
- organization and function of the indication committee
- follow-up of treated and untreated Dutch patients
- revision of guidelines including start- stopcriteria based upon experience in the Netherlands, literature and reports from the LALD Registry
- data analysis requested from the Registry.

After 5 years, a final report will be prepared which can assist ZIN in decision making for reimbursement.

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