Department of Veterans Affairs

Journal of Rehabilitation Research and Development
Vol. 40, No. 4, July/August 2003, Supplement
Pages 1–8

From the bench to the body: Key issues associated with research aimed at a cure for SCI

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Abstract—Significant advances have been made in the study of neuroprotection and neural regeneration following spinal cord injury (SCI). However, there is wide variability in the animal models used for these studies. Moreover, there is no consensus on which outcome measures are best used to document recovery in animals. On top of these issues, the transfer of research from the laboratory into clinical trials is also hampered by a lack of sensitive outcome measures to document the recovery of function in humans with SCIs. This paper identifies specific issues related to the transfer of research findings from animals into humans. In the laboratory, these issues include the choice of animal model and outcome measures selected; and in humans, the standardization of medical treatment and other therapies, patient selection, and the outcome measures chosen. In the transfer of research from animals into humans, safety and feasibility issues must also be considered.

Key words: basic science, clinical trials, spinal cord injury (SCI), translational research.

INTRODUCTION

Significant progress has been made in the search for techniques to promote the recovery of motor and sensory function after the spinal cord is damaged. One often hears media reports of studies documenting promising results from one form of therapy or another. Moreover, a number of clinical trials have been [1–3], and are being, conducted to promote the recovery of motor and sensory function in the injured human. Despite the excitement in this area of research, there are many unresolved issues that hinder our ability to effectively translate a promising therapy from animals to humans. These issues can be discussed conceptually as those related to basic research, those related to the translation of research to humans, and those related to the performance of clinical trials in humans.

Abbreviations: BBB = Basso, Beattie, Bresnahan, FDA = Food and Drug Administration, NIDRR = National Institute on Disability and Rehabilitation Research (U.S. Department of Education), NYU = New York University, QIF = Quadriplegic Index of Function, SCI = spinal cord injury, SCIM = Spinal Cord Independence Measure, WISCI = walking index for spinal cord injury.

This material was based on work supported by the Veterans Administration Rehabilitation Research and Development Center of Excellence in Spinal Cord Injury and the National Institute on Disability and Rehabilitation Research, U.S. Department of Education, grant H133N000017.

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BASIC RESEARCH

The performance of basic research—the study of injuries and new therapies in animal or cellular models—is generally considered the gold standard for scientific studies. However, there are many issues associated with basic science research that can affect its relevance to human pathology. These issues include the choice of animals, the mechanisms of injury, the outcome measures used, and the types of therapies used. Each of these issues affects the relative importance of individual research studies.

The choice of animal is of great significance in determining the importance of basic science studies. Rat models are probably the most consistently studied and standardized and are often used to study the effects of spinal cord damage [4–7]. However, a notable limitation, when one considers the normal movement patterns of the rat, is that able-bodied rats tend to use their forelegs rather than their hindlegs for locomotion.* Thus, for studies of spinal cord injury (SCI), it may be more appropriate to use a feline model [8–12] or a canine model [13,14]. With advances in genetics, genetically deficient mice are becoming popular as another model to study [15,16]. Other investigators have used guinea pigs [17,18]. The lamprey has been identified as a vertebrate animal that demonstrates the capacity for neural regeneration [19]. The limitations in most of these models, however, are that none of these animals walk on two legs or have the hand dexterity of humans; thus, the replication of promising results in a primate model [20–22] would be desirable.

Another area of great importance is the mechanism of injury and how this affects study results. Probably the most well studied injury model is the performance of thoracic contusion injuries through the use of the New York University (NYU) impactor [23]. It can be argued that this model is most relevant to the types of injuries in humans and is therefore best for the study of neuroprotective techniques. With the use of this model, injuries are standardized as severe, moderate, or mild [5]. Other contusion models of injury and forms of impactors exist [24]. An alternative technique for the creation of a spinal cord compression is the use of forceps to lesion the cord [25,26]. Other groups of investigators perform open laminectomies with complete cord transections [27], lesions of specific axons [28,29] or an injury hemisection [30]. These latter techniques may be the best for studies of neural regeneration.

Probably the most important issue related to any of these injury models is whether the injury produced is reproducible and consistent. This is an issue that obviously could affect degree of recovery; thus, consistency is of the utmost importance. In comparisons of different injury models, models that used the NYU impactor demonstrated consistency in spinal cord lesion volumes [23], morphological changes [31], and recovery of locomotor function [32] after injury; thus, the contusion model of injury using the NYU impactor is a good model. However, again, the performance of thoracic injuries in the rat may not be the best model for relevance to humans. Moreover, despite the standardization of this technique, others still continue to use other models for contusion injury [24–26].

