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Conference Report

Report of International Clinical Trials Workshop on Spinal Cord Injury February 20–21, 2004, Vancouver, Canada

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Introduction and goals

The International Campaign for Cures of spinal cord injury Paralysis (ICCP) is an affiliation of 'not for profit' organizations whose purpose is to expedite the discovery of cures for spinal cord injury (SCI) paralysis.[a] ICCP decided to take the historic step of organizing the first international workshop of leading SCI researchers, clinical investigators and companies engaged in the development of SCI applications to discuss the many issues surrounding the translation of relevant research to a clinical trial. We volunteered to coordinate this event and Vancouver was chosen as the location, with ICORD (International Collaboration On Repair Discoveries) serving as the local organizer. There were approximately 100 discussants with representation from five continents.[b]

The list of experimental interventions, therapies, and devices to facilitate improved functional outcomes after SCI is extensive and too broad to be adequately covered in a two day workshop. Therefore, we elected to focus the initial workshop on the rapidly increasing number of *experimental cellular-based and pharmaceutical drug treatments* for the repair of SCI. Since some clinical trials have already started and several more are at late stage preclinical maturity, there was a need for an international forum where all aspects of clinical trial design could be discussed.

The invited participants shared information about their clinical trial ideas, plans, progress, or outcomes and discussed how SCI trials can be conducted in a consistent, safe and effective manner. This workshop represented a starting point for a new, coordinated effort to promote the translation of experimental discoveries into valid clinical therapies for the benefit of all individuals with SCI across the world.

The long-term objectives of this exercise are:

1. To discuss what standards of preclinical evidence should be required before a clinical trial begins.
2. To establish appropriate outcome measures for SCI clinical trials.
3. To discuss and encourage best practices for all SCI trial protocols.

The specific objectives for the Vancouver workshop were:

1. To establish an international forum where the design and conduct of SCI trials is discussed.
2. To make available to the international community the experiences of current SCI clinical trial initiatives.
3. To begin discussions and enhance communications and collaborations between basic scientists, regulatory authorities, spinal injury clinicians, and people with SCI.
4. To inform clinical investigators of regulatory requirements for SCI clinical trials initiatives.

This was a very interactive meeting, aided by real-time wireless polling technology, which enabled all participants to vote on the many issues throughout the meeting. This worked well, although the validity of the answers was dependent on the clarity of the question, as well as each individual's interpretation of the issue.

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[a]Current ICCP members include: the Australasian Spinal Research Trust, Christopher Reeve Paralysis Foundation, Institut pour la Recherche sur la Moëlle Épinière, International Spinal Research Trust, Kent Waldrep National Paralysis Foundation, Miami Project to Cure Paralysis, Paralyzed Veterans of America, Rick Hansen Man In Motion Foundation, Spinal Research Fund of Australia. For a recent summary of ICCP goals, activities and partner organizations, see **Adams M, Cavanagh JFR**. International Campaign for Cures of Spinal Cord Injury Paralysis (ICCP): another step forward for spinal cord injury research. *Spinal Cord*, 2004; **42:** 273–280.

[b]All participants paid their own travel and accommodation expenses. No financial support, other than that from ICCP, was sought or accepted for this workshop.

Opening addresses

David Prast, of the Australasian Spinal Research Trust (ASRT) and chair of the ICCP, and Rick Hansen, President of The Rick Hansen Man In Motion Foundation (MIMF), opened the workshop. Both emphasized the amount of hope and sense of urgency that people with SCI have for more rapid progress in the translation of research discoveries to effective therapies. Many people with SCI hoped that this workshop would mark the moment when the research community fully embarked upon the translation of safe and effective treatments to clinical application. Rick Hansen concluded with a motivating account of his journey around the world to raise both research funding and an awareness of the challenges faced by people with SCI, calling on the participants to be equally inspired in their goals.

Current clinical trials

To best appreciate the status of SCI clinical trials, the meeting began with selected reports of some of the trials that have been completed or are currently underway. This two-part session was chaired by James Fawcett and Mark Tuszynski.

