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EDITORIAL

New disease modifying therapies for two genetic childhood-onset neurometabolic disorders (metachromatic leucodystrophy and adrenoleucodystrophy)

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In the past months new gene therapies for two genetic neurometabolic disorders have been approved by EMA granting a marketing authorization in the European Union. This holds great promise for the patients and their carers since both diseases are associated with a shortened life expectancy and a heavy disease burden.

Metachromatic leucodystrophy (MLD)

MLD is a rare, autosomal recessively inherited neurometabolic disorder. The prevalence rate of MLD is unknown, but is estimated to be between 1 in 40,000 and 1 in 160,000 (https://rarediseases.org/rare-diseases/metachromatic-leukodystrophy/). The central and peripheral nervous system and visceral organs are involved and the disease presents in early or late childhood, and also in juvenile and adult age. The disease spectrum includes impairment of motor and mental development or progressive loss of motor and cognitive capacities (ultimately dementia), behavioural impairment, peripheral neuropathy, epilepsy, optic atrophy with a progressive leucoencephalopathy at magnetic resonance imaging (MRI of the brain). The disease is a lysosomal disorder, due to a deficiency of Arylsulphatase A (ARSA) with cell storage of sulphatides. The late onset and adult forms are characterized by a less severe progression for many years, mainly related to the partial enzyme deficiency due to different ARSA gene mutations. The residual enzyme activity leads to an almost normal brain myelin maturation, but there is an incapacity of its maintainance and survival, with different degrees of severity.

In this disease, as in many lysosomal enzyme deficiencies, enzyme replacement therapies, allogeneic bone marrow transplantation and gene therapies are treatment options. Irrespective of the approach, the enzyme must be delivered to lysosomes of deficient patient cells. An enzyme substitution therapy has been recently suggested for this disease [1]. However, limitations of the capturing exogenous supplying enzyme have been reported [2].

Gene therapy in MLD has been performed in animal studies [3] and in human trials [4].

EMA has recommended granting a marketing authorisation in the European Union for the gene therapy Libmeldy to treat MLD. Libmeldy is indicated for use in children with the 'late infantile' or 'early juvenile' forms of MLD, who have been identified as carriers of the defective gene but who have not yet developed symptoms. It is also indicated in children who have been diagnosed with the early juvenile form who show some symptoms, but are still able to walk independently and have no cognitive decline.

An EMA press release on this topic communicated the following:

'Libmeldy is a gene therapy medicinal product, for which CD34 + haematopoietic stem and progenitor cells are collected either from the patient's own bone marrow or mobilised peripheral blood. These cells are modified to insert a functional gene to produce the ARSA enzyme. When the modified cells are injected into the patient as a one-time infusion, the cells are expected to produce the ARSA enzyme that breaks down the build-up of sulfatides in the nerve cells and other cells of the patient's body.

In its overall assessment of the available data, the Committee for Advanced Therapies (CAT), EMA's expert committee for cell- and gene-based medicines, found that

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the benefits of Libmeldy outweighed the possible risks in patients with the late infantile or early juvenile forms of MLD who have not yet any symptoms and in patients with early juvenile form with early symptoms of the disease. Once they had received the medicine, their performance with regard to cognitive and motor function was maintained and comparable to that of their healthy peers during the observation period.

However, in patients with the early juvenile form of MLD, who already showed symptoms when they were first given Libmeldy, the effects were less pronounced. A possible slower decline in motor function was seen while cognitive function was maintained compared to what is known about the disease progression in untreated patients. The further the disease had already progressed in these patients, the fewer positive effects could be seen. Therefore, in patients with early juvenile form of MLD who have already developed symptoms, the CAT concluded that treatment success is maximized if at the time of diagnosis, screening for treatment and treatment, children can still walk independently and have no signs of cognitive decline.

The main adverse reactions observed in trials were fever and a diminished ability to fight infections (febrile neutropenia), inflammation of the mouth and lips (stomatitis) and the gastro-intestinal tract (mucosal inflammation). These side effects are related to the conditioning medicine used to prepare the child for treatment with Libmeldy.

As for all haematopoietic stem cell interventions, there is a theoretical risk that patients develop malignancies such as leukaemia or lymphoma later in life.

The CHMP, EMA's human medicines committee, agreed with the CAT's conclusions and recommended approval of Libmeldy in these patients. As part of its recommendation for marketing authorisation, the committees requested that the company uses a registry of patients to learn more about the long-term efficacy and safety of the medicine. Results from this registry study will be submitted periodically for evaluation to EMA.

The company has also been requested to propose measures to safely reduce the overall time needed to supply the patient with the individualized product. This is because treatment is more effective before the onset of symptoms or in the presence of early mild symptoms, before symptoms become more severe and disease is rapidly progressive.

Treatment with Libmeldy should only be carried out in qualified specialised treatment centres, and patients and their carers should receive extra educational material to warn them of the symptoms of leukaemia and lymphoma.

The opinion adopted by the CHMP is an intermediary step on Libmeldy's path to patient access. The opinion will now be sent to the European Commission for the adoption of a decision on an EU-wide marketing authorisation. Once a marketing authorisation has been granted, decisions about price and reimbursement will take place at the level of each Member State, taking into account the potential role/use of this medicine in the context of the national health system of that country.

