

Salbutamol for Spinal Muscular Atrophy III

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Background

Spinal muscular atrophy (SMA) is a neuromuscular disorder caused by homozygous mutations of the survival motor neuron (SMN1) gene. Due to the exclusion of exon 7 in the majority of SMN2 transcript, insufficient levels of functional SMN protein are produced. Studies have shown that patients with higher number of SMN2 copies have milder phenotypes [1].

Salbutamol, a β 2-adrenoceptor agonist, has been shown to significantly increase in SMN2 full length mRNA and SMN protein in SMA fibroblasts [2] and SMN2 copy numbers also in the peripheral blood leucocytes of type II-III patients taking oral Salbutamol for 6 months [3].

Previous open pilot studies had suggested that Salbutamol may improve functional score and muscle strength in children with SMA II and III without major side effect [4,5].

Our centre offer daily oral salbutamol to children with SMA II and III aged over 2 years. Routine ECG is performed before starting of salbutamol and 3 months after. The physiotherapy assessment is conducted at baseline, 3 months after starting salbutamol and 6 months thereafter. The salbutamol maintenance dose is 2 mg tds for children younger than 8 years, and 4 mg slow release bd for those older than 8 years. Side effect is monitored.

Aim

To evaluate the effect of salbutamol in ambulant children with SMA type III.

Patients and methods

23 SMA type III patients who have oral salbutamol trial in our centre were included in this retrospective review. Motor assessment data pre-and-post salbutamol, including Time for 10 meter walk and SMA 3 scale were analyzed. Tolerability of salbutamol was reported.