Andy Blight, from Acorda Therapeutics in New York, reported on ongoing trials of a proprietary formulation of 4-aminopyridine (Fampridine). Fampridine is a potassium channel blocker that improves axon conduction along those axonal fibers that have been preserved after SCI and/or following demyelination. Initial indications from previous studies are that the compound may help with spasticity, stiffness, bladder and bowel function, as well as sexual functions. Based on his experience, he advised that to run a successful trial it is best to carefully define the inclusion criteria so that only subjects appropriate to measuring the specific clinical target of the therapeutic protocol are recruited. This will maximize the potential for detecting a benefit, while minimizing confounding and extraneous variability within the trial population. Thus, you need to have focused end points and well-matched inclusion–exclusion criteria, even if you expect your intervention to ultimately provide a variety of benefits across a broad spectrum of functional deficits.

Alain Privat, of Institut National de la Santé et de la Recherche Médicale (INSERM) at the University of Montpellier, has been involved in a trial of a noncompetitive *N*-methyl-D-aspartate (NMDA) receptor blocker, gacyclidine (a phencyclidine derivative), which had indicated neuroprotective effects in animal models of SCI. This was a large trial, involving over 200 patients injured throughout southern France. Most patients entering the trial were treated within 3 h of injury, with a second dose administered within the next 4 h. Overall, the experimentally treated patients showed no statistically significant improvement in functional recovery over the placebo-treated control subjects, although there was a trend suggesting that patients with the highest dose were improved. In addition, an analysis of the subgroups indicated individuals who had suffered a cervical injury showed the most improvement. The trial included blinded assessments. A major advance since this trial was completed in 1999, has been the development of more sophisticated magnetic resolution imaging (MRI) techniques. The advances in MRI technologies now enable the pathological extent of a spinal injury to be accurately mapped and tracked, over time, in a quantitative manner. This enables a spinal lesion to be examined at high resolution, as well as facilitating comparisons between animal models of SCI and human situations. Advanced functional MRI will enable better treatments to be tested and validated in animal models, as well as improve the ability to noninvasively follow tissue-specific clinical outcomes of experimental neuroprotective treatments.

Tarcisio Barros, of the University of Sao Paulo, reported his experiences with a small study of eight people who had suffered a clinically (functionally) complete gunshot injury of the cord. The trial involved the surgical insertion of autologous sural nerve segments as a peripheral nerve bridge to facilitate central axon regrowth. The sural nerve segments were fixed in place with fibrin glue, containing fibroblast growth factor-1. Over a 5-year recovery period, this intervention did not improve sensory or motor function outcomes, as assessed using somatosensory evoked potentials (SSEP), MRI, or the American Spinal Injury Association (ASIA) rating score. At times ranging from 2 to 12 years after their SCI, a subsequent group of 32 clinically complete SCI patients has had bone marrow cells, which contain a small proportion of stem cells, infused via arteriography into the anterior spinal artery, at the level of the spinal injury. Dr Barros stated that 15 of these patients have shown improvement in lower extremity SSEPs, and some patients have exhibited modest signs of clinical improvement. The trial did not involve blinded assessments or placebo controls. Definitive conclusions will require a larger scale trial with blinded assessments and placebo controls.

David Snyder, from Proneuron Biotechnologies in Israel, reported on a small phase I trial for the transplantation of a patient's own macrophages, activated by *ex vivo* preincubation with skin tissue, into the damaged spinal cord within 2 weeks of injury. This approach has been reported to be possibly neuroprotective and to facilitate axonal regeneration in animal models of SCI. There were two sites, in Israel and Belgium, where 16 patients have been treated. All patients were classified as functionally complete (ASIA A). While the primary objective of the trial was to establish the safety of the procedure and identify any toxicity, Dr Snyder stated that five patients showed a modest improvement in their subsequent ASIA scores (three patients to ASIA C and two patients to ASIA B). No toxic side effects related to this cell-based intervention were identified. This was a small, nonblinded, nonplacebo-controlled trial. The phase I results have led to the launch of a broader phase II trial with randomized control subjects and blinded outcome

assessments involving five centers. Snyder recommended acute experimental treatments, such as Proneuron's approach, be evaluated in functionally complete injuries to exclude as much as possible the spontaneous recovery that is sometimes observed after SCI (eg the conversion of an initial ASIA A to an ASIA B or C rating over the first few months after SCI). He also stressed the importance of common training for assessors, so that the uses of subjective scales, like the ASIA standards, are as consistent as possible between observers and centers. Finally, he emphasized the importance of controlling the consistency of any therapeutic product and the standardization of protocols across trial centers.

