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Therapeutic focus – Cell therapies await real answers in ALS

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The repeated failure of small molecules to make any impact in the fatal neuro-degenerative condition amyotrophic lateral sclerosis (ALS) means much hope is being placed in stem cell-based approaches. The question of whether useful therapies will emerge could begin to be answered in the next couple of years as the most advanced companies in this field push on with larger studies.

Neuralstem and Brainstorm Cell Therapeutics, both of which released early data in the past few months that no doubt raised the hopes of sufferers, are attracting most attention. With few other commercial entities actively pursuing this difficult disease their progress will be closely watched; for the sake of ongoing investment in this space, more convincing evidence of efficacy needs to be generated.

Commercial companies with active cell therapy ALS projects

Product	Company	Originator	Clinical trials
NSI-566	Neuralstem	The Johns Hopkins University	NCT01730716
NurOwn Program One	BrainStorm Cell Therapeutics	Tel Aviv University	NCT02017912; NCT01777646
HYNR-CS	Corestem	Corestem	NCT01758510

Source: EvaluatePharma

All those working on cell-based therapies in ALS hope to achieve essentially the same end: to slow or even halt the progressive destruction of motor neurones that characterises the disease, via the infusion of healthy cells. Various techniques are being employed, however.

Israel's Brainstorm has a platform called NurOwn, which creates a therapy from stem cells harvested from a patient's bone marrow. These are treated to promote differentiation into specialised cells that secrete nerve growth factors, and the therapy is injected back into the patient, either intramuscularly or into the spine.

Neuralstem, meanwhile, isolates and expands human neural, spinal cord stem cells from donated CNS tissue to create an "off-the-shelf" product injected into a patient's spine.

The South Korean company Corestem has also moved into the clinic with its autologous project, which again is created from a patient's bone marrow. There are also several studies being run by academic centres around the world, using various approaches.

The next few years could see other commercial companies enter the clinic. Q Therapeutics, for example, has said it wants to start testing its Q-Cells in ALS patients this year. The therapy is unique in that it is based on glial cells, which also carry out support and repair functions in the CNS and therefore hold the potential to rescue diseased or damaged neurones, the company believes. Q-Cells are purified human glial progenitor cells that have been isolated and cultured from brain tissue.

All of these approaches come with their own unique advantages, with the drawbacks being their relative complexity and cost, and the risk of donor rejection. However, assuming no spectacular safety blow-up happens to halt or slow this vein of research – and none has arisen to date – they will ultimately be judged on their relative efficacy given the lack of options available to patients.

Emerging data

The most recent evidence to emerge in this field came earilier this month from Neuralstem, which unveiled topline results from a phase II trial of 15 ALS patients.

The dose-escalating study treated patients in five cohorts and met the primary safety endpoints, with the maximum tolerated dose identified as 16 million cells transplanted over 40 injections.

Effects on functional endpoints including hand grip strength, breathing capacity and the ALSFRS scale, a composite of 12 activities, were included as secondary measures; only piecemeal data were released on these.

Neuralstem claimed a 47% response rate (seven patients) as measured by changes in both the ALSFRS score and grip strength. Patients going into the study had on average a score of 40 on the ALSFRS scale, and after nine months the so-called “responders” had declined on average to 37, the “non-responders” to 14.

The company pointed out that this difference was statistically significant. But the lack of explanation as to why patients were classified responders or non-responders lessens the claim – the company has not defined a way to identify responders – and anyway a range of outcomes would be expected in a single-arm study.

In total the average responses were much less impressive and could be interpreted negatively when considering that historic norms suggest that ALS patients can expect to decline by a point a month on the ALSFRS scale. So while half of the patients appeared to decline more slowly than expected, half experienced a much more dramatic loss of function over the nine months.

This raises the question: was the therapy responsible for a more swift deterioration in some patients? It might not matter if responders can be identified from the outset. Speaking at an investor conference after the topline results were released, Neuralstem chief executive Richard Garr said the company believes that upper body muscle strength could be an important predictive factor.

The logic behind this lies in the way in which NSI-566 works. As Neuralstem describes it, the new stem cells synaptically integrate into remaining motor neurone cells, nurturing and protecting them. Therefore the therapy could theoretically prove more effective in patients with a healthier remaining pool of cells.

Neuralstem will attempt to prove this in its next trial, which is slated to start this summer. Mr Garr said this would seek to recruit 50 patients, all of whom would get the top dose, and an “enhanced screening protocol” would be applied to help select responders. The primary endpoint will again be safety, and patients will be tracked for nine months; an important difference is that the next trial will have a control arm.

Seeking confirmation

BrainStorm has already started its confirmatory study in the US and is in the process of recruiting 48 ALS patients. The randomised, double-blind, placebo-controlled study will primarily evaluate the safety of a single combined intramuscular and intrathecal administration of NurOwn. Early-stage ALS patients will be tracked for three months before the injection to determine their baseline deterioration, then followed for another six months.

Functional measures are included as secondary endpoints, and data are expected in 2016. In February a data safety monitoring board recommended that the trial continue.

A fair amount of data has already been released from a similar, single-arm, 14-patient study conducted in Israel that met the primary safety endpoint and showed encouraging signals on functional measures.

Of the 12 evaluable subjects, 11 were classed as responders. Six showed an improvement in the rate of disease progression as measured by ALSFRS score, while eight registered a slowing in progressive loss of lung function; three patients responded on both measures.

On a conference call, company executives said that some patients in the early part of the study had even demonstrated improvements on some measures – something that is never seen in the natural course of the disease, they claimed.

Repeating these findings in the placebo-controlled study is now incredibly important. The company is also planning to start a multi-dose study this year, and will decide on the next steps forward when all the data are available. This looks likely to happen in late 2016 at the earliest.

Injecting confidence

Neuralstem is also unlikely to have more data until late 2016, although more detailed presentations promised by both groups will in the meantime be scrutinised with interest by those working in this field.

According to its entry in clinicaltrials.gov, Corestem, the third player with an active ALS cell therapy trial, is in the process of recruiting 18 patients into a single-arm dose-finding study in South Korea. But this trial has been running since 2012, and the actual status of the project is not immediately clear.

Aside from the work of these companies, related work with stem cells in spinal cord injury is no doubt being monitored closely by the ALS community, given the potential for cross utility. But again work remains early.

All of which means firm conclusions about the potential of these treatments are almost impossible to draw at this stage. Neuralstem's hazy disclosures did not inspire much confidence earlier this month – shares in the company have since lost 40%.

Brainstorm is also struggling to instil investor confidence, despite being run by a former Wall Street hedge fund manager since June last year and up-listing to Nasdaq in September. The company has a market cap of $74m, against Neuralstem's $212m.

It is not surprising that such an intractable and fast-acting disease should fail attract many corporate sponsors. This means the progress of these two companies will have substantial bearing on stock market investors' willingness to fund further research into this space – not an insignificant responsibility to bear.

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