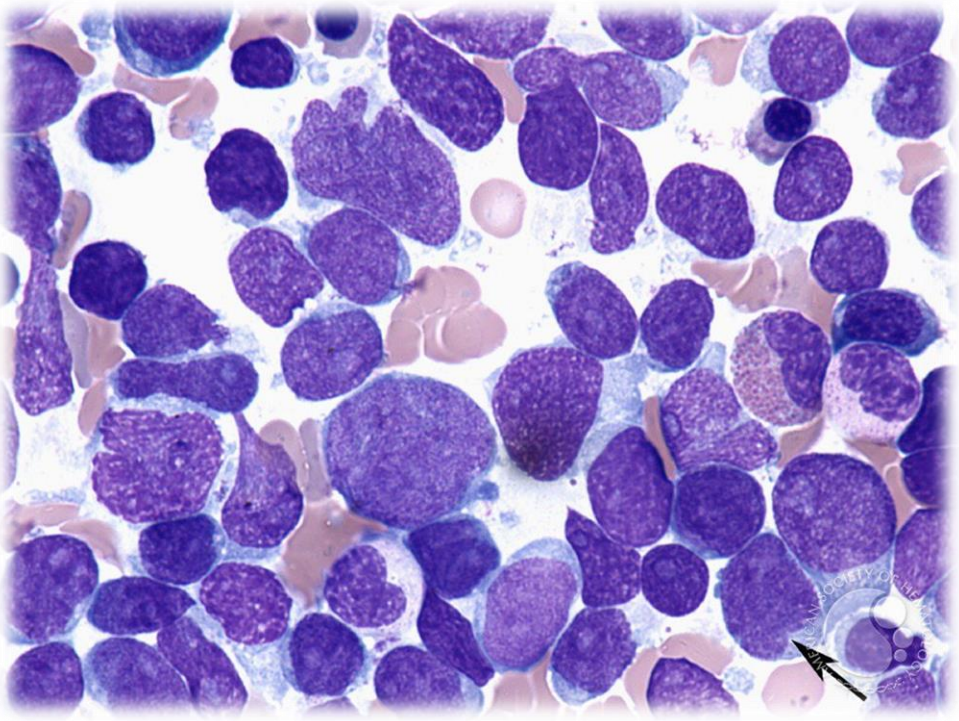
FIRST GENE THERAPY FOR LYMPHOBLASTIC LEUKAEMIA



On Wednesday, July 12, 2017, the US Food and Drug Administration (FDA) inaugurated a new era of medicine: an "Oncologic Drugs Advisory Committee" unanimously recommended (10 votes in favour, none against) the authorization of the first treatment that genetically alters the patient's immune cells so that they become veritable "living drugs". The strategy consists of strengthening the patient's immune system in its fight against tumour cells [(1)].

With very few exceptions, the FDA always follows the recommendations of its "expert committees". Consequently, the first gene therapy can be expected to reach the pharmaceutical market in the near future. Other gene therapies are on the way. For decades, different pharmaceutical companies have striven to be pioneers in perfecting this technology. Novartis AG seems to be the first to have done so, administering this treatment against a type of leukaemia, and also the treatment’s possible extension to multiple myeloma and various aggressive brain tumours.

This individualized treatment requires complex logistics: a sample of the patient's T cells are frozen and sent to a specialized laboratory run by Novartis AG, where they are thawed out and genetically modified. Once processed, they are forwarded, frozen, to the health centre of origin. Following strict protocol, they are thawed out and reinjected into the patient.

A single infusion of these genetically modified cells results in prolonged remissions of the cancerous disease; and even "cures" (meaning the disappearance of "tumour markers"). Note that this treatment applies to patients in whom all other treatment options have failed, either due to refractoriness or relapse.

The US Food and Drug Administration's "committee of experts" recommended the approval of this treatment for acute or relapsed B-cell lymphoblastic leukaemia in children and young adults up to 25 years of age.