Honyun Huang, from Beijing Chaoyang Hospital, reported the results of fetal olfactory cell transplants, which have now been performed in over 300 SCI cases, with surgical intervention ranging from 6 months to 31 years after injury. These cells have been obtained from human fetuses aborted at 12–16 weeks gestation, when the human olfactory bulb is not well developed. The cells were then isolated and expanded *in vitro*, with approximately 1 million cells injected into the cord rostral and caudal to the injury site. Dr Huang stated that patients reported some functional improvement within 2–3 days after the operation, particularly for the reduction of spasticity and improved control of sweating (diaphoresis). Dr Huang also stated that some patients showed improvement in ASIA sensory and motor scores. The study did not use placebo controls or blinded assessments. As Dr Huang stated, this was not a full clinical trial, but treatment with an experimental therapy. A complete trial would require that patients undergo standardized blinded evaluations both before operation and for an extended postoperative period, which is not currently available to Dr Huang. He stated that he would welcome collaborations that would enable the collection of such data.

Carlos Lima, from Lisbon's Egaz Moniz Hospital, has performed autologous whole olfactory mucosal transplants in 7 patients whose SCI was classified as ASIA A or ASIA B prior to surgery. All the subjects sustained their SCI at least 6 months prior to transplantation. An issue, at the time of the laminectomy, was the amount of collagenous 'scar' tissue at the site of injury and in some cases this tissue was partially resected prior to implantation of the whole olfactory mucosa. Postsurgical assessments employed a battery of observations, including: ASIA ratings, motor-evoked potential (MEP)/SSEP recordings, and MRI. Dr Lima stated that patients had somewhat improved autonomic and bladder functions, reduced spasticity, but minimal to no improvement in touch and pin-prick sensation or motor function. One patient was reported to have exhibited some functional deterioration, postoperatively. This study was small, unblinded and nonplacebo controlled.

Finally, Alan Mackay-Sim, from Griffith University in Brisbane, described the design of a phase I clinical trial for the transplantation of olfactory ensheathing glia (OEG) cells obtained from one of the patient's own olfactory mucosa, which are then purified and expanded over 6 weeks *in vitro* to yield 12–20 million cells of at least 95% purity. These are to be transplanted via 40 small injection sites in and on either side of the injury. The phase I safety trial, currently in progress, is scheduled to have four patients with transplants, and four with placebo treatment. All participants are to have a functionally complete SCI, and be at least 6 months to 3 years after their injury. All participants undergo blinded assessments before treatment and at regular intervals afterwards, including: medical, neurological, and quality of life assessments, as well as ASIA, MEP, SSEP, MRI exams.

Overall, this session revealed that it has been possible to conduct studies enrolling substantial numbers of patients over the past decade. All speakers stressed the experimental and preliminary nature of their work, much of which is currently unpublished. All discussants agreed that before an intervention can be suggested to have functional efficacy, there is the requirement for accurate and independent 'blind' validation of neurological function of experimentally treated patients, both before and after treatment, against the outcomes observed in appropriate control subjects. We also do not know the exact identity or fate of the transplanted cells; do they survive, proliferate, integrate with host tissue, or are they removed from the injured cord? It will be necessary to characterize and establish the precise mixture of cell types that are transplanted. Finally, as with all cell-based transplant studies presented here, the underlying mechanisms for any reported improvement (rapid or gradual) are not established. Understanding the mechanisms of these possible benefits would guide further development of improved therapeutic interventions.

Preclinical validation

Given there has been more research activity using *in vitro* assays and animal models of SCI, it was expected that this would be a lively workshop discussion and it did not disappoint. Nevertheless, consensus was quickly achieved on the critical concern that the safety of any proposed therapeutic intervention be clearly demonstrated in appropriate animal models of SCI prior to any clinical application. However, deciding which animal models of SCI are most appropriate was not as easy a conclusion.