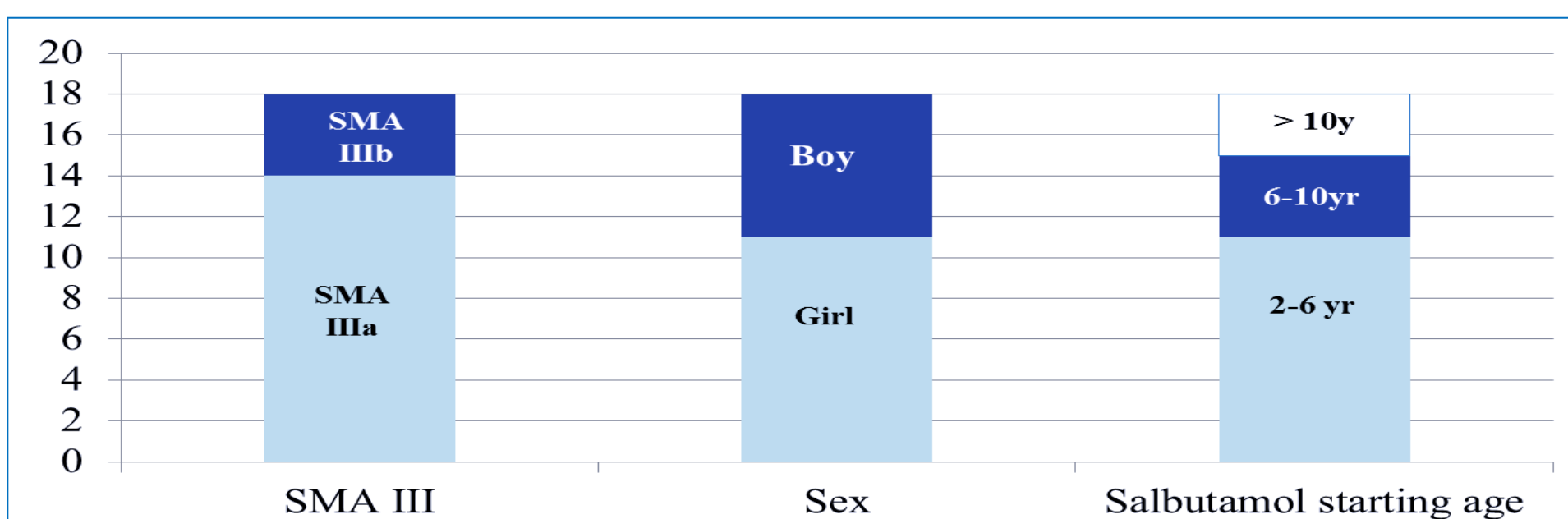


Figure 1

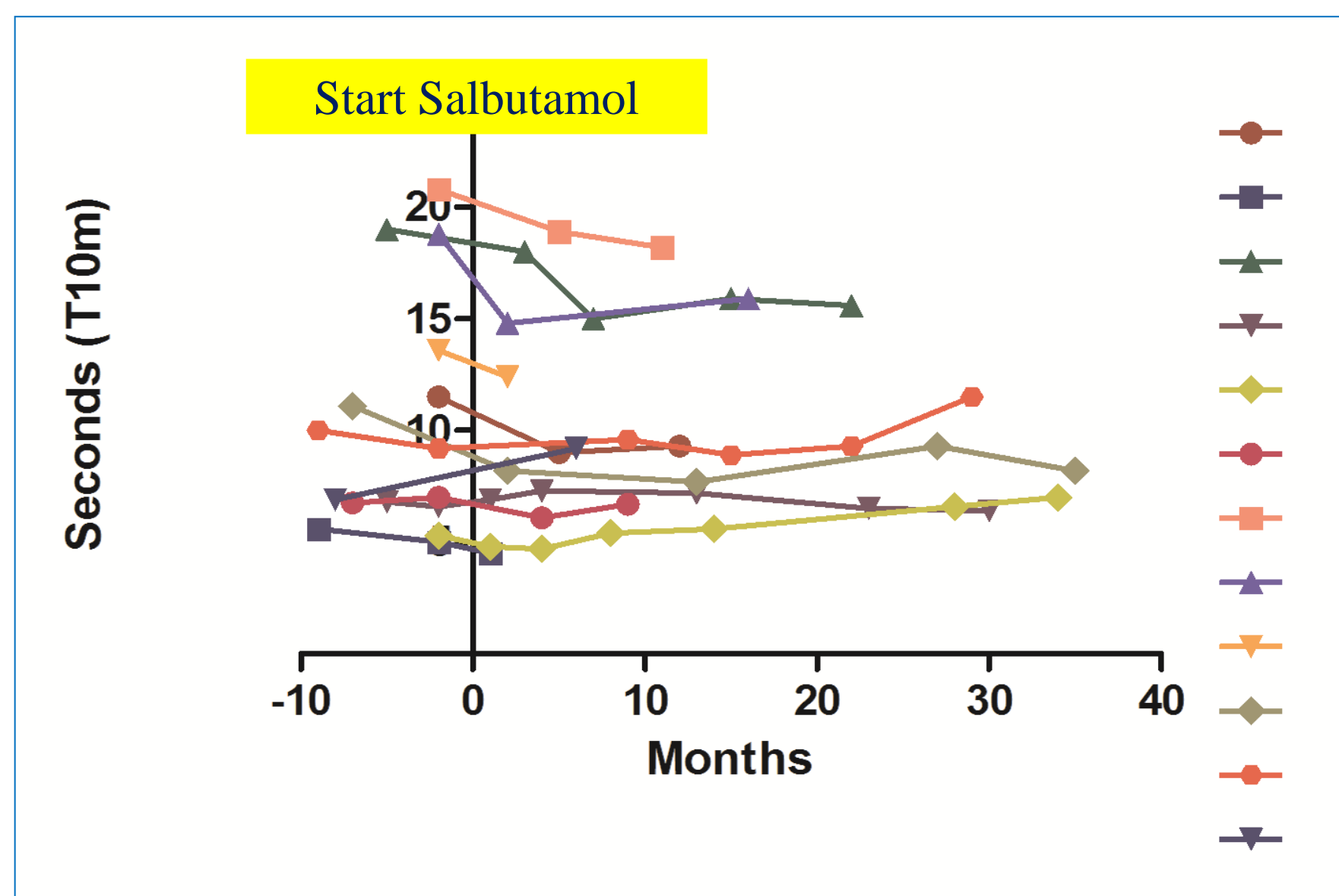


Figure 2a. Time 10 m walk for children with salbutamol started before the age of 8