The panel of experts heard personal stories from participants in the clinical trial. One of the testimonies was that of the now 12-year old Emily Whitehead. She was 6 when she underwent the experimental treatment at Children's Hospital, Philadelphia, USA. During the treatment she suffered serious adverse side effects (very high fever, hypotension, pulmonary congestion) which could have killed her. Luckily she survived. Her cancerous process had been "solved." And so this continues six years on. Her parents, of course, expressed their enthusiasm. This policy of listening to personal stories may seem unsuitable when a new therapy is assessed objectively and impartially. But this is not what the "committee of experts" believe; and neither do the authors of this editorial. Statistical processing of information should not be the only criterion for authorizing or rejecting treatments that condition health, disease, and survival.

However, the most notorious evidence presented by Novartis AG, came from a study of 63 patients who were treated between April 2015 and August 2016. Of these, 52 (82.5%) achieved remarkable remissions; with 11 patients dying.

Part of this expensive type of treatment was funded by the Leukaemia and Lymphoma Society, a philanthropic organization.

The next step will be to integrate this gene therapy within the context of more complex treatment programmes. This strategy can be very beneficial when the patient's immune system remains functional.

The "committee of experts" did not consider the approval of this genetic treatment solely on the basis of therapy as a last resort for desperate situations. The possibility of very serious side effects (such as those suffered by Emily) was taken into account; as well as other potentials side effects including the occurrence of secondary cancers years after treatment.

Oncologists have guidelines for treating the serious side effects associated with these drastic therapeutic approaches.

Patients receiving this treatment (all under the age of 25 years) will be supervised for the next 15 years of their lives.

One problem with these "biological" medicines is that the manufacturer should guarantee the process of quality control, since each treatment has to be tailor made for each patient.

The Food and Drug Administration's "committee of experts" also heard the case of a child, Connor, who, like Emily is 12 years old. His father, Don McMahon, described how his son debuted with leukaemia at the age of 3. All treatments applied were unsuccessful. He was eventually included on a treatment programme with genetically modified T-cells. The child was waiting to undergo a bone marrow transplant, but this was not necessary. He went on a programme at Duke University, where gene therapy was performed with genetically modified T-cells. His leukaemia "seems to have been completely resolved" [sic].

Another testimony came from Amy Kappen. He recommended the approval of this gene therapy, even though his 5-year-old daughter, Sophia, had died of leukaemia. Perhaps in this case, the treatment came too late. However, his family said that gene therapy gave her a few relatively acceptable months of life.

This "gene therapy with genetically modified T-cells" was developed by a research group led by Carl H. June [(2)] at the University of Pennsylvania, USA. The procedural license was acquired by Novartis AG, which designed the strategy that will enable the drugs to be commercialized.

The use of this treatment will not be massive. Lymphoblastic Leukaemia is infrequent, and only affects about 5,000 people in the United States; approximately 60% of these are children and young adults. 85% respond to conventional treatments; only 15% are refractory or suffer relapses after receiving conventional therapies.

Novartis AG has not stated the cost of this treatment. Several financial analysts familiar with the pharmaceutical market have estimated that it will cost around $300,000.

This cost, undoubtedly very high, must be contextualized within the framework of vexatious treatments and frequent hospital admissions.

One fundamental aspect is that the treatment is complex, and the patients need very specialized attention for the management of the adverse side effects. Novartis AG has decided to restrict the use of this gene therapy to 30 or 35 specialized American medical centres.

This gene therapy is assigned the code CTL019, and is called Tisagenlecleucel. After approval in the United States, having been given favourable report by the Food and Drug Administration, Novartis will consider applying for approval next year in the European Union. In the meantime, patients will only be able to go to authorized centres in the United States.

At the end of November 2016 (three months after the completion of this clinical trial), 11 of the 52 study patients relapsed after a marked initial improvement, 29 patients achieved excellent remissions, 11 patients required complementary interventions, such as bone marrow transplants, and one patient did not attend the clinical evaluation.

Of the patients (11) who relapsed, three died. Another died as a result of adverse side effects after receiving the treatment for a second time. At present it is impossible to carry out prospective estimates of survival rates.

There is still no consensus among researchers about the need to perform a bone marrow transplant to consolidate favourable responses.

