Interview with Tora's father

Would you please briefly introduce yourself?
My name is Rajdeep Patgiri and I am the father of Tora Patgiri, who was diagnosed with Spinal Muscular Atrophy. I was born in India, then moved to France for studies. After that, I came to London for work and have been living here for the last 13 years. I am a financial economist by training and work in financial services.

At what age was Tora diagnosed with SMA type 1 and what were the available treatment options at that time?
Tora was diagnosed with SMA type 1c at the age of 5 months and 11 days. Her symptoms started from the age of 3.5 months. She has 3 copies of SMN2 gene, and was able to sit with support at the time of diagnosis.

Unfortunately, there was no treatment available in the UK at the time. The expanded access programme for Spinraza had finished 4 months prior to diagnosis and no decision on coverage under NHS had been made.

How did you hear about Zolgensma and what made you decide to prefer this treatment?
At the diagnosis meeting at the Great Ormond Street Hospital in London, we were informed that the hospital was a trial site for Zolgensma (STR1VE-EU) and recruitment was still open. However, Tora did not qualify for the trial as she has 3 copies of SMN2.

Over the following weeks, we searched for ways to access Zolgensma. There were several leads, but every one of them turned out to be out of reach. The managed access programme was available only to US citizens and permanent residents. Recruitment for the STRONG trial in the US for type 2s was open and Tora qualified under SMN2 copy criteria (3 copies), but she was required to be able to sit independently for 10 seconds without using her hands for support.

In the end, we decided to move to the US and had hoped that Tora will somehow manage to achieve a new motor milestone even without treatment. I have only come across one similar case, where someone initially diagnosed as type 2 was later reclassified as type 3. But that was more than 30 years ago. The chances of Tora qualifying for the STRONG trial was miniscule in March 2019, but it seemed to us to be the only route to treatment.

Where did Tora receive treatment?
We moved to Columbus, Ohio in the US and Tora was seen at the Nationwide Children's Hospital by Dr Jerry Mendell and Dr Anne Connolly. By the time of her appointment in mid-May 2019, she did gain the ability to sit without support and was reclassified as a type 2, and thus became eligible for the STRONG trial. A few days later, FDA approved Zolgensma for kids up to 2 years age, and all SMA types.

After few days of deliberation regarding the choice of treatment, we decided to go the commercial route (intravenous) rather than the trial route (intrathecal) at the suggestion of Drs Connolly and Mendell. Tora finally received her Zolgensma dose on 25th July 2019, at the age of 10.5 months.

Could you share your experiences with the treatment and the after care?
We arrived at the hospital at 7 am on the treatment day. There was a small hiccup with Tora's medicine, which caused couple of hours of delay. The biggest problem was finding the veins on both of her hands. Finally, the dosing began around 11 am and was finished by noon. The whole process was handled by couple

of nurses – who are very experienced with the procedure as Nationwide Children's has probably dosed the largest number of patients.

Dr Connolly came by midway through the dosing to congratulate us and check that everything was going as expected. We were suggested to move Tora as much as possible to increase the blood flow during the dosing process. We stayed for 4 more hours for observation and finally got back home by about 6 pm – a 12 hours day.

Tora was on steroids (prednisolone) and ranitidine for 4 months after dosing. We kept her and ourselves in isolation to the extent possible, as she was immunocompromised due to the steroids. Her side-effects were relatively mild. Fever on day 3 that peaked at 38.3 C, vomitting once, slightly evelvated liver enzymes and troponin. Her platelet count dropped following the dosing, but stayed within normal range. She had weekly blood tests, 17 in total, to monitor her condition until she stopped the steroids completely.

When did you notice developments after treatment and what were they?
Intial response was in respiratory and swallow functions within the first couple of weeks. Her infrequent choking episodes stopped completely and sweating also stopped. We also noticed some minor motor improvements, e.g. grip strength, within the first couple of weeks.

Tora started her physiotherapy regime about a month after dosing. And her sitting improved quite rapidly – longer, more stable, able to tuck her chin, reach across and above etc. The first new milestone was about 3 months after dosing when she rolled over. Around the same time, she also started kneeling. First weight bearing through legs was around 5 months after dosing. She went from no weight bearing to spending an hour in the standing frame, plus 30 mins in AFO + knee immobilisers within a few weeks. Currently, she can stand in KAFO for 30 mins + without any additional support.