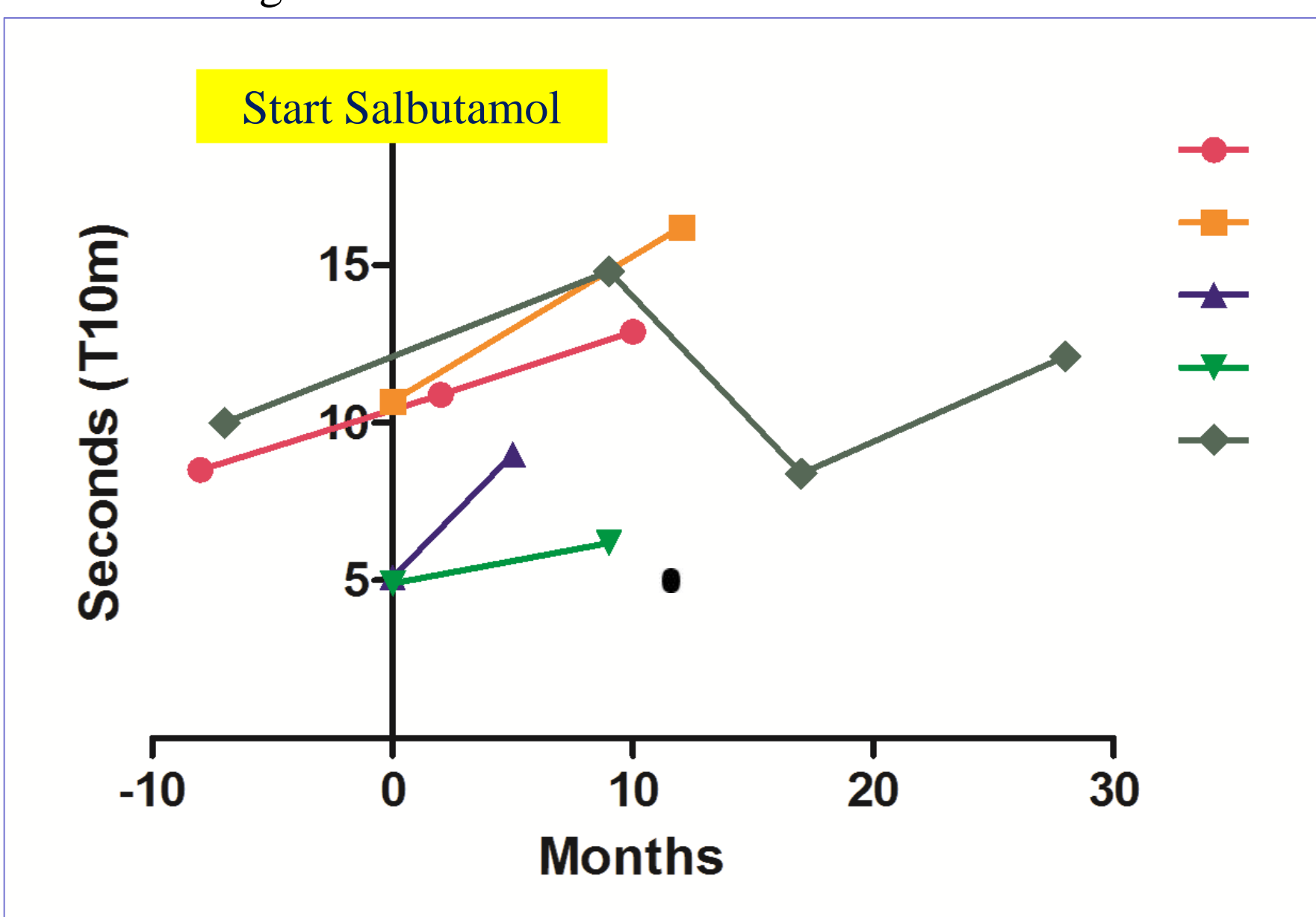


Figure 2b. Time 10 m walk for children with salbutamol started after the age of 8