The treatment requires the removal of millions of T-cells from a patient, and their processing (genetic modification) to boost their activity against the neoplastic cells. The technique uses an attenuated version of the human immunodeficiency virus (HIV) to transport new genetic material to the T cell to achieve genetic reprogramming. These T cells begin to attack B cells that have become malignant due to lymphoblastic leukaemia. To this end, T cells must recognize a membrane protein ("marker") of B cells, CD19 (CD standing for “Cluster of Differentation”).

Modified T-cells are infused into the patient, initiating their rapid multiplication. In a way, it is like taking a "drug" capable of multiplying itself once administered. Its efficiency is astounding: a single T cell can destroy 10^5 tumour cells and also, unfortunately, non-tumour cells, as both have the CD19 antigen ("marker") anchored into their membranes. The administration of intravenous gamma-globulins is required to maintain adequate immune status in order to protect the patient from infections.

During clinical trials, some patients died before receiving treatment. The processing of T cells initially required around 4 months. Some very seriously ill patients did not survive long enough to receive the treatment.

Novartis has reduced the time required for genetic reprogramming, which now stands at 22 days. Other strategies are underway, aimed at reducing costs and increasing production capacity.

However, Tisagenlecleucel is not the first "gene therapy" to be marketed.

The European Commission, following a favourable report from the European Medicines Agency, authorized a gene therapy. That was Glybera® (Alipogen tiparvovec) [3, 4, 5], developed by the Dutch biotech company UniQure.

Apoligen tiparvovec is an enzyme which metabolizes lipoproteins [6]. Hundreds of people in the European Union, and hundreds in the United States and Canada, suffer a genetic mutation which impedes the synthesis of this enzyme. The blood of these patients has an intolerable amount of fat, to the point that it looks so pale in colour that some clinicians describe it "as if it were a 10% emulsion". The symptomatology is systemic and complex; the pancreas being the first organ affected. Glybera® provides correct copies of the "protein-lipase" gene. It is thus possible for the patients to produce the enzyme for themselves. The treatment is relatively simple: multiple injections into the leg muscles, administered on the same day. The therapeutic benefit can last for several years.

Gene therapy has long been considered a “chimera”. Since the 1990s, a number of clinical trials have been conducted; many of them unsuccessful, partly due to the complexity of releasing intact genes into the cells, but also because of the difficulty of keeping these genes operative over a long time period.

In addition, the death of a teenager during a clinical trial, conducted at the University of Pennsylvania in 1999, was a major setback, both scientifically and emotionally, not only as far as ongoing clinical trials were concerned, but it was also detrimental to other trials yet to be carried out.

A "gene therapy" to treat cancer gained approval in China in 2003. However, experts from Western countries questioned the rigor of the reviews that led to its authorization.

There is still controversy about the effectiveness of Glybera®: the drug has been authorized based on a single study carried out on 27 patients ignoring the rigorous methodical requirements of controlled clinical trials.

In fact, the Committee for Medicinal Products for Human Use, which has similar functions in the regulation of drugs in the European Union as the "expert committees" of the US Food and Drug Administration, rejected the authorization of Glybera® three times in a single year. This rejection was based on the fact that the Dutch manufacturer, UniQure, had not proved with "sufficient evidence" that Glybera® caused a sustained decrease in blood lipids, and "there was insufficient evidence of a reduction in the incidence of pancreatitis". The last unfavourable decision came in April, 2012. However, in the August of that same year, the Committee for Medicinal Products for Human Use retracted its decision of April, justifying its change of heart stating that "the group of patients for whom the drug was intended had been restricted to those who had a more serious clinical picture." In addition, the manufacturer undertook to monitor the results of the administration of the drug to the patients, supplying their results and observations to the appropriate regulatory bodies.

The dark side of these regulatory "swings" is that UniQure (originally Amsterdam Molecular Therapeutics) was decapitalized. The company has resurged thanks to an important injection of capital, and the commitment of its workers - most of them highly qualified. Such resurgence is uncommon.

There are many problems with this new pharmaceutical technology, but also many hopes. Adversity brings out the best in human beings.

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