When asked by John Steeves, the session chair, whether 'a contusion injury in an animal SCI model has the best predictive value for benefit in a SCI clinical trial', 52% of the respondents strongly or mildly agreed, whereas 23% mildly or strongly disagreed, and the remaining 25% were uncertain. The diversity of opinion is probably best explained by the numerous variables encompassing SCI. From both a scientific and clinical perspective, SCI is a heterogeneous disorder with differing functional deficits as a result of:

1. The rostrocaudal level of the spinal damage (ie high cervical level through to low cauda equina).

2. The degree of anatomical and functional completeness of the SCI.
3. The intervening time since the SCI (short-term acute through to long-term chronic).
4. Whether the SCI is caused by trauma or a disease, such as cancer or infection.

All of these variables can influence the potential benefit of any therapeutic intervention, as well as the choice of the appropriate animal model of SCI or which preclinical assessment measure is the better predictor of clinical outcome.

The majority of injuries involve a rapid compression or contusion of the cord and thus a strong majority of the participants supported the suggestion that any potential treatment directed to improving overall spinal cord repair should be examined in a contusion injury model prior to clinical trails. Likewise, 78% of participants mildly or strongly agreed that 'for subsequent clinical development, it is necessary that a preclinical finding has to be robust: in other words, similar conceptual findings are obtained by different research groups, even if they are using different approaches'.

One of the central goals of the Vancouver workshop was to introduce basic scientists, regulatory authorities, spinal injury clinicians, rehabilitation therapists and people with SCI to one another's perspectives. These groups have somewhat different goals and views on what constitutes a potentially valuable treatment. SCI scientists are focused on understanding mechanisms of pathology or functional neuroanatomical repair. Much of the published evidence for benefit is based on a neuroanatomical outcome, such as observations of axonal sprouting or regeneration, and this is not always accompanied by a rigorous validation of improved function. Conversely, regulatory agencies are centered on safety and toxicology where details of therapeutic composition, dose, route of administration, and pharmacokinetics are important. Finally, clinicians, therapists, and people with SCI can only accept benefit when there is statistically valid evidence for improved function.

An important theme that ran throughout the meeting was the balance of risk and benefit. Any novel treatment carries risk, and preclinical models cannot always reliably predict clinical outcomes, although they can give a good estimate of the safety of an experimental intervention. There is clearly a greater risk with an invasive therapy, such as a cell transplant strategy, and thus, a higher standard of preclinical safety should be required.

Scientists will use different preclinical assays and SCI animal models, as well as highly invasive assessment tools to evaluate the initial significance of an experimental therapeutic. However, as a discovery is extended and approaches a potential clinical application, it should employ an animal model that best approximates the target of a future clinical trial. Late-stage preclinical experiments should also evaluate the noninvasive outcome measures that will be utilized in the clinical setting. This will not only facilitate comparisons of therapeutic efficacy, but assist the subsequent development of more beneficial 'second-generation' therapies, as the iterative process between preclinical and clinical unfolds.

There has been considerable discussion in the research community about the desirability of testing any potential treatment in large animal models of SCI (dog, cat or primate) before human trials. This issue was raised in Vancouver, with a diversity of views. The commonest view was that the more potentially hazardous a treatment, the greater the need for rigorous testing, including large animal models.

Regulation

Many of the treatments that are progressing towards clinical trials for spinal injury are often very different from conventional pharmaceutical drug trials. Only recently have the regulatory agencies begun in-depth consideration of how to regulate these experimental SCI treatments. However, the development of regulatory expertise is being facilitated by the relevant experiences in cell transplantation emerging from hematology, as well as from many antibody therapy trials. The Food and Drug Administration (FDA) in the USA has a specialized branch to deal with cell-based therapies, the Center for Biologics Evaluation and Research (CBER), whose task it is to regulate cell-based therapeutics as they enter clinical trials.

Cynthia Rask, a neurologist from the FDA, led a workshop on regulatory guidelines. She started off by polling the audience and establishing that only a few of the participants had in-depth experience in making a submission to the FDA. Similarly, SCI is uncharted territory for the regulatory agencies. She emphasized the necessity for a two-way flow of information between the regulatory bodies and the SCI research community to determine appropriate trials methodologies and assessment end points. She then led the audience through the processes of submitting an Investigational New Drug (IND) application. Many of the types of treatment envisaged would come under the jurisdiction of CBER. There was uncertainty among the participants about what types of cells and tissue would be regulated. In short, cell-based treatments become regulated as soon as any intervention greater than excision and reimplantation into the same site is performed. Thus, nonhomologous, autologous transplantation, such as implanting a patient's own peripheral nerve into the spinal cord would be regulated. Moreover, any preparative procedure applied to the cells or tissue, *ex vivo*, becomes part of the 'drug', and cannot be changed without refiling the treatment as a new pharmaceutical.

