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Editorial

Acidic Fibroblast Growth Factor in Spinal Cord Injury: A Potential Therapy Which Merits Further Investigation

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In the current issue of *Neurospine*, Ko et al.[1] reviewed the traumatic spinal cord injury (SCI) clinical trials completed this decade; focusing on the application of acidic fibroblast growth factor (aFGF) to promote neural regeneration. FGFs are a family of growth factors that are involved in angiogenesis, wound healing, embryonic development, and various endocrine signaling pathways.[2] When applied in the setting of SCI, FGF attenuates biological processes that are associated with secondary injury such as astrocyte activation, neuroinflammation, and scar formation.[3] These favorable attributes make aFGF a tempting therapeutic candidate for SCI. In a phase I study of aFGF, 9 patients with chronic cervical SCI were treated with aFGF in fibrin glue via a laminectomy, followed by booster aFGF administration at 3- and 6-month postinjury. Modest nerve regeneration occurred in all patients, and 2 patients showed improvement in American Spinal Cord Injury Association (ASIA) motor scores.[4] This was followed by an open label, nonrandomized, uncontrolled phase II trial in 2011 that demonstrated significant improvement in ASIA motor and sensory scores, as well as increased functional independence measures 1 year after aFGF intervention.[5] Furthermore, throughout the 4-year follow-up period of the clinical trial, the authors found that aFGF administration improved functional recovery without any clinically related major adverse events.[6]

The aforementioned clinical reports of aFGF are meaningful because they confirm the safety of aFGF administration, including the absence of any tumorigenic episodes within the injured spinal cord. However, the readers of the review article should be aware of a pitfall when interpreting the aFGF trials with regards to the timing of patient recruitment and intervention. Notably, the timing for initiation of aFGF administration was broad: from 2.3 to 105.4 months after injury in the cervical SCI group and from 1.5 to 135.8 months after injury in the thoracolumbar group. The recruited patients in the trial were subacute or chronic SCI patients described in the article as being in a 'relatively stable neurological status,' which implies that the potential natural recovery during the follow-up period would be comparable among enrolled patients. The international campaign for cures of spinal cord injury paralysis (ICCP), which supports an international panel tasked with reviewing the methodology for clinical trials in SCI, states that spontaneous recovery can be observed in

incomplete SCI patients; with the majority of spontaneous recovery occurring in the first 3 months after injury while continued recovery can occur up to 18 months following the injury.[7] Given that significant spontaneous recovery unrelated to the treatment is expected to occur in the enrolled patients, the trial would need to recruit a large number of participants or a sufficient number of control group patients in order to demonstrate statistically significant results. Importantly, considering that the majority of SCI treatments are most effective when administered soon after SCI, clinical trials examining patients in this time period would require large patient numbers. Therefore, the efficacy of aFGF cannot be effectively established unless the trial design contains data from randomized placebo-control groups with a sufficient number of patients to allow for correction of spontaneous functional recovery throughout the study.

Here, we ask the researchers and clinicians involved in clinical trials to optimize the study design carefully. Ideal clinical trials should meet the criteria of adequate sample size, careful intervention timing, and the utilization of a control group. Inclusion and exclusion criteria, study power requirements, and appropriate outcome measures can be ascertained from numerous sources based on the practical recommendations made by the ICCP and previous high-quality clinical trials such as the methylprednisolone (National Acute Spinal Cord Injury Study)[8] and GM-1 (Sygen)[9] studies. For reference, we refer the authors to the clinical trial entitled Riluzole in Acute Spinal Cord Injury Study (RISCIS), which is a multicenter, randomized, placebo controlled, double-blinded trial that commenced in 2014 (https://clinicaltrials.gov/ct2/show/NCT01597518).[10] Statistical review of the RISCIS trial parameters estimated the need for over 300 patients to be enrolled in this trial. All patients were recruited and administered riluzole within 24 hours after SCI, followed by an additional administration 2 weeks after SCI. In addition to the homogeneity of patients, which was ensured by the aforementioned criteria, the neurological level of injury was strictly limited between C4 and C8, whereas the distribution of patients' neurological level in the aFGF trials was spread between C3 and L3.

Despite the weaknesses of the aFGF trials, the authors should be congratulated for paving the way for aFGF application into actual clinical settings. The detailed mechanism underlying this treatment is still unknown, but demonstrating the safety and potential efficacy for the injured spinal cord builds a platform for future clinical investigations. The study design of future clinical trials would benefit from the knowledge presented in the ICCP guidelines.

CONFLICT OF INTEREST

The authors have nothing to disclose.

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Title: Brick Factory at Tortosa
Artist: Pablo Picasso
Year: 1909
When Picasso visited Horta de Ebro in the summer of 1909, it was his second visit to the village on the Aragon border, having earlier spent seven months there in 1898 with his friend Manuel Pallares. Horto, like Gosol was a quiet mountain village and here Picasso began a series of landscape views. These followed on from the paintings he had produced a gear earlier at La Rue-des-Bois, as well as Braque's views of L'Estaque, One of the best known of these works, Foctory at Horto de Ebro, again draws heavily from Cezanne both in colour and form.
More information: https://www.pablopicasso.org/factory-at-horta-de-ebro.jsp