betibeglogene autotemcel (ZYNTEGLO°) in certain forms of severe beta thalassaemia

Despite the uncertainties, an option for achieving transfusion independence in the absence of a compatible donor

Abstract

● Beta thalassaemia is a genetic disorder that affects the production of beta globin chains, one of the two protein components of haemoglobin. The quantity of beta chains produced can be reduced to varying degrees, or completely absent, and is a key determinant of disease severity. Patients with the most severe forms have haemolytic anaemia and bone deformities. Without treatment, they die at around 2 to 3 years of age.

● The only known cure for beta thalassaemia major is allogeneic haematopoietic stem cell transplantation. Symptomatic treatment is based on blood transfusions. In the most severe forms, when very little or no beta chain is produced, patients require regular transfusions. This leads to iron overload with potentially serious complications that are prevented by the use of iron chelators.

● *Betibeglogene autotemcel* (Zynteglo°, Bluebird Bio) is a gene therapy product. Haematopoietic stem cells are collected from the patient. They are then modified using an inactivated viral vector to insert a functional beta globin gene into the genome. The modified cells are reinjected into the patient following myeloablative chemotherapy.

● According to the data available from non-comparative trials in about 20 patients producing low amounts of beta chain, about 80% to 90% of patients who received *betibeglogene autotemcel* gene therapy were able to stop transfusion therapy without developing severe anaemia. This effect was sustained.

● In addition to the adverse effects of *betibeglogene autotemcel*, those associated with the steps prior to administration of the drug, including stimulation of haematopoietic stem cell production and myeloablative conditioning, must also be taken into account.

● After administering *betibeglogene autotemcel*, infusion reactions (hot flushes, dyspnoea, chest pain) have been reported, and the blood platelet count can take a long time to return to normal. Gene therapies using viral vectors can cause mutations, which in turn can cause cancer. The risk of this occurring with *betibeglogene autotemcel* cannot be evaluated until longer-term follow-up data have been obtained. Two cases of myelodysplasia were reported, one of which was associated with myeloablative chemotherapy in a patient treated for a condition other than beta thalassaemia.

● Myeloablative conditioning can cause infertility. Cryopreservation of semen or ova should be considered before treatment.

OFFERS AN ADVANTAGE

***Betibeglogene autotemcel* gene therapy has not been shown to be more effective than allogeneic stem cell transplantation in patients with beta thalassaemia who require regular blood transfusions and produce low levels of beta globin. The limited preliminary evaluation data available on *betibeglogene autotemcel* show that it enables about 80% to 90% of patients to achieve sustained transfusion independence. The adverse effect profile of this gene therapy product is uncertain due to the paucity of data and short follow-up. The treatments preceding the infusion of *betibeglogene autotemcel* can provoke serious adverse effects. In practice, as of 2020, *betibeglogene autotemcel* is an option to offer patients who are eligible for transplantation but have no compatible donor, informing them that this treatment has undergone very limited evaluation.**

ZYNTEGLO° - *betibeglogene autotemcel* cell dispersion for intravenous infusion

■ **gene therapy**

■ **Indication**: beta thalassaemia that requires regular transfusions in patients aged 12 years and older who do not have a beta-0/beta-0 genotype and are eligible for haematopoietic stem cell transplantation but lack a matched related donor. [EU centralised procedure - orphan drug]

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EDITORS' OPINION

The European Priority Medicines ("Prime") scheme cements industry influence over early marketing authorisation

Over the past few years, the European Medicines Agency (EMA) and national drug regulatory agencies have added new ways to provide early market access for certain drugs: accelerated assessment, conditional marketing authorisation, approval under exceptional circumstances, and compassionate use programmes such as France's Temporary Authorisation for Use (ATU) scheme (1,2).

The European Priority Medicines (Prime) scheme was launched in 2016. It aims to enhance cooperation between the EMA and pharmaceutical companies, as well as health technology assessment bodies (such as the French National Authority for Health (HAS)), in order to accelerate the market introduction of certain drugs (2,3). *Betibeglogene autotemcel* is one of the first drugs to have obtained European marketing authorisation through the Prime scheme (see opposite).

Access to early approval that strengthens agency-industry ties. Drugs are eligible for the Prime scheme from an early stage of development if the pharmaceutical company provides evidence that they may constitute a major therapeutic advance for patients with unmet medical needs (2,3).

The scheme gives the company access to support from a multidisciplinary group of specialists from various EMA scientific committees or working parties. The objective of this group is to periodically provide the company with advice on regulatory and administrative issues so that marketing authorisation can be granted earlier. They involve other organisations if necessary, such as health technology assessment bodies, to prevent conflicting decisions regarding marketing authorisation and reimbursement (2). There is no charge for requesting access to the scheme, but fees are generally charged for EMA advice (with some exceptions, including for public-sector or private non-profit research organisations or universities) (4,5).

Early marketing authorisation = minimal and often incomplete evaluation. Early marketing authorisation often means that the drug's evaluation was based on very limited and typically non-comparative clinical data, using surrogate endpoints that do not necessarily reflect clinical outcomes. This leaves many uncertainties, in particular concerning the drug's adverse effects, because it was evaluated in a small group of highly-selected patients (1).

Early marketing authorisations place great emphasis on post-marketing evaluation. But experience shows that pharmaceutical companies rarely honour their commitments to conduct post-authorisation studies, and that these studies provide a lower level of evidence than double-blind randomised comparative clinical trials conducted before marketing authorisation is obtained. Decisions on whether to withdraw a previously authorised drug from the market, or withdraw reimbursement, are politically awkward and take a long time, sometimes years, during which time patients continue to be exposed to the drug. These decisions are likely to be even more difficult when agencies have participated in the drug's development (1,2,6). Patients' interests are often best served by continuing the drug's evaluation to obtain more robust data, including enrolment of a more diverse sample of target patients, rather than by rushing the drug onto the market.

For example, despite the apparent benefits of *betibeglogene autotemcel*, its still-partial assessment makes continued evaluation crucial, yet it could be hindered by the fact that marketing authorisation has been granted.

In practice **A scheme that gives drug companies even more influence over EMA decisions.** The EMA has been providing "scientific advice" to pharmaceutical companies for a fee since 2005. The Prime scheme further cements a well-known practice that can lead to regulatory capture (7). Early cooperation between drug companies, the EMA and national health technology assessment bodies is one more mechanism that strengthens the pharmaceutical industry's influence over these agencies' decisions. Do these agencies have the necessary detachment to conduct impartial evaluations? This cooperation also compromises the role of national health technology assessment bodies as a "watchdog". This scheme further destabilises the power balance between the pharmaceutical industry and agencies, benefiting industry at the expense of patients.

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