Spinal Muscular Atrophy - Emerging therapies: Experience from a tertiary care hospital

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INTRODUCTION

- Over the past decade, newer emerging therapies in SMA- such as splicing modulation of *SMN2* and *SMN1* gene replacement by gene therapy have been developed - have shown encouraging short-term outcomes in terms of motor function scores and life expectancy
- Nusinersen, Zolgensma and Risdiplam approved by the US-FDA for SMA - prohibitive exorbitant costs - being provided to SMA patients under humanitarian access programs at our center

OBJECTIVES

- We present data for children with SMA on newer disease modifying agents - who have received these medications at our center over the last 2 years and 3 months

MATERIALS AND METHODS

- Two groups of patients (12 and 35) have been receiving intrathecal Nusinersen and are under follow-up
- Change in the Modified Hammersmith functional motor scale extended version(HFMSE) is being evaluated
- Nine patients (humanitarian-access:7, 2 via crowd funded sources) have received intravenous Zolgensma and are under follow-up
- Nine children (humanitarian-access:7) have been receiving Risdiplam, out of which 3 have a follow-up of more than 1 year
- All children received multidisciplinary care including individualized physiotherapy, rehabilitation, nutritional care and inpatient care in care of severe respiratory illnesses

RESULTS

Baseline characteristics - Children on Gene therapy AVXS-101 (Zolgensma) (Table 1); Risdiplam (Table 2); Nusinersen (Table 3)

Table 1: Zolgensma

Patient no.	Age at therapy	Sex	SMA type	SMN2 Copy number	CHOP INTEND (pretherapy)
1	1yr 5m	M	I	3	43
2	1yr 5m	M	I	3	21
3	8.5m	F	I	2	19
4	1yr 3m	M	I	2	19
5	1yr 9m	F	I	3	50
6	1yr 4m	F	I	2	22
7	1yr 8m	M	II	2	57
8	2 yr 1m	F	II	3	15
9	1yr 8m	M	II	3	34

Table 2: Risdiplam

Patient no.	Age at therapy initiation	Sex	SMA type	SMN2 Copy number	HMFSE (pre therapy)
1	4yr 6m	F	II	3	8
2	2yr 2m	M	II	3	21
3	5yr 11m	F	II	3	24

Fig 1 & 2: Pre and post-therapy images shows a child who received **Risdiplam**

Fig 1: Pre therapy - The child is creeping on the floor with difficulty

Fig 2: 8-months post-therapy - The child is able to sit independently without support for long duration and can also pull herself to stand with support from sitting position

Table 3: Nusinersen

Patient No.	Age at 1st loading dose	Sex	SMA type	SMN2 Copy number	HMFSE (baseline)
1	3yr 9m	F	II	3	20
2	3 yr	M	II	3	8
3	3yr 6m	F	II	2	17
4	3yr	F	II	2	17
5	6m	F	I	2	0
6	2yr 2m	F	II	2	22
7	10m	F	I	2	0
8	3yr	M	II	2	6
9	4yr	M	II	2	16
10	3yr	F	II	2	16
11	3.5yr	M	II	2	17
12	3.5yr	M	II	2	16

- Nine children who have received Zolgensma, showed significant improvement in motor function (those with SMA-II can now stand with orthoses and those with SMA-I can sit independently without support)
- Reduction in the incidence of lower respiratory tract infections in 8 of 9 children. Child no. 3 (Table1) had severe pneumonia requiring ventilation and died of pulmonary hemorrhage at 9 months post therapy.
- Other children had post therapy transaminitis and thrombocytopenia as major side effect which were managed with steroid - only 1 child required platelet transfusion.
- Three children who have been receiving Risdiplam for > 1 year, have shown significant improvement in HFMSE scores, with gain in motor milestones
- No major serious events were reported in the Risdiplam receiving cohort
- Twelve children have been receiving Nusinersen for > 2 years and are under regular follow ups
- Out of these 11 have shown improvement in HFMSE scores (non-compliance to therapy in 1)
- A second cohort of 35 children is currently on Nusinersen but have a follow up of <6 and changes in functional scores can't be commented upon currently in this cohort

CONCLUSIONS

- Newer emerging therapies in SMA have shown favorable results in improving the short-term functional outcome
- Number of serious respiratory illnesses have also been reduced in the population under follow up
- All three therapies seem to be relatively safe with major adverse events reported in the Zolgensma group only

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