Another point that must be considered when evaluating basic science research for transfer to clinical trials is the outcome measure used. One recently developed behavioral outcome measure, the Basso, Beattie, Bresnahan (BBB) Locomotor Rating Scale [33], has proven to be a valid and predictive measure of locomotor recovery. Inter-rater reliability tests have been performed and found that a wide variety of examiners will be able to apply the scale consistently and obtain similar scores. Although the BBB scale is available for rat models of injury, many investigators still use other behavioral outcome measures, such as open-field testing using different scales, testing of placing, withdrawal reflex, and toe spread [9]. In addition to traditional histological and tracing studies, other supplementary types of testing include electrophysiologic tests, such as somatosensory and motor-evoked potentials [34,35]; neuroimaging, including MRI [36]; and testing for the presence of specific reflex functions [25].

TRANSFER OF RESEARCH FROM ANIMAL MODELS TO HUMANS

In basic science research related to SCI, there is an immense variability in the types of animals studied and the mechanisms of injury. Additionally, the outcome measures used are quite variable. So one can well understand why replicating basic science studies in two different animal models before the transfer of a therapy to humans is the ideal practice. Moreover, one could argue

*Personal communication, Timothy Schallert, 3 April 2003.

that invasive therapies should be tested in primates before they are tested in humans. However, if we are truly interested in facilitating the use of therapies in humans, we must also consider the role of safety in the transfer of a particular therapy into humans.

Some treatments being tested in animal models may have been used previously in humans for other conditions [37]. With these therapies, the need for phase I trials in humans may be eliminated. Other therapies for SCI that have not been used previously in humans will need to undergo safety testing [38]. To speed up the process of translations into humans, those therapies that are known to be safe in humans should be given greater priority for testing than those in which the safety is unknown.

Another issue to consider when evaluating basic science research for transfer into humans is the practicality of the therapy. It is unlikely that treatments that are timed precisely with injury will be able to be used practically in humans. On the other hand, therapies with a larger window of opportunity (e.g., therapy administered 8 to 12, or even 24, hours post injury) will be more easily used in humans. The importance of this issue was emphasized in the studies related to methylprednisolone [1], where the efficacy was directly related to the timing of therapy.

With respect to practicality, the type of therapy must also be considered when moving from an animal model to humans. Medications are probably the easiest to administer, thus their use in humans is relatively simple [1,2]. Administration of modalities—e.g., electrical stimulation [17] or hypothermia [39]—would require the use of specialized devices, so this could delay their translation. Administration of cellular therapies is more invasive and costly, requiring specialized facilities. Moreover, it will require the development and standardization of techniques to prepare cells and a determination of the most appropriate means of administering those cells. All these issues make the transfer of cellular therapies from animal models to humans more difficult. Lastly, therapy that includes a surgical procedure would require extensive training in the surgical techniques.

CLINICAL TRIALS RELATED TO RECOVERY OF FUNCTION IN SCI

There are many issues to consider in the clinical trials in humans with SCIs, just as there are with basic science research. The standardization of medical care is important, because clinical trials are performed at multiple sites, and care generally varies among these sites. Another issue is that some of the drugs administered to patients might have yet undiscovered beneficial or deleterious effects on the recovery of function after SCI. The pattern of adverse events could be different in patients receiving different drugs, and the administration of different drugs might affect the blood levels of new therapies. Another important consideration is whether surgery will be performed to stabilize a patient's spinal column and the timing of such surgery.

Patient selection is another important issue in clinical trials. From a research standpoint, it is often beneficial to target patients with specific levels and degrees of injury. This might mean studying only individuals with ASIA A and B tetraplegia [40], for example; however, the number of subjects with SCIs is relatively small, and posing such limitations on the selection of subjects may limit the feasibility of study performance. While one might think this problem is easily solved by the performance of multicenter studies, it is this author's experience that recruitment of subjects with specific levels and degrees of SCIs is still challenging, even with multicenter studies. Moreover, in multicenter studies the issue of standardization of therapies becomes paramount. Another issue is the etiology of the injury and how this will affect the study design and feasibility. For instance, limiting research to the study of individuals with gun shot wounds might eliminate the issue of surgery; however, it would so limit the number of subjects that the research might not be able to be practically completed. Also of concern are the ages of study subjects and how these affect study feasibility. Finally, if the therapy is a medication, once indications for administration of the medication are then approved by the Food and Drug Administration (FDA), all these patient selection issues will likely carry forward to the official labeling of the medication—in other words, approval of the treatment could be limited to individuals with those specific characteristics.

