Our initial experience with intraputaminal delivery of Upstaza using MRI-guidance for cannula placement and confirmation of infusion target coverage

L D'Angelo [1] F Pappone [1] V Leuzzi [2] F Pisani [2] P Pantano [3] M V Pesce [4] C Imperiale [4] N De Blasiis [4] F Pugliese [4] A Santoro [1]

1: Neurosurgery Division, Department of Human Neurosciences, Sapienza University of Rome, Rome, Italy
2: Division of Child Neurology and Infantile Psychiatry, Department of Human Neurosciences, Sapienza University of Rome, Rome, Italy
3: Neuroradiology Division, Department of Human Neurosciences, Sapienza University of Rome, Rome, Italy
4: Department of Anesthesia and Intensive Care Medicine, Sapienza University of Rome, Rome, Italy

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SAPIENZA UNIVERSITÀ DI ROMA

Background:

Intraparenchymal (IP) infusion refers to the administration of a therapeutic directly to the brain and represents a groundbreaking approach to targeting neurological disorders at their source. One of the advantages of using the IP route of administration is that it bypasses the blood brain barrier (BBB) entirely. Additionally, IP delivery is local and therefore has less off-target side effects as seen with systemic delivery.**Eladocagene exuparvovec (Upstaza™)** is the first gene therapy commercially approved in the EU (July 2022) to be delivered directly to the brain for the treatment of **aromatic L-amino decarboxylase (AADC) deficiency** in individuals ≥18 months. This case report details the experience of our first successful MRI-guided, intraparenchymal infusion of Upstaza™ delivered directly into the human brain and was performed at **Policlinico Umberto I (Rome)**. The patient treated is a 3 year old pediatric diagnosed with AADC deficiency.

Methods:

Four trajectories (two per hemisphere) were planned to target the **anterior and posterior aspects of each putamen**. The surgical workflow consisted of using an **MRI-guided stereotactic platform (ClearPoint® Neuro**, Inc.) to accurately place the cannula tip in the area of interest. The infusion was then administered with an infusion pump and a cannula containing a stepped-tip design (SmartFlow MR Compatible Ventricular Cannula®) to enable convection enhanced delivery (CED). MRI-guidance was utilized to guide the precise placement of the cannula tip to the desired target, but MRI can also be used to intra-procedurally monitor the infusion in real-time to ensure proper target coverage, if desired. Previous studies have shown that direct, intraparenchymal infusion of therapeutics for AADC deficiency resulted in improvements with cognition, communication, body weight, hypotonia, dystonia as well as a reduction of oculogyric crises. Additionally, an increase in putaminal enzymatic activity has also been noted.

Results:

At this time, we can confirm the **safety and feasibility of intraparenc**hymal gene therapy infusion as no major adverse events were observed during or following the procedure. At the patient's 3-month follow up appointment, **motor improvements** have been observed along with head and neck stability. The patient is now able **to walk with assistance and is no longer experiencing oculogyric crises.** Additionally, CSF metabolites have also improved, as shown in Figure 1. We are hopeful that our patient will continue to exhibit greater efficacy given that the therapeutic has been delivered at such a young age.

Conclusion:

Overall, this study demonstrates the safety and feasibility of direct, intraparenchymal gene therapy infusion to the brain. Furthermore, MRI-guidance can be used to confirm accurate placement of the cannula and also provide intra-procedural visualization of the infusion which can be extremely important considering the potential for reflux and perivascular off-target spread.

CSF Neurotransmitter Metabolites

Metabolite	Concentration (nmol/L) PRE	Concentration (nmol/L) After 3 Months
HVA	26 nmol/L	76,7 nmol/L
5-HIAA	90 nmol/L	111 nmol/L
3-OMD	1843 nmol/L	350 nmol/L
5-HTP	114 nmol/L	41.9 nmol/L
Neopterin	4.19 µg/L	4.5 µg/L

Figure 1. Demonstrates the changes in CSF neurotransmitter metabolites pre- and post-infusion of eladocagene exuparvovec

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