Adrenoleucodystrophy (ALD)

Adrenoleukodystrophy (ALD) is a rare, X-linked metabolic disorder that is estimated to affect one in 21,000 newborns worldwide [5]. ALD is caused by mutations in the ABCD1 gene that affects peroxysomal metabolism involving the production of the adrenoleukodystrophy protein (ALDP) and subsequently causes toxic accumulation of very long-chain fatty acids (VLCFAs), primarily in the adrenal cortex and white matter of the brain and spinal cord. The childhood-onset disease, which is the most severe form, is characterized by developmental arrest, motor and mental deterioration, adrenal insufficiency, blindness and at MRI progressive white matter changes usually starting in the posterior area. In adults, the disease may be less severely progressive, with a large clinical heterogeneity. Cases may have isolated adrenal insufficiency, or associated with progressive leucoencephalopathy or with spinal involvement presenting as spastic paraparesis. Diagnosis is confirmed by evidence of high levels of VLCFAs in the serum and gene mutations.

Treatments were based on the use of a low VLCFAs diet (Lorenzo's oil) and on bone marrow transplantations [5–7].

During the Presidential Symposium at the 47th Annual Meeting of the European Society for Blood and Marrow Transplantation (EBMT 2021) (March 14–17, 2021), new data from the clinical development program for elivaldogene autotemcel (eli-cel, Lenti-D™) gene therapy in patients with cerebral adrenoleukodystrophy (CALD) have been presented, including updated results from the pivotal Phase 2/3 Starbeam study (ALD-102) and the long-term follow-up study LTF-304, as well as safety outcomes from the Phase 3 ALD-104 study.

Eli-cel is a one-time investigational gene therapy designed to add functional copies of the ABCD1 gene into a patient's own hematopoietic (blood) stem cells (HSCs) that have been transduced ex vivo with the Lenti-D lentiviral vector. The addition of the functional ABCD1 gene allows patients to produce the adrenoleukodystrophy protein (ALDP), which will activate the breakdown of VLCFAs. The goal of treatment with eli-cel is to stabilize the progression of CALD and consequently preserve as much neurological function as possible. Importantly, with eli-cel, there is no need for donor HSCs from another person [8].

At the end of May, EMA has recommended granting a marketing authorisation in the European Union for the gene therapy Skysona (elivaldogene autotemcel) for the treatment of children with cerebral adrenoleukodystrophy, following the previous approval by FDA.

Here, we report the EMA's press communication.

Skysona is made up of immature bone marrow cells that are taken from the patient. The cells are then modified by a virus — a so-called 'lentivirus' that has been changed in order not to cause disease in humans — that contains a functional copy of the gene ABCD1 for the ALDP protein, so that this gene is carried into the cells. When these modified cells are given back into the patient by a drip (infusion) into a vein, they are expected to spread through the body and develop into different types of healthy cells, including brain cells that produce the ALDP protein lacking in the patients with CALD. As a result, patients should be able to break down the accumulated VLCFA with an improvement of the symptoms of the disease.

Skysona is a one-time treatment which can only be given in a specialised hospital by doctors who are experienced in treating patients with CALD, transplanting bone marrow, and using gene therapy medicines.

Skysona was accepted into PRIME, a support scheme EMA developed for promising new medicines that address an unmet medical need.

EMA's recommendation for a marketing authorisation is based on evidence from a single-arm clinical trial that enrolled 32 male patients with CALD aged 17 years or younger. The results from this study were compared to those from a study in which 59 patients had a stem cell transplantation (either from a matched sibling donor or a matched non-sibling donor). All the patients in the main clinical trial were enrolled in a long-term follow-up study.

An analysis conducted after 24 months from the infusion on 30 subjects enrolled in the study concluded that for 27 of them (90%) treatment with Skysona preserved motor function and communication ability and improved survival when compared to untreated patients at an early stage of cerebral disease.

The most severe adverse reaction in the clinical trials for Skysona was low levels of all types of blood cells (pancytopenia).

Adding a new gene into the stem cells could theoretically cause blood cancers. This was not seen during the clinical trial but after the treatment, patients will be monitored with blood tests to check for any signs of cancer of the blood.

Because Skysona is an advanced-therapy medicinal product (ATMP), it was assessed by the Committee for Advanced Therapies (CAT), EMA's expert committee for cell- and gene-based medicines. Based on the CAT's assessment and positive opinion, EMA's human medicines committee (CHMP) recommended approval of this medicine.

Additional long-term efficacy and safety data are being collected through one ongoing study and a long-term registry. All results must be included in post-marketing safety reports, which are continuously reviewed by EMA.

The opinion adopted by the CHMP is an intermediary step on Skysona's path to patient access. The opinion will now be sent to the European Commission for the adoption of a decision on an EU-wide marketing authorisation. Once a marketing authorisation has been granted, decisions about price and reimbursement will take place at the level of each Member State, taking into account the potential role/use of this medicine in the context of the national health system of that country.

Conclusions

These two new drug approvals for rare childhood-onset disorders by Drug Authorities underline several points:

(a) The importance of an early diagnosis allowing for an early therapy. This pertains particularly to inherited disorders in which neonatal screening will identify the gene mutations at birth and broaden the therapeutic perspectives;
(b) The necessity for the neurology community to collaborate with other specialities, including genetics, pediatrics, immunology and transplant medicine;
(c) The necessity to address patients to specialized clinics which are able to supply gene and monoclonal antibody therapies and which are also suited to closely monitor the patients;
(d) The need to include the knowledge on these diseases in the curricula of neurological, genetic and pediatric specialties. These specialists should become familiar with the progress which is made in the neurometabolic field. It is very likely that these new therapeutic approaches in the near future will also hold for other neurometabolic diseases.

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