Another issue to consider is the outcome measures being used to document recovery of function in humans. While the International Standards [40] are internationally accepted, widely used, and standardized, there are still many limitations on their ability to detect subtle changes in neurological function. For instance, any decreases in sensory function to pinprick are graded as 1, with an absence of function graded as 0. Sensation may be minimally impaired or almost completely impaired, and

yet the same grade of 1 is given. Although the standards provide more complete information about the location and degree of spinal cord dysfunction than other methodologies, they are not sensitive enough to detect subtle improvements or declines in sensory function. Additionally, the inter-rater reliability of the International Standards has been shown to range from 0 to 0.83 for pinprick, 0 to 1 for light touch, and 0 to 0.89 for motor function [41]. Because of these issues, exploration has begun on quantitative sensory testing as an adjunctive means to document sensory function in patients with incomplete SCIs [42,43].

In addition to outcome measures that specifically look at neurological function, the therapy's impact on function is also important. Most SCI clinical trials use the Functional Independence Measure [44] to document function. However, this instrument was designed primarily as a tool to document a patient's progress in rehabilitative therapies and is not sensitive for measuring changes of function in patients with tetraplegia. Other outcome measures that may be more appropriate to document the recovery of functional ability associated with increased upper extremity strength include the Spinal Cord Independence Measure (SCIM) [45] and the Quadriplegia Index of Function (QIF) [46]. These instruments can be extremely time-consuming to use, however, and thus a short form of the QIF was recently proposed [47]. To measure the recovery of ambulatory function, the walking index for spinal cord injury (WISCI) was recently developed and has been shown to have good inter-rater reliability [48]. After initial testing of the WISCI scale, it was revised to include an additional level of ambulatory function [49].

Also associated with the performance of clinical trials in SCI is the issue of concomitant rehabilitative therapies: one would ideally like to control this variable. However, the amount, duration, and provision of therapies is based on patient's location, neurologic status, body habitus, concomitant medical problems, family support, motivation, and insurance status. Thus, it would be impossible to perform a clinical trial without some degree of variability in therapies. Recently, the use of body-weight support has also gained popularity for clinical use in the rehabilitation of patients with acute SCIs, and a number of clinical trials are now ongoing to document whether the use of body-weight supported treadmill training [50,51] is superior to traditional therapies. Here is yet another new variable that must be accounted for when we translate therapies from animals into humans with acute SCIs.

In addition to the issues associated with the clinical provision of care, two notable neurologic sequelae associated with SCI must also be considered. Neuropathic pain has been shown to affect approximately two-thirds of persons with SCIs and is described as severe by one-third [52]. Spasticity also affects approximately two-thirds of persons with SCIs, is known to interfere with function, and often requires the use of medications [53,54]. Each of these issues will have a significant impact on patients with SCIs; thus, the impact of any treatments for SCI on pain and spasticity should be considered. Moreover, in some cases the issues of pain and spasticity become more disabling than the patient's SCI; thus, it is theoretically possible that one could lose any benefits gained from improved motor function if pain and spasticity remained problematic.

CONCLUSIONS

Despite all the issues associated with the performance of clinical trials in humans, a number of advantages remain in studying curative strategies for SCI in humans as opposed to animals. Probably the main advantage to studying therapies in people is that people can communicate, and thus our motor and sensory examinations—despite being less than perfect—are much more exact than those used in animals. On the other hand, the fact that humans are subject to other treatments and therapies makes the study of curative strategies more difficult. All these issues must be taken into account when we consider the issue of translation of research from animals into humans.

Although significant work remains to develop therapies that provide a significant recovery of neurologic function to persons with SCIs, we have made great strides in the past few years in many animal models. In order to accelerate the translation of these findings into humans, it is important that more basic scientists and clinical researchers continue to speak and meaningfully address these issues. The development of consensus on an optimal pathway for the study of therapies for SCI in animals would be helpful. Moreover, the formulation of a team of investigators to perform clinical trials on patients with SCIs may be one way to begin to address some of

the issues associated with clinical research in this patient population.

ACKNOWLEDGMENTS

This paper was supported by the Veterans Administration Rehabilitation Research and Development Center of Excellence in Spinal Cord Injury and the National Institute on Disability and Rehabilitation Research, U.S. Department of Education, grant H133N000017. The author would like to thank Kimberly Reid for her assistance in manuscript preparation and planning of the course.

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