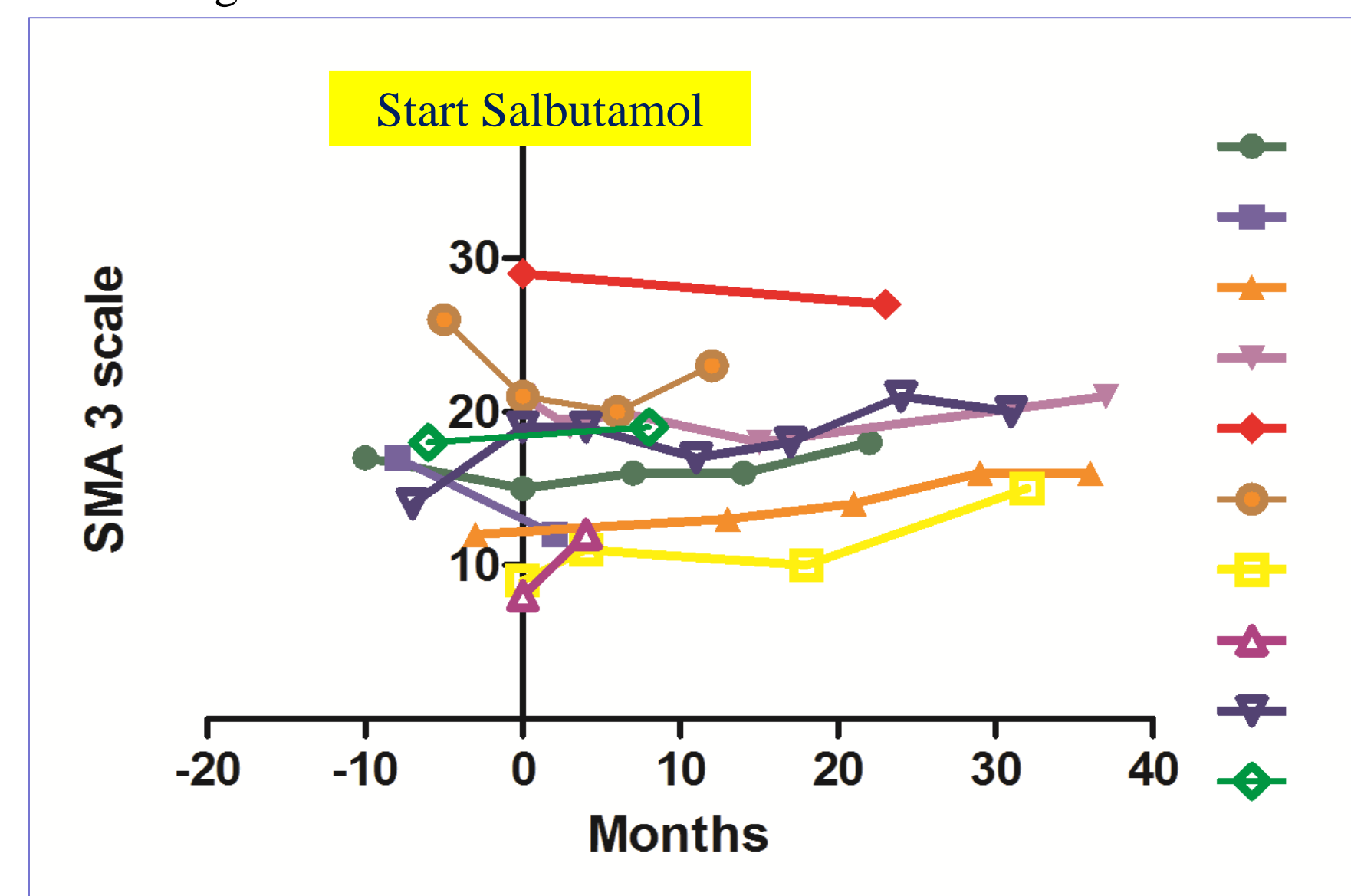


Figure 3. SMA 3 scale for children pre-and-post salbutamol

Results

Out of 23 SMA III patients, 18 patients continued oral salbutamol and 5 patients stopped after brief trial.

- Current age range: 3.7 to 20 years (mean age: 10 years)
- 11/18 are girls
- 14/18 patients are SMA III A (onset before 3 years)
- 15/18 started on salbutamol before age 10 (mean salbutamol starting age: 6.5 years) (Figure 1)
- Time 10 meter walk test is stable or with mild improvement trend for children with salbutamol started at younger age (Figure 2a and 2b)
- SMA 3 scale shows similar trend (Figure 3)
- All patients but 3 tolerate well the recommended dose
- The 3 patients who temporarily suspended the treatment (increased tremors in 1 patient, behavioural difficulties in another one, and transient prolonged QTc in the last one) restarted on salbutamol with no major side effects.
- The reasons for stopping salbutamol in 5/23 patients include significant tremor in 3 patients, poor appetite in 1 patient and significant allergic rash in 1 patient.

Conclusion

Oral salbutamol has been well tolerated and appears to maintain, and in some cases improve motor performance in SMA III.

Our findings together with previous in vitro studies that had proven salbutamol was being able to significantly improve SMN protein at SMN transcript level, and previous pilot studies suggested possible beneficial effects in SMA II and III patients, call for further multi-centre randomised control trial as the way forward.

The clinical trials with stratification of IIIa & IIIb, and for longer follow-up period of more than 1 years, and systemic collection of outcome measures with more effective measures for ambulant and non-ambulant SMA III children is recommended.

References

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4. Kinali M, Mercuri E, Main M, et al. Pilot trial of albuterol in spinal muscular atrophy. *Neurology* 2002;59:609-610
5. Pane M, Staccioli S, Messina S, et al. Daily Salbutamol in young patients with SMA type II. *Neuromuscular Disorder* 2008;18:536-540

Remarks:
This is an extended work of a previous project that had been presented in a poster in the European Paediatric Neurology Society (EPNS) Meeting in May 2011.
This is an on going project that we will try to complete before the end of this year.

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