Dr Rask emphasized that the primary aim of the regulatory agencies is to ensure the safety of treatments. How would an SCI trial be regulated? Many of the potential treatments are invasive, and thus, a phase I (safety) trial in healthy volunteers is hard to imagine. In the absence of any 'clearly proven' effective and

approved therapy for SCI, any new treatment could be compared to the current best available care. It may or may not be necessary to have a placebo-treated control group, even in some phase II trials. However, this does not remove the need to have accompanying assessments of untreated patients, with both experimental and control groups being evaluated in a blinded manner.

The officers of most regulatory bodies are available for informal consultations before a formal IND is submitted. In the case of such a complex condition as SCI, the regulatory agencies, along with SCI clinicians and scientists, will need to engage in meaningful dialogue to chart the best protocols and requirements to ensure safe and effective therapies.

Clinical Trial Assessment

There was a two-part workshop, chaired by Peter Ellaway of Imperial College London, on assessment protocols and tools for clinical trials. The development of robust tests that will reveal objectively whether patients have improved as a result of a novel treatment intervention was seen as a key issue for future clinical trials. The current standardized assessment tools are the internationally adopted standards for neurological classification initially developed by the American Spinal Injury Association (ASIA). The ASIA standards was optimized for use in the current clinical environment, where the primary aims are determination of overall sensory-motor deficits after SCI and their general progress throughout rehabilitation. It was never intended to detect the subtle improvements in function that may result from an axonal regeneration therapy. The ASIA standards are continually being updated and because it is relatively easy to administer (requiring little or no equipment), the ASIA standards will probably remain a key feature of any functional clinical assessment.

Nevertheless, it was recognized that more sensitive measures, optimized to evaluate specific clinical targets, will be needed. Designing these assessment methods is complicated by the fact that each treatment:

1. Has a different biological action or targets.
2. May be delivered at different times after SCI.
3. Is provided to people with distinctly different levels of SCI damage.
4. Will potentially have distinct benefits or detriments, since every person with SCI has a somewhat unique set of functional capabilities.

The appropriate design of a trial also depends critically on how soon after injury the treatment is given. During the acute stages after SCI the outcome of individual patients is not known with any certainty and there will, therefore, be considerable variability. Therefore, large sample sizes, using a number of different outcome measures, with randomized controls and double-blind protocols, will be necessary to establish benefit. For treatments delivered later, the assessment of efficacy may be somewhat easier. People who have lived with SCI for over 2 years often have a relatively stable situation in terms of functional capacity, have learned to report subtle functional changes and thus might serve as their own control group. Moreover, the longer after injury a treatment is given, the more predictable the outcome for individuals and the smaller the sample sizes needed to establish efficacy.

The first speaker was John Ditunno, from Thomas Jefferson University in Philadelphia, who reviewed the development of the ASIA standards, discussing its standardization and future evolution. As stated above, the scale will probably remain a fundamental clinical assessment tool, but since it is a subjective evaluation method, there is a need for all assessors to use the same criteria. Subsequent speakers addressed the ongoing development of additional outcome measures for the functional assessment of SCI.

Nick Davey of Imperial College London, belongs to the ISRT team, which has been developing assessment methods particularly aimed at thoracic level spinal injuries. He described a new and very repeatable perceptual threshold map, which uses graded electrical skin stimulation at each spinal level to quantify sensory thresholds. It provides an accurate measure of complete or partial sensory loss at, above, and below the level of SCI. New motor tests are being developed that are based on electromyographic (EMG) recordings of muscle activity triggered by cortical magnetic stimulation. At thoracic levels, the multiple innervation of back muscles by motor neurons, emanating from different thoracic spinal segments, complicates interpretation. However, recording muscle activation thresholds and stimulation latencies from intercostal muscles may provide a more accurate indicator of functional changes at thoracic cord levels. Similarly, EMG latency measurements from mechanically evoked reflexes in paraspinal muscles may also prove useful.

