Treatment of Spinal Muscular Atrophy with Intrathecal Mesenchymal Cells

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Background and Objectives: SMA1 is a genetic disease that leads to a progressive apoptosis of the second motoneuron and then to a complete paralysis. There are reports of efficacy of mesenchymal cells in the treatment of other neurological diseases; therefore we decided to treat some children with these cells.

Methods and Results: Four children suffering from SMA1 were treated by means of intrathecal injections of mesenchymal cells. All patients improved their motility after three weeks. The effect was relevant at the distal muscles, while the proximal ones were less affected. The treatment was repeated once a month for 3~8 months as the effect of the treatment lasted not more than 30 days. One patient who withdrew the treatment died after 45 days. Another patient resulted completely paralysed after two months after quitting the cell therapy but he regained the skills after a new injection. Two patients are stable after the first improvement.

Conclusions: Intrathecal injections of mesenchymal cells improve the motility of children suffering from SMA1. We argue that an early treatment, before the onset of irreversible neurological damages, could result in the cure of this disease.

Keywords: Mesenchymal, SMA1, Stem cells

Introduction

Spinal muscular atrophy (SMA) is a cohort of diseases with the same genetic defect (gene SMN1) with different severity according mainly to the expression of a second gene (SMN2). The autosomal recessive defect of SMN1 gene leads, in a way not completely understood, to a progressive apoptosis of the second motoneurons. The prevalence of the disease is approximately 1 in 6000~10,000 births.

The most severe form is SMA1, first described by Werdnig and Hoffmann in 1890, that has an early onset, in the first months of life, a short length of survival without

ventilatory and nutritional supports. A child with SMA1 has an irreversible worsening of the muscular activity, will never be able to sit, and is doomed to die of respiratory failure.

At the moment some drugs are able to slow down the progression of the disease; salbutamol, dopamine and other drugs seem to increase the expression of SMN2 gene and are likely to increase the strength by increasing the number of muscular fibers (1). This effect is well known by the breeders of calves and swines that use beta adrenergic drugs in order to increase the lean body mass of the animals. However this effect is limited in efficacy, hampered by cardiovascular effects and of short duration. Other drugs seem able to increase the expression of SMN2 gene (2-4).

It is highly likely that in few years a gene therapy will solve this problem (5) but in the meantime hundreds of children will die.

Mesenchymal cells have been used in the last years to treat some neurological diseases, as Parkinson disease,

Accepted for publication March 16, 2012

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brain injuries, spine cord injuries (6). These cells have the features of:

- passing through the blood brain barrier when injected both in vein and intrathecally.
- producing soluble factors that interfere with apoptosis and neuronal growth.
- being able to mature into different tissues as neurons and glia.

For this reason we decided to try to treat some children with SMA1 with intrathecal injections of mesenchymal cells.

Materials and Methods

Four children suffering from early onset SMA1 were enrolled since January 2011.

The ages ranged between 7 and 18 months. All the patients were almost completely paralysed, being able, two of them, to move their hands and nothing else. The respirations was only diaphragmatic, severe problems of feeding were present. In particular the first patient that underwent this treatment had initial severe problems of respiration (gasping) and of swallowing of saliva.

Trial design

The procedure, according to the Italian law (DM 12/5/2006), was managed on a compassionate basis; each patient was considered at immediate risk of death, and his treatment agreed with the Ethical Committee after the signature of the informed consent.

Since it was a compassionate treatment, we avoided invasive and painful procedures of assessment as repeated EMGs. The clinical results were witnessed by two independent neurologists, as well as by patients personal paediatricians and physiotherapists.

Cells supply

Mesenchymal cells, from marrows of bone marrow donors, were cultivated in culture medium (D-MEM) and platelet lysate in the GMP "Verri" Laboratory in Monza, Italy. Vials containing frozen aliquots of 15 million cells and 10% DMSO, were supplied after the approval of the hospital Ethical Committee, and the permission of AIFA (Italian Agency for Drugs).

Treatment

The vials containing the cells suspensions were thawed quickly in a waterbath. The mesenchymal cells were washed twice in saline by means of centrifugation at 200 g in order to get rid of DMSO. Cells number was adjusted to

5 million in 2 ml of saline. The remaining cells were discarded, or used for experimental purposes.

Within 15' the cells were injected into the lumbar spine of the patient after the withdrawal of a same amount of liquor.

The patients were kept in hospital for at least 12 hours, checking any rise of body temperature. No untoward effect was observed.

Results

No effect was evident for three weeks.

All the patients had the same outcome in the fourth week: increase of muscular tone, appearance of movements never seen before. In particular the first patient became able to swallow saliva, improved respiration and started feeding better. All the patient had an improvement of distal movements, at level of hands, arms, thy, legs. The adduction of thy was maybe the most amazing feature.

Nevertheless only few effects were seen at the proximal muscles: minor neck movements only in one patient, none started using intercostal muscles for breathing.

The first patient received one injection per month for 7 times; after a stop of the treatment for 50 days she lost almost all the skills and had some troubles with respiration. A new injection of mesenchymal cells restored the movements after three weeks.

The third patient, that had the least advantages from the treatment, even if an improvement of movements of arms and legs were observed, withdrew the treatment after two injections. After 45 days he died of respiratory failure.

The second and the fourth patient are still in treatment (4 and 6 injections). After the initial improvement that went on after the second and third injection, they experienced a clinical plateau with no further improvement, even if there was no regression of motility.

Discussion

SMA1 is a unavoidably progressive lethal disease. Even there could be some plateau of progression, this cannot last for a long time. No patient experiences a regain of skills once lost.

Even if we did not perform EMG for MUNE assay (7), for the ethical reason written before, we have no doubt that this treatment had significant results in term of muscular strength of distal muscles.

In SMA a progressive death of spinal motoneurons is likely to be irreversible after a period of "honeymoon" in which they do not work even still alive. We believe that

in this period mesenchymal cells could stop the progression to death of the neurons and restore the viability of the suffering ones. The partial effect on these poor children in advanced disease permits to postulate that if a SMA patient would be treated very early a “cure” of the disease could be theoretically offered.

In our opinion the short lived effect of intrathecal mesenchymal cells is due not to a regenerative effect, but rather to a sort of pharmacological effect by means of local release of soluble factors that lasts as long the allogeneic cells survive.

Hopefully in the next future our children and others could enjoy of a different treatment with mesenchymal cells differentiated in vitro along the neurological line. These cells could be the right answer even for irreversible neuronal damages.

Potential conflict of interest

The authors have no conflicting financial interest.

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