Evaluate Vantage

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Ash 2017 – An early beta-thalassaemia challenge from Glaxosmithkline

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Glaxosmithkline continues to mine an alliance with San Raffaele Hospital in Italy that gave rise to the now-approved bubble boy syndrome gene therapy Strimvelis. The latest project, against beta-thalassaemia, is an asset Glaxo opted in to last year, and at Ash today promising signs of early activity were reported.

Perhaps most striking is that one child with the severe β0/β0 form of the disease swiftly achieved transfusion independence, and remains transfusion-free at over a year's follow-up. The data will be of relevance to followers of Bluebird Bio, whose fortunes have waxed and waned along with the potential of its own gene therapy, Lentiglobin, to treat beta-thalassaemia.

Both Lentiglobin and the Glaxo gene therapy are generated *ex vivo*, but uniquely Glaxo's is injected directly into the patient's bone marrow, while Lentiglobin is given intravenously. They also employ different viral vectors, and Glaxo's uses a different conditioning regimen – treosulfan and thiotepa.

The phase I/II study presented at Ash is relatively small, so it is not clear how much of an advantage these differences confer, but San Raffaele's Dr Sarah Marktel told an Ash press conference on Saturday that stem cell collection and transduction efficiency were both high.

The most relevant result relates to transfusion independence – a measure of whether a patient has effectively been cured of beta-thalassaemia. Three of four children in the study have discontinued transfusions, said Dr Marktel, including the β0/β0 child.

The study included three adults, and while all remain on transfusions these are at a reduced rate. An eighth subject, a child that was the only other patient with β0/β0 thalassaemia, experienced a swift drop in genetically modified cells, and any production of beta-globin was insufficient to sustain transfusion independence.

Dr Marktel hypothesised that the better efficacy seen in children versus adults was due to younger stem cells being more favourably corrected by gene therapy and engrafting better.

Bluebird's ups and downs

The Glaxo data might be from just eight patients, but that is still more than the four-strong results in the Northstar study that had suggested Bluebird's Lentiglobin could cure beta-thalassaemia, and caused the group's stock to surge at Ash 2014.

Things became less promising when a Northstar update showed tailing off of Lentiglobin activity in the severe β0/β0 form of the disease, and an Ash abstract shows that two of eight such patients are transfusion-free, with the other six showing 19-81% reductions in transfusion volumes. Bluebird is due to present the update at Ash on Sunday afternoon.

While not referring specifically to Lentiglobin, San Raffaele researchers have suggested that infusing the genetically modified cells directly into a patients' bone marrow can improve and speed up engraftment versus trials using intravenous delivery into the bloodstream.

Since Glaxo's rare disease collaboration with San Raffaele was signed seven years ago the UK group has formally opted in to projects targeting Wiskott Aldrich syndrome, metachromatic leukodystrophy and beta-thalassaemia, in addition to the now approved Stimvelis for SCID (severe combined immunodeficiency, or bubble boy syndrome).

The Wiskott Aldrich syndrome gene therapy generated interest at Ash two years ago, but any news on filing plans have yet to emerge (*ASH – Glaxo scores with second rare disease gene therapy, December 5, 2015*).

With the discounted pricing strategy for Strimvelis already showing rare diseases to be a minefield for big pharma companies, Glaxo might proceed cautiously in beta-thalassaemia. Progress of the transfusion-free β0/β0 patient will be closely watched too.

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