Andrei Krassioukov, of ICORD, spoke on autonomic control after SCI. Many patients have problems of autonomic control, but this aspect of dysfunction has received insufficient attention. Krassioukov showed examples of autonomic hyperreflexia and areflexia, and showed how these can and should be measured as a clinical end point. Amiram Catz, of Lowenstein Rehabilitation Hospital in Israel, emphasized the importance of assessment protocols that address the recovery of abilities that are functionally important to people with SCI. He has led the development of the spinal cord independence measure (SCIM), which covers 18 daily living tasks, as a more accurate and sensitive measure for SCI outcomes than the more broadly applied rehabilitation score known as the functional independence measure (FIM). A new variant, the SCI-ARMI (ability realization measurement index) is also being developed to introduce a new measure of disability/ability, weighted for the specific neurological deficits of each person with SCI, and thus evaluate the efficacy of rehabilitation strategies, in isolation from the effects of neurological change.

Armin Curt, of the University Hospital Balgrist, presented the findings of a multicenter European collaboration organized from Zurich. The group has focused on comprehensive assessments of the progression of SCI functional outcomes extending from the earliest stages of SCI. The European consortium has used standard clinical assessment tools including ASIA, FIM, SCIM and the walking index for spinal cord injury (WISCI). They have also made parallel electrophysiological recordings, such as SSEP, MEP, and EMG, in each patient. Independently, the functional assessments and electrophysiological recordings each provided reproducible changes over the time course following SCI. However, the correlation between the electrophysiological measures and the assessed functional outcome scores was less clear, leaving everyone to consider what is a more accurate measure and predictor of outcome.

Overall, several groups have made significant advances in updating the current assessment tools based on their rigorous examination of those measures. In addition, the development of more sophisticated and potentially more accurate outcome assessment tools should be able to detect even subtle changes in function, resulting from a therapeutic intervention. It will soon be possible to put together a comprehensive and appropriate battery of outcome measures to validate an experimental treatment paradigm for both its primary and secondary end points.

Clinical trial design

Historically, there have been few invasive therapeutic SCI clinical trials. Therefore, most participants found it a novel process to design a suitable clinical trial of an experimental cellular-based or pharmaceutical drug treatment. In the first part of the session, there was a discussion of the basic principles and phases of trial design. Phase I (safety) trials generally involve a small number of patients and may not utilize controls. Along with safety, the objectives are to begin establishing the pharmacokinetics of the 'drug', and to establish the highest tolerated dose, and perhaps some preliminary evidence of possible efficacy. Phase II (preliminary efficacy) trials are almost always larger, with more exacting protocols. The aim is to maintain safety (eg possible toxicity or deleterious side effects of a therapeutic), but also establish which instruments will be most useful in showing efficacy in phase III trials. Phase III trials are definitive. They are usually large-scale multicenter trials, rigorously comparing the efficacy of a new treatment with the current standard treatment. It is necessary to have clearly defined inclusion and exclusion criteria, a small number of defined clinical end points and a blinded evaluation of accurate outcome measures.

The organizers of the session, Bruce Dobkin, of the University of California at Los Angeles, and Robert Grossman, of Baylor College of Medicine in Houston, picked out a few hypothetical treatment possibilities, and then invited the audience to discuss how a trial could be carried out to determine whether the treatment was effective. The discussion to some extent reflected the inexperience of the research community in planning and running trials. The variables discussed were the optimum timing of an intervention, the level of the injury and the ways in which any functional recovery could be accurately assessed. It was immediately clear that the optimum for these criteria differed radically for different types of treatment.

As regards timing, a neuroprotective treatment would have to be given soon after injury, with the window of opportunity being defined by previous experience for that therapeutic in another clinical setting or from preclinical animal experiments. An axonal regeneration-inducing treatment might be effective if it were given weeks after injury, by which time it might be possible to accurately predict the neurological outcome should the individual not be treated. A plasticity-inducing rehabilitation strategy might be effective for people with SCI who were injured months or years previously, provided they have an incomplete injury with some preserved function, indicating spared axons projecting across or around the lesion.