These days, Tora's physiotherapy sessions are mainly focussed on transitioning (lying to sitting, sitting to standing etc.), which she is unable to do. She also practices walking in a gait trainer (Rifton Pacer). Additionally, she does exercises for her arms and neck.

What is your opinion on the different treatment options Spinraza, Zolgensma and Risdiplam?
After the diagnosis of our daughter, I immersed myself in learning about all the different treatment options and to connect to as many families as possible to learn from our peers. I also have had regular discussions with several neurologists in the US, UK and Europe. So the following is a relatively well informed opinion of a non-medical person.

Spinraza was the first treatment that came on the market for SMA patients. And it was a life-saver. It is very good in arresting the disease progression and the side-effect profile of the drug itself is relatively mild. It's biggest benefit seems to be on lower extremities – so younger patients seem to gain significant motor skills. The evidence is a bit more mixed for older children and especially adults, who may have lost too many motor neurons by the time of treatment initiation. The biggest drawback of Spinraza is the administration procedure – which places a significant burden on the medical system, the physical and mental health of the patients and their families. Also, improvements in respiratory and especially swallow has been less significant than the other two treatments.

Given our own experience, I consider Zolgensma to be the state of the art in terms of SMA treatment options. Dosed presymptomatically, Zolgensma can allow most SMA patients to lead a normal life. Even symptomatic patients have seen very significant gains, and this has been across the entire age range that has been dosed so far. On efficacy itself, Zolgensma works a lot better than Spinraza for respiratory and swallow functions, and somewhat better than Spinraza for motor fuctions. Additionally, the administration procedure is relatively simple, side-effect profile is mild, and percentage of non-responders seem to be less than 5%.

Risdiplam is the third treatment which will be available in the US next month and in Europe by 2021. The trial results are very promising. And it's systemic effect will be beneficial to all SMA patients. Risdiplam's strongest results seem to be in swallow function, where it seems to be the best out of the three. For respiratory, it works about as well as Zolgensma and for motor functions at similar level to Spinraza. Once we have more data from Sunfish trial for different subgroups (by type, age, baseline etc.), we'll be able to make a better judgement regarding relative merits of Risdiplam. Additionally, it's a very easy to administer treatment as it's a liquid syrup to be taken daily via mouth or feeding tube.

As a summary, my opinion as of today for the 3 treatments for different functions are as follows:

Respiratory: Zolgensma = Risdiplam > Spinraza
Swallow: Risdiplam > Zolgensma >>> Spinraza
Motor functions : Zolgensma > Spinraza >= Risdiplam

How did the Zolgensma treatment changed the life of your family?
Tora is doing very well since treatment and her 1-year outcome has exceeded our expectations. She is going to be motor function impaired given the 7 months gap between symptoms onset to treatment. However, she's similar to a normal child in respiratory and swallow functions – which are the most crucial ones for quality of life. She has made a lot of gains in motor functions as well and now can stand in Knee-Ankle-Foot-Orthotics (KAFO) without any additional support. We hope that her gains will continue and long-term, may present as a type 3a. At least, this is our dream!

How will SMA treatment look like five years from now, in your opinion?
This is somewhat easy to guess in the US and Europe – more difficult for rest of the world. As we move more and more towards newborn screening and treatment shortly after birth, Zolgensma will become the standard of care for this population group. Majority will remain presymptomatic and will live a very different life to the traditional SMA patient. For a minority – even the 2-3 weeks until treatment may result in symptoms manifestation. So, these group of patients, together with the group that Tora belongs to, will look towards combination therapy. Here, I expect Zolgensma + Risdiplam to be the primary option pursued. For the older SMA population, I expect Risdiplam to be the primary treatment option, with a minority continuing to pursue Spinraza. Intrathecal Zolgensma is likely to be avaible for the older SMA population at some point and a minority in that age group will possibly pursue this route.

Apart from these 3 treatments, I am fairly certain that we will not see a 4th SMN-based treatment on the market by 2025.