Clinical Experience of gene replacement therapy in children with Spinal Muscular Atrophy: A single center retrospective study of 25 children

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INTRODUCTION

Spinal muscular atrophy (SMA) is a fatal autosomal recessive disorder and is the most common genetic cause of infant death [1]. SMA is caused by deletion or mutation of survival motor neuron 1 (*SMN1*) gene, which results in the loss of motor neurons in the anterior horn cells in the spinal cord and brain stem [2]. The incidence of SMA is ~1 in 6000–10,000 live births, with the majority (60%) being SMA type 1 [3]. If left untreated, SMA Type 1 leads to death or the need for permanent ventilation by the age of two years in more than 90% of cases [4]. Therapeutic strategies to increase the levels of SMN protein in motor neurons have focused on either enhancing the effectiveness of SMN2 or replacing the SMN1 gene.

Onasemnogene abeparvovec (Zolgensma) is a one-time intravenous *SMN* gene transfer therapy using a non-replicating adeno-associated virus (AAV) serotype 9 was approved by FDA in May 2019 for treatment of children less than 2 years of age with SMA type 1 [5]. In May 2020, the European Commission (EC) granted conditional approval for SMA type I patients with a bi-allelic mutation in the *SMN1* gene and up to three copies of the *SMN2* gene. The approval covers infants and young children with SMA with a weight up to 21 Kg

OBJECTIVE

Being a new medication, post marketing studies describing the use of onasemnogene abeparvovec for the treatment of SMA are limited especially outside Europe and the United States. In this study we mainly looked at the side effect profile, duration of steroids and efficacy of Zolgensma in our cohort of patients.

METHODS

This is a retrospective cohort analysis of clinical data collected from all SMA patients treated with gene transfer therapy between November 2020 and January 2022, at the Neurosciences Center at our hospital in Dubai. Laboratory Investigations before and after gene therapy were performed as recommended by the drug manufacturer's protocol. All patients were either under two years of age or with a body weight less than 21 Kg with 5q SMA with a bi-allelic mutation in the *SMN1* gene and a clinical diagnosis of SMA type 1 or 2 when given the gene transfer therapy. Oral Prednisolone treatment was started at a dose of 1 mg/kg/d and adjusted according to the protocol and the blood investigations. The Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders (CHOP-INTEND) was performed at baseline, one month and 3 months after the gene therapy.

RESULTS

Patient Characteristics:

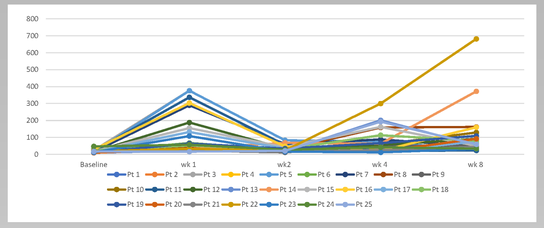
A total of 25 children received the SMA gene transfer therapy (Zolgensma) during the study period. The mean age at the time of therapy was 20.76 months (range 4 – 43 months), 18 (72%) had 2 copies, 5 (20%) had 3 copies and two had 4 copies of *SMN2* gene. The median age of onset of symptoms was 3.6 months with more than half (15/25) of the patients presenting in the first 3 months of life, while 8/25 had the onset of symptoms between 4-6 months. The mean age at diagnosis was 6.52 (range 0.5-17.0) months.

Adverse effects:

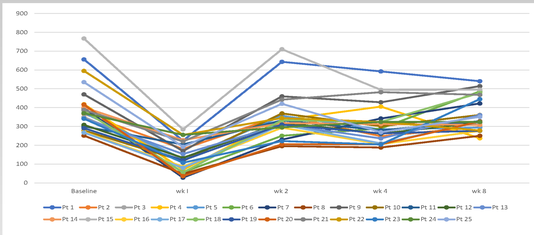
Immediate (24 hours post infusion): None of the patients had anaphylactic reaction to the gene therapy or a major adverse effect within the first 24 hour following gene therapy.

Post-treatment blood monitoring:

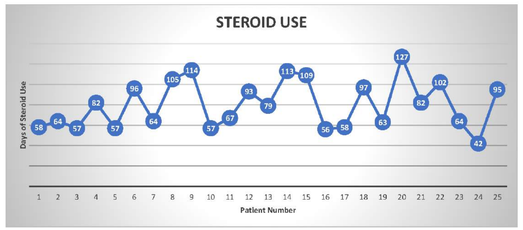
Changes in liver enzyme (ALT) at baseline, 1, 2, 4 and 8 weeks after gene transfer therapy



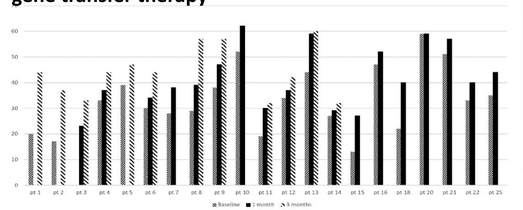
Changes in platelet counts at baseline, 1, 4 and 8 weeks after gene transfer therapy



Corticosteroids (Prednisolone) treatment duration



The CHOP-INTEND scores at baseline, 1 and 3 months after gene transfer therapy



CONCLUSIONS

To our knowledge, this post-marketing study has one of the largest cohorts of SMA gene therapy so far reported in the literature. It showed that Zolgensma is well tolerated in SMA patients and there were no life-threatening side effects noted.

Transient elevation in liver enzymes and thrombocytopenia are common side effects which have been well documented in many studies. The combined treatment in our cohort did not seem to cause worsening of side effect profile.

There was a significant increase in the CHOP-INTEND scores among our cohort with all the patients either achieving a score of over 40 points or had minimum increase of 4 points by 1 or 3 months after the gene transfer therapy

However, more studies and clinical trials are needed to further confirm the long-term safety and efficacy of gene transfer therapy and the significance of use of combined treatments for SMA.

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