For many reasons it would be desirable to treat patients with high cervical injuries, where it is easier to document beneficial changes in hand function and where the outcomes could dramatically improve the quality of life. But the risk of possibly inducing more damage and raising the level of a functional cervical injury would be catastrophic. With these safety concerns in mind, invasive therapeutic interventions (direct surgical manipulation of the cord or the surrounding tissues) might be first examined in people with a thoracic level injury where a small upward extension of functional deficits, as the result of an unexpected adverse reaction, would have less catastrophic consequences (an audience poll showed that the majority expected the first trials to focus on thoracic level SCI). However, a treatment that had previously been clinically documented to have low toxicity and could be delivered systemically might be tried over a broader range of SCI levels, including cervical lesions. The reports of relatively few medical complications after cell-based transplants into spinal lesions (see above) are encouraging, but must be tempered by the fact that we have a small sample size and little long-term experience.

The assessment protocols for trials were discussed in several workshop sessions, as the development of robust and accurate methods is an essential prerequisite to good trial design. Various issues were discussed, but again it became clear that an appropriate assessment protocol depends critically on the nature and target of the treatment being examined. Thus if the objective is neuroprotection, the treatment will be applied soon after injury, before the functional outcome for an individual can be reliably predicted. The variability of the patient population in terms of the amount of (confounding) spontaneous recovery could be huge, and thus a large trial, with a greater number of outcome measures will likely be needed to show efficacy. If, however, a patient

is to be treated long after their injury (eg greater than 6 months) then their functional baseline is likely to have stabilized, and each patient might act as their own control. Thus, only a relatively small trial may be required to establish benefit and it would also be possible to perform complex and detailed physiological and behavioral outcome assessments.

The conclusion of the session was that is was likely that in the initial stages of SCI clinical trials there would be a variety of trial protocols, individually designed and deployed as appropriate to the different therapies.

Inclusion and exclusion criteria

An important part of clinical trial design will be identifying and contacting the optimum patient group. Naomi Kleitman, of the National Institutes of Health, led this discussion, which included the benefit and utility of constructing SCI registries (databases) in countries cooperatively undertaking SCI trials. Opinions varied on this topic with the major concern being how to ensure the comprehensive enrollment of people with SCI, as well as maintaining the necessary updating of such patient registries. The major perceived benefit of an SCI registry was the potential value for the rapid recruitment of trial participants having the appropriate inclusion criteria. For example, the relative number of thoracic level spinal injuries is significantly smaller than for other levels of SCI, and if initial clinical trials focus thoracic SCI, then SCI registries could be valuable to identify possible participants. Finally, SCI registries could enable the dissemination of trial results in an efficient and rapid manner.

There was also discussion about whether there were absolute criteria that would disqualify patients from a trial. How would participation in a previous SCI trial complicate effective recruitment of participants; how long would they have to wait after one trial, before they could participate in the next? The list can grow exponentially and there are a number of ethical issues, fundamental to the selection of appropriate criteria. When asked about overall inclusion criteria, the majority of participants agreed that protection of patients was the major goal, and that for this reason functionally complete patients were preferable for invasive therapies. However, the group also agreed that each potential treatment needs to be assessed relative to the risk involved in its use and the intended target of the intervention. To date, the most impressive recoveries after SCI have been observed in people with incomplete injuries undergoing active rehabilitation regimens.

Conclusions

The first international meeting on clinical trials for SCI was a milestone. The participants came from a variety of disciplines and backgrounds including: acute spinal injury units, rehabilitation centers, pharmaceutical and biotechnology companies, basic science research labs, government agencies, nongovernmental organizations and foundations, as well as representatives of the SCI community. The main achievement of the meeting was to bring this varied team together and introduce them to the progress in clinical trials and the complexities involved in effective clinical trial design. Another outcome of the ICCP Clinical Trials Workshop in Vancouver was a vote by the participants to establish a working committee/panel to bring forward more detailed guidelines for how to develop future SCI clinical trials in the most accurate and effective manner. An initial meeting of this international panel has been scheduled for late 2004.

The first clinical trials have started, and many more are planned to begin over the next few years. Continuing the dialogue and the development of more effective guidelines will require continued international cooperation and collaboration. The ICCP is to be congratulated on taking the initiative for the starting and supporting this process.

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