COMMENTARY-Novartis and gene therapy to treat Rett Syndrome.

Novartis, a multinational biotechnology company, issued a statement in August 2020 to confirm full commitment to their gene therapy program for Rett Syndrome. This was followed by a press release from the company in March 2021 which reported recent results of gene therapy to treat patients with spinal muscular atrophy (SMA). These results are of enormous interest to those of us who are related in some way to girls with Rett Syndrome and have important ramifications. In this short article, I have attempted to explain why this is so.

Like Rett Syndrome, SMA is a monogenic affliction i.e., it is caused by a mutation(s) in a single gene, in this case Survival Motor Neuron (SMN) and like Rett Syndrome there are two forms of the gene. The gene is expressed in motor neurons, specialised cells in the central nervous system (brain and spinal cord), that pass impulses (signals) from the brain to the muscles. Expression of the mutant SMN protein results in loss of signals to the muscles, resulting in poor muscle tone and severe weakness so that children are often unable to stand or sit. The age of onset of SMA is approximately 1 month of age and without therapy or support, death usually results before the age of 1 year. This is accompanied by a rapid decline in respiratory and swallowing functions.

As SMA is a monogenic disease, mouse models have been developed in a similar manner to the mouse models of Rett Syndrome. Like the mouse models of Rett Syndrome, this has permitted studies to examine the effect of different treatments on the welfare and survival of SMA mice. Therapy with DNA, small molecules or gene therapy have all been shown to have some efficacy, and gene therapy was shown to result in expression of the SMN gene in motor neurons and other tissues, resulting in reduction in symptoms and extended survival times. Consequently, Novartis embarked on a series of human clinical trials designed to investigate the outcome of gene therapy in SMA.

The results of the first of these clinical trials were reported in the highly prestigious journal, *The New England Journal of Medicine*, in 2017. This was a Phase 1 clinical trial essentially designed to test safety of the therapy; 15 children aged between 3-7 months were treated with an Adeno-associated virus (AAV) designed to deliver a functional SMN gene via the intravenous route. (AAV has also been used to deliver the MeCP2 gene to mouse models of Rett Syndrome). The results of this trial were remarkable! At the time of publication, all patients had reached the age of 20 months, showed a significance increase in the scores used to categorise severity (high scores are good) and required no mechanical ventilation. In contrast, only 8% of control patients achieved this latter biomarker. More recent data presented in the March, 2021 press release (https://www.novartis.com/news/media-releases/new-zolgensma-data-demonstrate-age-appropriate-development-when-used-early-real-world-benefit-older-children-and-durability-5-years-post-treatment) indicated that all 10 of the patients who agreed to a long-term follow up were alive, 5 years after the therapy, and required no ventilation support.

The results of other clinical trials were noted in the same press release and reported that more than 1000 patients have now been treated; as a result, these patients were able to sit, stand, talk and eat without the need for mechanical ventilation. Patients in these trials who were treated by intravenous or intrathecal (directly into the spinal canal) injection have shown a sustained benefit and are now in long term follow up.

Why is all this important for the Rett community? Well, AAV is the method of choice for Novartis to deliver the MeCP2 gene to patients with Rett Syndrome. The SMA gene therapy strategy is approved by the US FDA (the Food & Drug Administration-an extremely powerful regulatory body) and in 38 other countries including Australia. The data show that the AAV therapy is safe, able to deliver the gene to defective cells and result in long term benefits to patients, likely indicative of long-term expression of the SMN gene. This suggests that a similar strategy using AAV to deliver the MeCP2 gene may have fewer hurdles to overcome before approval for clinical trials is granted, and Novartis is already working with the FDA to achieve this. It also indicates that, although intravenous injection of the AAV-MeCP2 may breach the blood-brain barrier to deliver the gene to neurons in the brain, direct injection into the spinal canal may be very much more effective, and as this route of delivery has already been tried and tested in the SMA patients, then this will be of considerable benefit to Rett patients. On a practical aspect, the company has refined the design and production of the AAV delivery vector, so that the AAV-MeCP2 product, marketed under the trade name Zolgensma, should be readily available.

However, there are several points of difference between SMA and Rett syndrome, not least the difference in the age of children at diagnosis as it is recognised that early treatment is beneficial. It is unclear if AAV-MeCP2 therapy will also be of most benefit to younger patients, although gut feelings suggest that this will be the case, and if delivery of a functional gene will benefit all patients or only those with specific mutations/deletions in the MeCP2 gene, which are diverse and often unique.

Nevertheless, there is considerable cause for optimism given the expertise and experience gained by Novartis over the past 5 years. We look forward to- and eagerly anticipate- details of the proposed clinical trial to treat Rett syndrome that is planned in the near future.

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